Evaluation of the impact of an intradialytic exercise program on sarcopenia in very elderly hemodialysis patients

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Short Title: Sarcopenia management in elderly hemodialysis patients
Sarcopenia is a highly prevalent condition in persons on hemodialysis. In stable very elderly (75- to 95-year-old) persons on chronic hemodialysis, we prospectively studied the European Working Group on Sarcopenia in Older People (EWGSOP2) steps stability over time in 37 controls and their response to a 12-week intradialytic lower limb exercise program in 23 persons. Overall dropout was 15% and the main cause for dropout was death (8%). Thus, 33 controls and 18 exercise participants were evaluated at 12 weeks. In controls, comorbidity, nutrition, dependency and frailty scales, anthropometric assessments, EWGSOP2 step values and the prevalence of suspected, confirmed, and severe sarcopenia as assessed by EWGSOP2 remained stable. By contrast, in persons that completed the exercise program a significant improvement in the sit-to-stand-5 test was noted at the end of the 12-week exercise program (19.2±4.9 to 15.9±5.9 seconds, p =0.001), consistent with the lower limb nature of the exercise program, that persisted 12 weeks after completion of the program. Exercise also improved the FRIED frailty scale (1.7±1.0 to 1.1±0.6, p= 0.004). In conclusion, EWGSOP2 steps remain stable in stable very
elderly persons in hemodialysis and sit-to-stand-5 is responsive to a short-term intradialytic lower limb exercise program. These results may help define EWGSOP2-based primary endpoints in future large scale clinical trials assessing exercise interventions.

**Keywords:** elderly, exercise, frailty, hemodialysis, sarcopenia
INTRODUCTION

Sarcopenia is a clinical condition characterized by the loss of muscle mass and strength in the context of aging with a negative impact on quality of life and care(1). The loss of muscle mass starts from the age of 40 years and progresses at a rate of 8% per decade from that age and accelerates to 5% per decade from the age of 70 years. It is estimated that 50% of people over the age of 80 years have sarcopenia(2). The diagnosis of sarcopenia is challenging in clinical practice as loss of muscle mass and of muscle strength do not necessarily correspond to each other(3,4).

Muscle strength, power, and performance result from multiple components of skeletal muscle including size, fiber type, quality, and innervation. Therefore, even in patients with muscle mass within normal limits, weakness may be apparent in functional performance or activities of daily living(5). Diagnosis of sarcopenia should focus on the identification of a loss of muscle strength regardless muscle size. Recently, the European Working Group on Sarcopenia in Older People (EWGSOP2)(6) established new diagnostic steps for sarcopenia. The first step is a novel case-finding test, called SARC-F (Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls), composed of five easy-to-answer questions(7). The second step establishes the diagnosis of probable sarcopenia through the assessment of muscle strength and in the third steps confirms the diagnosis by measuring muscle mass. The final step assesses severity by the ability to perform certain physical tests(6).

Sarcopenia is common in adults with chronic kidney disease (CKD), and its prevalence increases markedly with declining kidney function(8). In persons in hemodialysis, the prevalence is highly variable depending on the assessment method, ranging from 4% to 64% (4,9,10). Bioelectrical impedance analysis (BIA) and anthropometric predictive equations estimate whole body skeletal muscle mass (SMM) and appendicular skeletal muscle mass (ASM)(11), but not strength. However, persons with CKD may have poor muscle function despite an acceptable muscle mass(12).

There is much debate about the best therapeutic approach to sarcopenia in hemodialysis. Dietary interventions(13,14) and dialysis optimization have been proposed(15). However, physical activity is the most effective and cost-effective therapy to counteract the changes in muscle mass and strength caused by age and chronic diseases(16). The Sarcopenia, Cachexia and Wasting Disorders Society recommends aerobic and muscular endurance exercise for 20-30
minutes 3 times a week (17). The implementation of exercise programs within hemodialysis sessions has been proposed (18), including low intensity exercises, adapted to older population groups (19). These programs are frequently limited in time, there is little information on their longer-term impact, and it is unknown whether and how they impact the EWGSOP2 steps.

The aim of the present study was to assess changes over time in sarcopenia assessed by the new EWGSOP2 diagnostic tool in very elderly (75-95 years) persons on hemodialysis under control conditions or following an intradialytic physical exercise program.

MATERIALS AND METHODS

This was a prospective, non-randomized, interventional study. Participants were clinically stable persons with kidney failure on chronic hemodialysis at three outpatient centers and a hospital dialysis unit of the Fundación Renal Íñigo Álvarez de Toledo. The study was approved by the ethics committee of the Hospital Universitario Fundación Jiménez Díaz (number 03/19) and complied with the standards recognized by the Declaration of Helsinki of the World Medical Association, as well as by the Standards of Good Clinical Practice, in addition to compliance with Spanish legislation on biomedical research (14/2007 Law). All participants signed informed consent forms. The study period was from February to November 2019. The intervention consisted in an intradialytic exercise program for 12 weeks.

Inclusion criteria were age between 75- and 95-year-old, capability to perform physical fitness assessment tests or dynamometry, a hemodialysis vintage longer than 3 months and signing the consent form. Exclusion criteria were the presence of intra-dialysis instability, comorbid conditions that contraindicated exercise or dementia preventing the signature of the consent form.

This was a pilot study and no formal sample size calculations were made. A total of 60 patients participated in two non-randomized groups, the control group (n=37) who did not perform physical activity during hemodialysis sessions and the exercise group (n=23) who performed the physical exercise program during hemodialysis.

All subjects meeting the inclusion criteria in one of the dialysis centers were assigned by convenience to the exercise group, given the need for the presence of specialized personnel, while patients from the other 2 participating centers were assigned to the control group. Of 25
patients meeting inclusion criteria for the exercise group, 23 accepted to perform the exercise program and 2 refused but agreed to follow-up evaluations and were included in the control group. All patients offered to participate in the control group accepted. Except for the exercise program, care was as per routine clinical.

_Intradialytic exercise program_

The intradialytic program began with warm-up respiratory and joint mobility exercises and followed with 4 groups of lower limb strength exercises: hip flexion, hip/knee extension, hip abduction and adduction, and ankle flexion-extension/abduction-adduction. Elastic bands, weighted ankle braces, foam balls and Pilates rings were used to perform the exercises. The foot peddler was used as aerobic resistance work, progressively adapting the intensity and duration, with a maximum of 30 minutes, at an intensity corresponding to 12-14 points on the Borg 6-20 range scale. Exercise was supervised by physical activity and sport science professionals, who personalized the most appropriate program for each participant following evaluation of their capacities, dependence, and comorbidities. 2 sport science professionals and 4 trainees. Exercise was carried out in the 3 weekly hemodialysis sessions for 12 weeks. In each session, exercise started 30 minutes after the initiation of the hemodialysis session. Each session duration was 60 minutes. The physical exercise program involved the lower limbs. Additionally, to ensure vascular access stability during the program, needle clamping in the AVFs was reinforced.

Vital signs (blood pressure, temperature, heart rate and glycemia in diabetics) were recorded before and after the start of the activity. Adverse effects during dialysis sessions such as vascular access incidents, hypotension, headache, cramps, and pain and, if necessary, the cause of abandonment of the program were recorded.

_Study variables_

Study variables were assessed at baseline and at the end of the 12-week program. In addition, in the exercise group, they were assessed again 12 weeks after completing the exercise program, that is 24–weeks since the start of the study. The observer-dependent variables were obtained by the two Physical Activity and Sport Sciences professionals. The primary outcome
variables were those used to diagnose sarcopenia according to the EWGSOP2 steps (Figure 1)(6):

**Find.** Clinical suspicion/case finding defined by the SARC-F survey score. It is a simple scale that identifies suspected sarcopenia, composed of 5 questions scored differently according to their intensity (Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls)(7).

**Assess.** Loss of strength, defined by the following upper limbs and lower limbs variables:
**Grip strength by dynamometry (GSD).** Measure handgrip strength, that is, upper limb strength. A CAMRY® EH101 electric dynamometer was used. Participants were standing, arm extended and parallel to the body and without supporting or moving the wrist. The maximum grip strength was analyzed for 3 seconds, with a 1-minute rest between repetitions, performing two attempts in both arms. The best of the dominant arm (the arm with the greater strength) was used for the study.

**Sit-to-stand 5 (STS-5) for lower limbs.** STS-5 evaluates the time required by patients to get up from a chair without any support, performing this movement 5 consecutive times(20).

**Confirm sarcopenia. Amount of muscle mass.** Defined by the variable **Appendicular Skeletal Muscle Mass (ASM)** assessed by a MALTRON® BioScan touch i8 BIA device. Assessments were performed in the second session of the week, between the first and second hour of dialysis, given that the device allows measurements during the hemodialysis session.

**Severity of sarcopenia. Physical condition,** assessed by:

**Gait speed (GS).** Measures the time required to walk 4 meters (also included as the 2nd test of the short battery of physical performance, SPPB). The readout is the walking speed in meters per second, considering the need for assistance (cane, walker, another person, etc.) to maintain balance during the walk. To increase test reliability, a meter in front and a meter behind these 4 meters were not considered, so that results are not influenced by acceleration or deceleration(21).

**Timed Up and Go test (TUG).** This test assesses agility and dynamic balance. Subjects must get up from a chair; walk for 3 meters; turn around a cone; and sit down again. The test is performed at the maximum speed at which persons can walk, three times, the result is the fastest time(22).

**Short Physical Performance Battery (SPPB),** modified by Guralnik(23). It consists of three tests. The first is an adaptation of the Romberg tests for balance. Persons are asked to stand with feet together, then instructed to place one foot next to the other, with the heel of one foot halfway to the other foot. And finally, to place one foot in front of the other, resting the heel in front of the toes. In all three instances, balance preservation is evaluated. The second test of this battery is GS over 4 meters, as described above. The third test is the STS5.
The cut-off points for sarcopenia markers for each variable are described in Table 1.

Table 1. Cut-off points for sarcopenia markers included in EWGSOP2

| Diagnostic steps | Test | Cut-off, males | Cut-off, females |
|------------------|------|---------------|-----------------|
| **Find**         | SARC-F (points)(7) | ≥4 | ≥4 |
| **Assess**       | GSD (kg)(24) | <27 | <16 |
|                  | STS5 (s for 5 rises)(25) | >15 | >15 |
| **Confirm**      | ASM (kg)(26) | <20 | <15 |
| **Severity**     | GS (m/s)(26,27) | ≤0.8 | ≤0.8 |
|                  | TUG (s)(28) | ≥20 | ≥20 |
|                  | SPPB (points)(29,30) | ≤8 | ≤8 |

SARC-F: sarcopenia screening survey; Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls; GSD: grip strength by dynamometry; STS-5: sit-to-stand 5 test; ASM: appendicular skeletal muscle mass; GS: Gait speed, TUG: Timed-Up and Go test, SPPB: Short Physical Performance Battery.

Other variables

Anthropometric variables included body mass index (BMI), arm perimeter and waist-hip index (WHI) and analytical variables were albumin, hemoglobin, C reactive protein (CRP), 25 (OH) vitamin D and Daugirdas Kt/V urea. Additionally, scales of malnutrition (MIS: malnutrition-inflammation score)(31), comorbidity (Charlson)(32), dependence (Barthel)(33), frailty FRIED(34) and physical activity (PASE)(35) were used. Demographic variables such as sex and age, cause of kidney disease and dialysis vintage were collected. Anthropometric measurements were made by the two professionals in Physical Activity and Sport Sciences.

Statistical Analysis

IBM SPSS Statistics v20 was used for statistical analyses. Quantitative variables were presented as mean and standard deviation and qualitative variables as absolute numbers and percentages. The chi-square test was used to evaluate the homogeneity of the groups under study. To analyze the impact of exercise on the variables under study, the t-student test and McNemar's test were used. The level of statistical significance was set at p ≤ 0.05 and when multiple testing was performed, modified as per the Bonferroni’s correction and the p value threshold for statistically significance in multiple testing corresponding to α level equal to 0.05 in single testing is indicated in a footnote in each table.
RESULTS

Study design and patient population

A cohort study was conducted in three FRIAT dialysis centers, a total of 60 persons participated in the study, 37 (61.7%) controls and 23 (38.3%) in the exercise group. Of them, 41 (68%) were men, mean age was 81.85±5.58 years and hemodialysis vintage 49.88±40.29 months. The causes of kidney disease were diabetes mellitus (28%), unknown (22%), hypertension (20%), interstitial nephritis (7%), glomerulonephritis (5%) and others (8%).

At 12 weeks, 51/60 (85%) participants remained in the study, 33/37 (89%) in the control and 18/23 (78%) in the exercise group. Reasons for not completing the study were death (5/60, 3 in control group and 2 in exercise group, 8.3%), hospital admission (2/60, 3.3%), holidays (1/60, 1.6%) and stopping the exercise program (1/60, 1.6% of the full cohort and 1/23, 4.3% of those in the exercise program).

Table 2 describes baseline demographic characteristics, scales, laboratory analytical data and dialysis adequacy for participants who completed the protocol. Baseline significant differences were only observed between the groups for the MIS malnutrition scale, serum albumin and Kt/V urea that were no longer observed after applying Bonferroni’s correction for multiple testing. Additionally, no significant differences were observed in the mean baseline values for the components of the EWGSOP2 steps (Table 3).

Table 2. Demographic, scales, anthropometric and analytical data and dialysis parameters at baseline. Mean ± SD

|                               | Control group, n=37 | Exercise group, n=23 | p value |
|-------------------------------|---------------------|----------------------|---------|
| **Demographic data**          |                     |                      |         |
| Gender (Males)                | 75.8% (25)          | 61.1% (11)           | 0.218   |
| Age (years)                   | 81.7±5.3            | 82.0±5.8             | 0.854   |
| Hemodialysis vintage (months) | 52.5±45.8           | 50.4±35.9            | 0.867   |
| **Comorbidity, nutrition, dependency, frailty and physical activity scales** | | | |
| Charlson comorbidity (points) | 10.1±2.2            | 9.5±1.8              | 0.358   |
| MIS nutrition (points)        | 6.9±4.3             | 3.9±1.6              | 0.006   |
Impact of an intradialytic physical exercise program on scales, adverse effects, hospital admissions, anthropometry, analytical and dialysis variables

The impact of the intradialytic physical exercise program on scales, anthropometry, analytical and dialysis variables was assessed at 12 weeks, that is, at the end of the exercise program for participants exercising during the hemodialysis sessions and at the same time point in controls that did not exercise. The exercise program was associated with a significant improvement in the frailty score from baseline to the end of the exercise program (12 weeks).

### Table 3. EWGSOP2 components at baseline. Mean ± SD.

| Find: Clinical suspicion | Control group, n=37 | Exercise group, n=23 | p value |
|--------------------------|---------------------|----------------------|---------|
| SARC-F(points)           | 2.5±2.3             | 2.3±2.1              | 0.861   |

| Assess: Loss of strength | Control group, n=37 | Exercise group, n=23 | p value |
|--------------------------|---------------------|----------------------|---------|
| GSD (kg)                 | 19.6±6.1            | 20.9±6.3             | 0.416   |
| STS5 (s)                 | 21.3±7.4            | 19.2±4.9             | 0.266   |

| Confirm: Muscle wasting  | Control group, n=37 | Exercise group, n=23 | p value |
|--------------------------|---------------------|----------------------|---------|
| ASM (kg)                 | 19.5±3.8            | 18.9±3.8             | 0.553   |

| Severity: Physical condition | Control group, n=37 | Exercise group, n=23 | p value |
|------------------------------|---------------------|----------------------|---------|
| GS (m/s)                     | 0.76±0.2             | 0.75±0.2             | 0.458   |
| TUG (s)                      | 16.2±5.1             | 16±6.2               | 0.338   |
| SPPB (points)                | 6.4±2.4              | 7.2±2.9              | 0.307   |

SARC-F: sarcopenia screening survey; Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls; GSM: grip strength (dynamometry); STS-5: sit-to-stand 5 test; ASM: appendicular skeletal muscle mass; GS: Gait speed, TUG: Timed-Up and Go test, SPPB: Short Physical Performance Battery.
Exercise was well tolerated with no differences in headache, cramps and pain. Hypotension was observed in 24/33 (73%) patients in the control group and in 9/18 (50%) in the exercise group (p = ns) during the 12-week exercise (or control) period. In the 12-week follow-up period, hypotension was observed in 13/18 (72%) patients in the exercise group and control 22/33 (67%), (p=ns). No vascular access incidents were recorded.

During the 12 weeks of the study there were 12 admissions involving 8 patients in the control group, with a mean hospital stay of 9.1±5 days, while in the exercise group there were no admissions. In the following 12 weeks, 5 patients in the control group and 2 in the exercise group were hospitalised, with hospital stays of 5.6±2.6 and 7.5±7.8 days (p=ns).

### Table 4. Scales, anthropometry, analytical and dialysis variables after 12 weeks. Mean ± SD.

|                                | Control group, n=33 | Exercise group, n=18 | p value | p value |
|--------------------------------|----------------------|-----------------------|---------|---------|
| **Comorbidity, nutrition, dependency, frailty, and physical activity scales** |                      |                       |         |         |
| MISS (nutrition)               | 6.9±4.3              | 6.8±4.2               | 0.363   | 3.9±1.6 | 3.8±1.2 | 0.816   |
| Barthel (dependency)           | 88±18.9              | 86.5±20.1             | 0.150   | 93.6±11.7 | 94±10.2 | 0.830   |
| Fried (frailty)                | 2.2±1.3              | 2.2±1.4               | 0.786   | 1.7±1.0 | 1.1±0.6 | 0.004*  |
| Pase physical activity (points)| 20.4±28              | 19.4±21.8             | 0.152   | 31.3±34.9 | 45.6±39.1 | 0.085   |
| **Anthropometric data**        |                      |                       |         |         |
| BMI (kg/m²)                    | 25.2±3.8             | 25.3±3.9              | 0.297   | 25.3±3.7 | 25.3±3.5 | 0.713   |
| Arm perimeter (cm)             | 26.7±2.6             | 27.0±3.1              | 0.358   | 26.3±2.9 | 27.3±3.4 | 0.024   |
| WHI                            | 0.92±0.1             | 0.93±0.1              | 0.304   | 0.95±0.1 | 0.94±0.1 | 0.121   |
| **Serum biochemistry**         |                      |                       |         |         |
| Albumin (g/dl)                 | 3.6±0.4              | 3.7±0.4               | 0.100   | 3.9±0.2 | 4.0±0.3 | 0.034   |
| Hemoglobin (g/dl)              | 11.2±1.03            | 10.8±1.2              | 0.099   | 11.7±0.8 | 11.7±1.1 | 0.899   |
| CRP (mg/L)                     | 0.91±1.1             | 1.46±2.1              | 0.107   | 1.75±2.3 | 0.88±0.8 | 0.117   |
| 25 OH Vitamin D (ng/mL)        | 22.5±12.6            | 28.1±16.8             | 0.009*  | 20.3±14.5 | 21.5±13.9 | 0.635   |
| **Dialysis adequacy**          |                      |                       |         |         |
| Kt/V urea                      | 1.9±0.4              | 1.9±0.4               | 0.657   | 1.6±0.3 | 1.7±0.3 | 0.020   |

BMI: Body mass index; WHI: Waist-hip index. * Statistically significant after Bonferroni correction. Application of Bonferroni’s correction to this data set would result in a p value threshold of 0.00426 for statistically significance corresponding to a level equal to 0.05 in single testing.
Impact of an intradialytic physical exercise program on values for the individual EWGSOP2 steps components

The impact of the intradialytic physical exercise program on EWGSOP2 steps was assessed at 12 weeks, that is, at the end of the exercise program for participants exercising during the hemodialysis sessions and at the same time point in controls, as well as at 24 weeks, that is, 12 weeks after the end of the exercise program for program participants (Table 5). At the end of the intradialytic physical exercise program (12 weeks), only the STS5 values in the EWGSOP2 steps had significantly improved in the exercise group, after Bonferroni’s correction. This is consistent with a lower limb exercise program. Moreover, the improved STS5 persisted 12 weeks after the end of the exercise program (24 weeks timepoint), as p values versus 12 weeks remained >0.05. By contrast, no significant changes were observed in the control group.

Table 5. EWGSOP2 at baseline, at the end of the intradialytic exercise program (12 weeks) and 12 weeks after completing the intradialytic exercise program (24 weeks). Mean ± SD.

| Control Group, n=33 | Exercise group, n=18
|---------------------|---------------------|
|                     | Baseline  | 12 weeks | p value | Baseline  | 12 weeks | p value | 24 weeks | p value 24 vs 12 weeks |
| Find: Clinical suspicion |
| SARC-F (points)     | 2.5±2.3   | 2.6±2.3  | 0.103    | 2.3±2.1   | 1.9±2.00  | 0.110    | 2.5±2.2  | 0.056               |
| Assess: Loss of strength |
| GSD (kg)            | 19.6±6.1  | 19.7±6.6 | 0.855    | 20.9±6.3  | 22.5±6.8  | 0.019    | 22.9±6.4  | 0.237               |
| STS5 (s)            | 21.3±7.4  | 23±11.5  | 0.398    | 19.2±4.9  | 15.9±5.9  | 0.001*   | 14.4±2.9  | 0.707               |
| Confirm: Muscle wasting |
| ASM (kg)            | 19.5±3.8  | 19.5±3.8 | 0.795    | 18.9±3.8  | 19.5±3.9  | 0.010    | 19.2±3.5  | 0.560               |
| Severity: Physical condition |
| GS (m/s)            | 0.76±0.2  | 0.77±0.3 | 0.801    | 0.75±0.2  | 0.92±0.3  | 0.013    | 0.99±0.3  | 0.267               |
| TUG (s)             | 16.2±5.1  | 15.3±5.3 | 0.392    | 16.02±6.2 | 13.6±7.2  | 0.041    | 13.5±6.4  | 0.623               |
| SPPB (points)       | 6.4±2.4   | 6.3±2.8  | 0.732    | 7.2±2.9   | 8.6±2.8   | 0.027    | 9.6±1.9   | 0.165               |

SARC-F: Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls; GSD: grip strength by dynamometry, STS-5: sit to stand to sit 5, ASM: appendicular skeletal muscle mass, GS: gait speed, TUG: Timed-Up and Go test, SPPB: Short Physical Performance Battery.
* Statistically significant after Bonferroni correction. Application of Bonferroni’s correction to this data set would result in a p value threshold of 0.0071 for statistically significance corresponding to α level equal to 0.05 in single testing.

Impact of an intradialytic physical exercise program on EWGSOP2 steps

We next assessed the impact of an intradialytic physical exercise program on EWGSOP2 steps (Figure 2). That is, we assessed the percentage of patients that would fit into the sarcopenic category for each EWGSOP2 step. In the exercise group, numerical decreases in the percentage
of individuals meeting each sarcopenia step criterion were observed for all EWGSOP2 steps. However, these changes only reached statistical significance for STS-5 that assesses lower limbs strength: the percentage of sarcopenic individuals among participants in the exercise program, as assessed by this criterion, decreased from 86% to 53% (p=0.031). These results are consistent with the exercise program being focused on lower limbs. By contrast, no significant changes were observed in the control group.

Figure 2. Percentage of participants that met different EWGSOP2 steps associated to sarcopenia at the 12 weeks. Control baseline (blue) and 12 weeks (dark orange), exercise baseline (grey) and 12 weeks (light orange). SARC-F: Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls; GSD: grip strength by dynamometry, STS-5: sit to stand to sit 5, ASM: appendicular skeletal muscle mass, GS: gait speed, TUG: Timed-Up and Go test, SPPB: Short Physical Performance Battery. CG: control group, EG: exercise group.

Impact of an intradialytic physical exercise program on the prevalence of sarcopenia as assessed by EWGSOP2

Supplementary Table 1 shows the percentage of participants meeting each step of the EWGSOP2 sarcopenia diagnosis algorithm before and after exercise. Each probability step criterion and each severity step criterion were analyzed independently. Probable sarcopenia at
baseline was found in 94% in exercise group participants and 97% in controls. At 12 weeks, no statistically significant differences from baseline were observed in either group.

**DISCUSSION**

The present study explored the changes over time of components of the EWGSOP2 steps to diagnose sarcopenia in very elderly persons who were stable on chronic hemodialysis, both under control conditions and following a 12-week program of intradialytic lower limb exercise. The main findings were that over a 12-week follow-up, values for the individual components of the EWGSOP2 steps as well as the prevalence of probable and confirmed sarcopenia and the severity of sarcopenia remained stable under control conditions. Exercise improved physical frailty as measured by Fried as well as the lower limb parameter STS-5. Lower limb frailty is related to adverse outcomes in HD patients(36). A positive trend was also observed for the mean values for almost all components of the EWGSOP2 steps which was evident both at the end of the program and persisted 12 weeks after the end of the program. Thus, the exercise program achieved a persistent improvement of sarcopenia-related parameters assessed by the EWGSOP2 steps and the EWGSOP2 steps were responsive to the exercise program. Despite numerical differences in the prevalence of probable sarcopenia, confirmed sarcopenia and severe sarcopenia, differences were not statistically significant, likely because the study was rendered underpowered by a high dropout rate.

Sarcopenia detection is necessary to design therapeutic plans that may involve correction of comorbidities, an exercise plan, improve nutritional support and optimize dialysis itself(14). This pilot study identified potential endpoints for clinical trials aiming at improving sarcopenia in very elderly persons on hemodialysis but also illustrated the difficulty of performing interventional studies on sarcopenia in very elderly hemodialysis patients, as the dropout rate was 15% in 12 weeks. Extrapolation to an annual drop out would balloon to a whopping 60% dropout. While some may consider this too high, we should remember that the expected remaining lifetime of prevalent dialysis patients in this age range is much closer to that of the general population than that of hemodialysis patients in their twenties(37).
Intradialytic exercise is prescribed to improve sarcopenia in persons with kidney disease\textsuperscript{(38–41)}. It increased muscle strength, especially of the lower extremities and manual dexterity\textsuperscript{(18)}. A 2019 systematic review and meta-analysis of 27 RCTs involving 1215 subjects concluded that intradialytic exercise resulted in benefits in terms of improving haemodialysis adequacy, exercise capacity, depression and quality of life for haemodialysis\textsuperscript{(38)}. However, the mean age of participants in the trials ranged from 34 to 69.7 years, well below the 82 years mean age among participants in the present study, and only three trials enrolled participants with a mean age ≥65 years. Moreover, none of the trials explored the impact on sarcopenia as assessed by EWGSOP2 which was published in 2019. More recent reviews emphasized the benefits of exercise training, although they were not limited to intradialytic exercise\textsuperscript{(40,41)}. Again, the age range of the studies were either not mentioned\textsuperscript{(40)} or stated to range from 36 to 71 years\textsuperscript{(41)}. Thus, although the authors concluded that there is convincing evidence that exercise training improves physical function measured as aerobic capacity, muscle endurance strength and balance at all ages and all stages of CKD\textsuperscript{(41)}, in fact, the evidence so far is thin regarding the age range of participants in the present study. A more recent exploratory trial showed that intradialytic cycle ergometry reduced cardiac stunning in 20 hemodialysis patients with a mean age of 59 years\textsuperscript{(42)}. An ongoing large (n=335) pragmatic randomized controlled trial is assessing the impact of intradialytic cycle exercise training quality of life, but again, the median age of participants is 59 years\textsuperscript{(39,43)}.

The concept of dynapenia refers to loss of muscle strength, differentiating it from low muscle mass, although both are components of sarcopenia. It may be argued that functionally, dynapenia is an important concept for patient well-being. Exercise improves physical performance tests, hence muscle strength or dynapenia, in both legs and arms\textsuperscript{(44)}. Lower extremity resistance exercise during hemodialysis was previously shown to increase muscle strength but not muscle mass\textsuperscript{(12,45,46)}. We observed that the 3-month exercise program did impact generic tests such as those for frailty but not those for dependence or MIS. A novelty of the present report is the analysis of the impact of exercise on EWGSOP2 parameters. Indeed, all EWGSOP2 parameters assessed improved, while they remained stable in the control group. The only exception was the case detection survey score. SARC-F is highly sensitive and thus, a good screening tool, but it may be non-specific. Other authors\textsuperscript{(19)} have found improvement after exercise in some of these tests but did not systematically analyse all EWGSOP2 steps.
The main and only significant change after applying Bonferroni’s correction was the mean STS-5 decrease from 19.2 to 15.9 s, close to the sarcopenia cut-off point (15s)(47). For the severity step, the GS EWGSOP2 cut-off point of 0.8 m/s has been questioned as too demanding for the elderly(48). In our study, GS reached 0.92 m/s. GS, TUG and STS-5 are simpler to perform than the SPPB test and would allow assessing changes in strength and functionality in dialysis units. Overall, individual EWGSOP2 step parameters were responsive to an exercise program in very elderly patients on dialysis, suggesting that EWGSOP2 represents an appropriate tool to assess progress and may be used as primary endpoint in interventional studies. At 6 months after exercise initiation of the exercise program, the achieved improvement remained stable. This suggests that in a resource-limited environment, intermittent periods of exercise programs may be tested to improve and maintain muscle mass and strength, but that continuous exercise programs would be needed if continuous improvement is the aim.

The present data also suggest that muscle functionality is lost before muscle mass according in very elderly persons on hemodialysis. The first muscle groups to be affected by sarcopenia are those of lower limbs, but they are also the first to recover with exercise(49). We hypothesize that in dialysis patients it is preferable to use functional variables for the detection of sarcopenia, rather than muscle mass measured by BIA, that may be influenced by fluid status hydration(50), as pointed out by EWGSOP2. Indeed, considering muscle mass measured by ASM reduced the number of severe sarcopenia cases. In our opinion, in uremic patients’ muscle mass and strength can be dissociated and ASM should not be taken into account in assessing severity of sarcopenia. The EWGSOP 2 steps allow observation of the impact of exercise on sarcopenia, although the requirement of simultaneous use of muscle mass and strength should be re-evaluated in a routine clinical setting in this population. Despite this, ASM by BIA remains a key predictor of mortality outcomes that should be monitored in clinical practice(51). Exercise was not associated with adverse effects and it did not modify hypotension episodes when compared to control(19,52).

Some limitations should be acknowledged. This was a non-randomized and non-blinded study, which may have resulted in bias. Thus, EWGSOP2 identified severe sarcopenia in 42% of control and 22% of exercise participants, although there were no statistically significant differences. In this regard, the results obtained in control and exercise patients cannot be directly compared. Follow-up was for 12 weeks for both groups but was only prolonged 12 more weeks.
in the exercise group. In addition, comorbidities may limit the ability to exercise for many very elderly dialysis patients and, thus, the results regarding the efficacy exercise cannot be extrapolated to the wider very elderly population in hemodialysis. BIA is not considered a gold-standard method to assess sarcopenia. However, MRI or CT are either not accessible for routine clinical care assessment of sarcopenia or marred by radiation. Dropout was higher than initially expected and clinical impact of the intervention on falls or quality of life was not assessed. Finally, patient allocation was pragmatic but not optimal, which may also have resulted in bias. Despite these limitations, the present study provides valuable insights for the design of clinical trials aiming at improving sarcopenia in very elderly persons on hemodialysis, both from the point of view of sample size calculations and regarding the selection of specific primary endpoints.

In conclusion, assessment of the EWGSOP2 steps is stable over time in stable very elderly persons on hemodialysis and STS-5 is responsive to a 12-week lower limb exercise program. Furthermore, assessment of the EWGSOP2 step STS-5 shows persistent benefit three months after completing the exercise program. Thus, it represents a feasible primary endpoint to assess the efficacy of exercise programs or other interventions to improve sarcopenia in very elderly hemodialysis patients. Furthermore, based on the present results, we anticipate that numerical changes in specific parameters within EWGSOP2 steps may be appropriate primary endpoints for small sized trials. However, a primary endpoint of change in sarcopenia diagnosis (either probable or confirmed) or of an impact on severity of sarcopenia according to EWGSOP2 steps will require a larger sample size that should consider the potentially high dropout rate, that may reach 60% annually.

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AUTHORS’ CONTRIBUTIONS

Subject recruitment: MLST and BMS; Physical intervention and assessment: MLST, AMPA; ALG and MGO; Interpretation of results: MLST, EGP, CGI, BMS and SMF; Statistical methods and analysis: MLST and ALG; Manuscript writing: MLST, EGP, CGI, AO and SMF.

CONFLICT OF INTEREST STATEMENT

A.O. is the Editor-in-Chief of CKJ. None of the other authors have any conflict of interest in this study.

DATA AVAILABILITY STATEMENT

A spreadsheet with all clinical data collected from patients (whose information is anonymized) is available on request.
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