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Impact of dietetic intervention on skin autofluorescence and nutritional status in persons receiving dialysis: a proof of principle study.

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Abstract:	Objective: Advanced glycation end-products (AGEs) are uremic toxins that result from oxidative stress and food consumption. We have previously reported that markers of malnutrition are more important determinants of increased skin autofluorescence (SAF), a measure of AGE accumulation and risk factor for mortality, than high dietary AGE intake in a hemodialysis (HD) population, suggesting that correcting malnutrition may decrease SAF. Design and methods: We investigated this hypothesis in a single center, non-randomized proof of principle study. We enrolled 27 HD and one peritoneal dialysis (PD) patient with malnutrition who received individualized nutritional advice and support over 6 months. SAF was measured at baseline, 3 and 6 months. Dietary intake and nutritional status were assessed at baseline and 6 months. Results were compared with a control group of malnourished dialysis patients (n= 41 HD and 8 PD) from a previous observational study. Results: The intervention group showed a significant increase in dietary intake, including AGEs, Subjective Global Assessment (SGA) score and serum albumin, while SAF levels remained stable over 6 months (3.8±0.7 arbitrary units [AU] vs. 3.7±0.7 AU; p=0.3). Conversely, in the control group SAF increased significantly during the observation period (3.5±0.9 AU vs. 3.8±1.2AU; p=0.03) during which there was no improvement in nutritional intake and other markers of nutrition, though dietary AGE intake and SGA score did increase. Conclusion: Dietetic support was associated with stable SAF levels despite an increase in dietary AGE intake, suggesting that interventions to improve nutrition may be important in preventing the rise in SAF observed in malnourished dialysis populations. Further long-term studies are needed to test this hypothesis and evaluate the impact on survival.

Cover Letter

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Linda W. Moore, PhD and Kamyar Kalantar-Zadeh, MD, PhD
Editors-in-Chief
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Dear Drs Moore and Kalantar-Zadeh

Impact of dietetic intervention on skin autofluorescence and nutritional status in persons receiving dialysis: a proof of principle study.

We are pleased to submit the above manuscript for consideration for publication in *Journal of Renal Nutrition*. Several randomized clinical trials have reported that restriction of dietary advanced glycation end-product (AGE) intake is associated with a reduction in circulating AGE levels, suggesting that dietary AGE intake restriction may be also associated with a decrease in skin autofluorescence (SAF), a marker of AGE accumulation and risk factor for mortality in the dialysis population. However, we have previously observed an association between increased SAF and several markers of malnutrition in a hemodialysis population, whereas higher dietary AGE intake was not associated with increased SAF, raising the possibility that correction of malnutrition may be a more important strategy to decrease SAF levels than restriction of dietary AGE intake. In this proof of principle study, we sought to investigate whether improvement of nutritional status by providing dietetic support would result in a decrease in SAF in malnourished persons receiving dialysis.

We observed that with dietetic support nutritional intake and markers of nutritional status improved which was associated with stable SAF levels, despite an increase in dietary AGE intake, whereas failure to increase nutritional intake in a historical control group was associated with an increase in SAF. Our findings therefore support our hypothesis and provide additional data to support the provision of dietetic support to all dialysis patients with malnutrition. Our data will also inform the design of larger studies that are now warranted.

Thank you in anticipation for your consideration.

Yours sincerely

Maarten Taal, on behalf of the authors
Professor in Medicine

Impact of dietetic intervention on skin autofluorescence and nutritional status in persons receiving dialysis: a proof of principle study.

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ABSTRACT

Impact of dietetic intervention on skin autofluorescence and nutritional status in persons receiving dialysis: a proof of principle study.

Objective: Advanced glycation end-products (AGEs) are uremic toxins that result from oxidative stress and food consumption. We have previously reported that markers of malnutrition are more important determinants of increased skin autofluorescence (SAF), a measure of AGE accumulation and risk factor for mortality, than high dietary AGE intake in a hemodialysis (HD) population, suggesting that correcting malnutrition may decrease SAF.

Design and methods: We investigated this hypothesis in a single center, non-randomized proof of principle study. We enrolled 27 HD and one peritoneal dialysis (PD) patient with malnutrition who received individualized nutritional advice and support over 6 months. SAF was measured at baseline, 3 and 6 months. Dietary intake and nutritional status were assessed at baseline and 6 months. Results were compared with a control group of malnourished dialysis patients (n=41 HD and 8 PD) from a previous observational study.

Results: The intervention group showed a significant increase in dietary intake, including AGEs, Subjective Global Assessment (SGA) score and serum albumin, while SAF levels remained stable over 6 months (3.8±0.7 arbitrary units [AU] vs. 3.7±0.7 AU; p=0.3). Conversely, in the control group SAF increased significantly during the observation period (3.5±0.9 AU vs. 3.8±1.2AU; p=0.03) during which there was no improvement in nutritional intake and other markers of nutrition, though dietary AGE intake and SGA score did increase.

Conclusion: Dietetic support was associated with stable SAF levels despite an increase in dietary AGE intake, suggesting that interventions to improve nutrition may be important in preventing the rise in SAF observed in malnourished dialysis populations. Further long-term studies are needed to test this hypothesis and evaluate the impact on survival.

Keywords: Advanced glycation end-products; dialysis; dietetic intervention; malnutrition; skin autofluorescence.

INTRODUCTION

Advanced glycation end-products (AGEs) are uremic toxins that accumulate in persons on dialysis due to reduced renal clearance and increased production[1, 2]. AGEs cause cross-linking of tissue proteins and promote inflammation by binding to a specific receptor for AGEs (RAGE)[3]. It seems that collagen in the skin and elastin in vascular basement membranes are especially susceptible to AGE accumulation[4] and AGE accumulation may therefore increase arterial stiffness, a key factor in the pathogenesis of cardiovascular disease associated with chronic kidney disease.

Key endogenous pathways leading to the formation of AGEs include hyperglycemia due to diabetes, increased oxidative and carbonyl stress, and systemic inflammation. AGEs are also formed exogenously, either by cigarette smoking or through food consumption[5]. High fat and high protein diets, dry-heated processed foods and cooking techniques using dry heat and high temperatures (e.g. grilling, roasting, broiling, baking and frying) significantly increase AGE formation[5, 6]. On the other hand, malnutrition may also be associated with AGE formation by provoking systemic inflammation and oxidative stress[7]. Due to the fluorescent nature of some AGEs, tissue AGE accumulation can be assessed using a non-invasive, operator independent and easy to perform technique called skin autofluorescence (SAF), which has been shown to be an independent predictor of mortality in the dialysis population[3, 8-10].

Several randomized controlled trials conducted in healthy overweight and/or obese volunteers[11-13], persons with diabetes and the metabolic syndrome[14-16], and in those with chronic kidney disease (CKD)[17] and performing peritoneal dialysis (PD)[18] have reported that restriction of dietary AGE intake is associated with a reduction in circulating AGE levels,

suggesting that a low AGE diet may be also associated with a decrease in SAF. On the other hand, we have previously reported in a cross-sectional analysis conducted in persons on hemodialysis (HD) that the presence of malnutrition was associated with higher SAF levels. In addition, lower serum albumin, lower handgrip strength (HGS) and lower dietary protein intake (all markers of malnutrition) were independent determinants of increased SAF, whereas high dietary AGE intake was not associated with higher SAF[7]. These findings suggest that in persons receiving dialysis, correction of malnutrition may be a more important strategy to decrease SAF levels than dietary AGE restriction. We therefore aimed to investigate whether improvement of nutritional status by providing intensive individualized dietetic advice and support would result in a decrease in SAF in malnourished persons receiving dialysis.

METHODS

Study population

This observational non-randomized proof of principle study initially included 30 HD and 2 PD patients with malnutrition (i.e. Subjective Global Assessment [SGA] score of $\leq$5) who were $\geq$18 years old and were able to give written informed consent. Participants on HD were dialyzing 3-4 times per week for 3-4 hours (12 hours per week) with high-flux polysulphone, polyarylethersulfone and/or polyvinylpyrrolidone dialyzers, while PD participants were dialyzed using combinations of lactate/bicarbonate-buffered 1.36% glucose (Physioneal; Baxter®), 7.5% icodextrin (Extraneal; Baxter®) and/or 1.1% aminoacid-containing solutions (Nutrineal; Baxter®). The following exclusion criteria were used: pregnancy or intending pregnancy, breastfeeding and having dark skin color. Written informed consent was obtained from all participants in accordance with Good Clinical Practice guidelines. This study was conducted according to principles having their origin in the Declaration of Helsinki.

Controls

We considered it unethical to randomize persons with malnutrition to no intervention and therefore compared the results of the intervention with a historical control group of malnourished persons on dialysis (n=41 HD and 8 PD) taken from a previous observational study[7], who were assessed at the same time points and using the same methodology.

Data collection

Hospital electronic medical records were used to collect relevant baseline participant characteristics, which included the following: chronological age, sex, ethnicity, dialysis vintage (i.e. time since first dialysis treatment), dialysis adequacy, presence of diabetes (defined by clinical diagnosis), and history of cardiovascular disease. Information regarding educational level, occupation status and history of smoking was obtained by direct interview with the patients. Routine clinical blood tests were also recorded at baseline and 6 months.

Intervention

Participants received individualized nutritional advice and support formulated and delivered by experienced dietitians (DVH and FCW) consisting of food fortification recommendations and oral nutritional supplementation aiming to achieve estimated nutritional requirements (i.e. energy [30-35 kcal/kg/day] and protein intake [1.1-1.2 g/kg/day])[19]. Participants were then followed up for 6 months. Food fortification involved enhancing the energy and protein content of meals and snacks without increasing the portion sizes of foods. Advice was individualized according to patient needs and food preferences. Oral nutritional supplements included Fortisip Compact (2.4 kcal/ml), Fortisip (1.5 kcal/ml) and Fortijuice (1.5 kcal/ml) (Nutricia Advanced Medical Nutrition®, Wiltshire, United Kingdom), as well as Renapro®

shot (Stanningly Pharma, BioCity, Pennyfoot Street, Nottingham, United Kingdom) and Fresubin® 5kcal Shot (Fresenius Kabi Ireland, Balbriggan, Dublin, Ireland).

Participants received precise oral and written instructions on how and when to take the supplements and how to follow the food fortification advice provided. Participants were closely monitored by the dietitian at least once a week to encourage adherence to nutritional advice, and 24-hour dietary recalls were also conducted to ensure compliance with the advice provided. Each participant was also reviewed quarterly with the clinical lead renal dietitian (FCW) in order to modify the dietetic advice, if required.

Outcome measures

- *Primary outcome:* change in SAF levels after 6 months of intensive individualized dietetic advice and support.
- *Secondary outcomes:* change in nutritional status as assessed by the SGA, nutritional intake, dietary AGE intake, anthropometric measurements, HGS and biochemical variables after 6 months of intensive individualized dietetic advice and support.

Skin autofluorescence measurement

Tissue AGE accumulation as assessed by SAF was measured with a validated Autofluorescence Reader Standard Unit (SU) version 2.4.3 (AGE Reader SU, DiagnOptics Technologies BV, Aarhusweg 4-9, Groningen, The Netherlands) at baseline, 3 and 6 months. The technique for measuring SAF has been previously described in more detail by Meerwaldt et al.[8]. In brief, the AGE Reader SU directs an ultraviolet excitation light (wavelength 300-420 nm) through an illumination window of approximately 1 cm^2 on a skin area of the volar surface of the forearm at ~10 cm below the elbow. Care is taken to ensure that the area is free

of visible vessels, scars, tattoos or any other skin irregularities. The AGE Reader SU then measures the amount of light that is reflected back from the skin (i.e. emission light, wavelength 300-600 nm) using a spectrometer (AVS-USB2000, Avantes Inc., Eerbeek, The Netherlands) and a 200-µm glass fiber. SAF is calculated by dividing the average emitted light intensity in the range between 420-600 nm by the average excitation light intensity in the range between 300-420 nm, and expressed as arbitrary units (AU).

Three SAF readings were conducted on the non-fistula arm and within the first hour of HD treatment in the case of HD participants, while the dominant arm was used in the case of PD participants, if this did not have a fistula. The mean value of the three SAF readings was used for statistical analyses. Valid SAF readings cannot be obtained when the skin reflectivity is lower than 6%[20]; therefore, persons with dark skin color (i.e. Fitzpatrick skin color type V-VI), who have an ultraviolet reflectance of less than 6%, were excluded from this study. It has been previously reported that SAF readings have good reproducibility and repeatability (i.e. coefficient of variation of 7-8%)[21].

Nutritional assessments

Detailed nutritional assessments were undertaken at baseline and 6 months, and included the following:

- *Dietary intake:* Information regarding energy, protein and fat intake was obtained from three 24-hour dietary recalls including one dialysis day and one week-end day. Participants were asked to recall the type, portion size, source, brand names and cooking methods of all foods and drinks they had the day before. Dietary recalls were analyzed with the software Dietplan 7 (Forestfield Software Limited, West Sussex,

United Kingdom) to calculate the average energy, protein and fat intake. The average daily intake of calories and protein was then calculated in kilocalories and grams, respectively, and expressed per kilogram of ideal body weight. Quantification of AGEs in food was determined with a food frequency questionnaire previously validated in a diabetic population[22]. Dietary AGE intake was reported in kilounits/day (kU/day).

- *Anthropometry and HGS:* Anthropometric measurements were conducted in line with international standard methods of assessment[23]. Post-dialysis weight and height were measured to calculate body mass index (BMI; reported in kg/m^2), while measurement of mid-arm circumference (MAC) and triceps skinfold thickness (TSF), reported in cm, was conducted to calculate mid-arm muscle circumference (MAMC) using the following equation: MAMC (cm^2) = MAC – (3.14 * TSF). HGS measurement was conducted within the first hour of HD treatment or during PD clinic visits using the Takei 5401 handgrip digital dynamometer (Takei Scientific Instruments Co., Ltd., Tokyo, Japan). HGS was measured in the non-fistula arm or the dominant arm if the participant did not have a fistula. HGS measurement was ideally conducted in a standing position with feet a hip width apart; however, if this was not possible, participants were sitting upright on a bed/chair and holding the dynamometer straight down and close to their bodies. The dynamometer was adjusted to fit the hand size of each participant. Participants were instructed to apply maximum handgrip pressure and then relaxed.

- *Subjective Global Assessment:* The 7-point scale SGA, which is a comprehensive and validated nutritional scoring tool[24], was performed to evaluate nutritional status.

Based on the ratings of six individual core components (i.e. history of weight loss, dietary intake, gastrointestinal symptoms, functional status, metabolic stress and subjective physical examination of loss of subcutaneous fat and muscle mass), nutritional status can be classified into normal nutritional status (scores of 6 or 7), mild-moderate malnutrition (scores of 3-5) or severe malnutrition (scores of 1 or 2). Because of the nature of the intervention (i.e. dietetic), blinding of participants and investigators was not possible. Nevertheless, in order to reduce the risk of bias, nutritional status evaluation by SGA was conducted by an experienced dietitian (FCW) who did not participate in other methods of nutritional assessment and did not conduct SAF measurements.

Statistical analyses

All statistical analyses were performed using SPSS version 24.0 (IBM Corporation, Chicago, Illinois). Data are expressed as mean ± standard deviation (SD), median (interquartile range [IQR]) or percentages, as appropriate. For intragroup comparisons, Wilcoxon test was used in the case of continuous variables. Intergroup comparisons were performed using Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. For all statistical analyses, a p-value less than 0.05 was considered to have statistical significance. Since this was a proof of principle study, we considered it reasonable to include 40 dialysis participants (either HD or PD).

RESULTS

Participants

A total of 188 dialysis patients were assessed for eligibility from January to June 2018. Of these, 142 did not meet inclusion criteria, 13 declined to participate and one died after

agreeing to take part in the study. A total of 32 dialysis patients were therefore enrolled. Four patients did not complete the study protocol (3 deaths and 1 consent withdrawal). Twenty eight patients completed 6 months of intervention and were therefore included in the final analysis. Historical controls were selected from a previous cohort of 151 dialysis patients[7]. Of these, 56 were classified as being malnourished (i.e. SGA score $\leq$5) at baseline. Forty nine patients completed 6 months of follow-up (i.e. 5 deaths and 2 transplants) and were included in the final analysis (Figure 1).

Baseline participant characteristics

Demographic, clinical, biochemical and nutritional characteristics of the intervention and historical control groups are shown in Table 1. Participants in the intervention group had significantly longer dialysis vintage, higher energy and fat intake and lower BMI in comparison to the historical control group at baseline, though dietary energy intake was below estimated nutritional requirements in both groups. There were no other significant differences between the groups at baseline.

Follow-up

Table 1 shows changes in SAF, biochemical variables and nutritional markers from baseline to 6 months. In the intervention group, we observed a significant increase in intake of all dietary components, including AGEs (13823 [10840 to 20441] kU/day vs 19074 [13372 to 27340] kU/day; p=<0.0001), as well as in SGA score and serum albumin. SAF levels did not change significantly over 6 months in the intervention group (3.8 ± 0.7 AU vs. 3.7 ± 0.7 AU; p=0.3) (Figure 2). In contrast, in the historical control group there was no increase in nutritional intake, which remained below estimated nutritional requirements, except for dietary AGE intake, which did increase (11940 [8787 to 15833] kU/day vs 14697 [9427 to

19071] kU/day; p=0.03). SGA score increased in the historical control group but other markers of nutrition did not change. SAF increased significantly in the control group (3.5 ± 0.9 AU vs. 3.8 ± 1.2 AU; p=0.03) (Figure 2).

DISCUSSION

In this proof of principle study, we found that intensive individualized dietetic advice and support in malnourished persons on dialysis was associated with improvement in dietary intake and markers of malnutrition as well as stable SAF levels over 6 months, despite an increase in dietary intake of AGEs. In contrast, failure to improve dietary intake in a historical control group was associated with an increase in SAF over the same time period.

Malnutrition is a highly prevalent complication in the dialysis population that is very difficult to reverse due to the interaction between several etiological factors such as uremic toxicity, poor appetite associated with dialysis routine and symptom burden of dialysis resulting in inadequate dietary intake, presence of co-morbidities, nutrient losses during dialysis, metabolic acidosis, systemic inflammation and oxidative stress[25, 26]. Nevertheless, in our study, we observed that an intensive and individualized dietetic intervention was associated with achievement of recommended dietary energy and protein intake[19, 27] and with an improvement in serum albumin, SGA score and fat intake. A number of interventional studies conducted in persons receiving dialysis support our findings that with personalized nutritional counselling alone[28-30] and/or dietetic advice plus specific oral nutritional supplements[31-37] it is possible to achieve improvements in nutritional markers including serum albumin, serum prealbumin and total cholesterol, energy and protein intake, BMI, TSF and MAC. These findings highlight the importance of individualized nutritional advice and support as the cornerstone of the treatment of malnutrition in the dialysis population[19].

In the setting of improved dietary intake and nutritional status, we observed that SAF levels remained stable over 6 months in the intervention group. Conversely, in the historical control group all components of nutritional intake and other markers of malnutrition did not improve, and this was associated with a significant increase in SAF levels. The SGA score did improve in the historical control group; however, SGA may be influenced by factors that are not directly attributable to nutrition such as infections and other comorbid conditions. Our observations support the hypothesis that factors that contribute to the development of malnutrition, such as systemic inflammation and oxidative stress, are likely to increase tissue AGE accumulation, and malnutrition in turn exacerbates these factors, creating a vicious cycle[25, 38].

A small number of randomized controlled clinical trials in the CKD and PD populations[17, 18, 39], with small sample sizes and short follow-up periods, have shown that dietary AGE restriction was significantly associated with a decrease in serum N-carboxymethyl-lysine and methylglyoxal levels (i.e. circulating AGEs). On the other hand, following a high AGE diet resulted in a significant increase in these same serum AGEs, suggesting that dietary interventions that increase AGE intake may therefore increase SAF. However, we have previously reported in a cross-sectional analysis that SAF was significantly higher among malnourished persons on HD and that markers of malnutrition such as lower serum albumin, lower protein intake and lower HGS were more important determinants of increased SAF than high dietary AGE intake, which was not positively associated with SAF[7]. The present intervention study extends these observations by showing that SAF levels stabilized over 6 months in association with improvements in nutritional status in malnourished persons on dialysis, even though dietary AGE intake increased significantly, suggesting that correction of malnutrition is a more important intervention to prevent an increase in SAF than restriction

of dietary AGE intake in a dialysis population. The latter may risk exacerbating malnutrition and should therefore probably be avoided in those who are malnourished.

This study has some important limitations that need to be highlighted. First, this was a single center proof of principle study. Second, the number of participants was small and the follow-up period was relatively short, which resulted in low statistical power to detect changes in some of the variables measured. We did not observe a reduction in SAF in the intervention group but this may have been due to the relatively small number of participants and short duration of follow-up. Nevertheless, we have established the feasibility of intensive individualized dietary intervention to improve nutritional status and stabilize SAF, which continued to increase in the historical control group. Further multicenter clinical trials with larger sample sizes and longer follow-up are therefore needed to test more robustly whether correction of malnutrition may result in a decrease in SAF and improved outcomes. The intervention and historical control groups were matched for most variables at baseline, though the intervention group evidenced longer dialysis vintage, as well as higher dietary energy and fat intake but lower BMI. Dietary energy intake was below estimated nutritional requirements in both groups and both were selected for evidence of malnutrition, so we do not consider these differences to have impacted our findings. Ideally, this intervention should be tested in a prospective randomized controlled trial but we had concerns that not providing adequate nutritional support to persons with malnutrition would be unethical. Finally, the results observed in this study may not be applicable to populations with dark skin color (who were excluded from our study) because SAF measurements cannot be performed in persons with darker skin color due to the high absorption of the excitation light.

In conclusion, with intensive individualized dietetic advice and support we observed improvement in dietary intake and markers of nutritional status that was associated with stable SAF levels over 6 months, despite an increase in dietary AGE intake. In contrast, failure to improve dietary intake in a historical control group was associated with an increase in SAF. This suggests that individualized nutritional advice and support may be effective in preventing the rise in SAF observed in malnourished persons on dialysis over time and that the benefits of improving nutritional intake are probably outweighed by any adverse effects of increased dietary AGE intake. Studies of nutritional interventions with larger sample sizes and longer follow-up are needed to test this hypothesis and evaluate the impact on long-term outcomes, including survival.

PRACTICAL APPLICATION

In this study in malnourished dialysis patients, improved nutritional intake and status was associated with stable SAF levels, despite an increase in dietary AGE intake. Persons on dialysis who show evidence of malnutrition should therefore be offered individualized nutritional advice and support. Further long-term studies of nutritional intervention are needed to test the effectiveness of dietetic support in preventing the rise in SAF observed in malnourished persons on dialysis and to assess the impact on survival.

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LEGENDS TO FIGURES

Figure 1. The Consolidated Standards of Reporting Trials (CONSORT) flowchart of participant progression through the study

Figure 2. Changes in skin autofluorescence during the follow-up period

AU, arbitrary units.

*Baseline vs. Month 3; p=0.005

†Baseline vs. Month 6; p=0.03

Table 1

Table 1. Changes in skin autofluorescence, biochemical data and nutritional markers from baseline to 6 months in intervention and historical control groups

Variable	Intervention group (*n*=28)			Historical control group (*n*=49)		
	Baseline	Month 6	p Value	Baseline	Month 6	p Value
Age (years)	65 (IQR 56 to 74)	---	---	63 (53 to 75)	---	---
Male [n (%)]	14 (50)	---	---	23 (47)	---	---
White ethnicity [n (%)]	24 (86)	---	---	43 (88)	---	---
Educational qualifications [n (%)]	19 (68)	---	---	27 (55)	---	---
Unemployed [n (%)]	26 (93)	---	---	41 (84)	---	---
Current smoking [n (%)]	5 (18)	---	---	14 (29)	---	---
Diabetes [n (%)]	13 (46)	---	---	18 (37)	---	---
Coronary heart disease [n (%)]	12 (43)	---	---	25 (51)	---	---
Dialysis vintage (months)	69.0 (35.0 to 147.0)†	---	---	29.0 (9.5 to 66.0)	---	---
Serum albumin (g/L)	30.0 (26.0 to 33.0)	31.5 (30.0 to 34.0)	0.01	32.0 (27.0 to 34.0)	31.0 (27.0 to 34.5)	0.9
C reactive protein (mg/L)	8.5 (2.3 to 30.0)	6.0 (2.0 to 21.8)	0.7	8.0 (3.0 to 22.5)	8.5 (3.0 to 18.8)	0.7
Total cholesterol (mmol/L)	3.7 (3.2 to 4.7)	3.8 (3.1 to 4.6)	0.5	4.0 (3.1 to 4.9)	4.1 (3.4 to 4.9)	1.0
Serum creatinine (µmol/L)	508 (403.5 to 623)	587(453 to 667)	0.09	571 (443.5 to 717)	559 (467.5 to 729.5)	0.5
Serum phosphate (mmol/L)	1.44 (1.19 to 1.82)	1.41 (1.10 to 1.90)	0.9	1.61 (1.25 to 1.85)	1.48 (1.29 to 1.97)	0.4
Serum potassium (mmol/L)	4.9 (4.2 to 5.5)	4.8 (4.3 to 5.2)	0.3	4.5 (3.9 to 5.2)	4.5 (4.1 to 5.1)	0.6
Skin autofluorescence (AU)	3.8 ± 0.7	3.7 ± 0.7	0.3	3.5 ± 0.9	3.8 ± 1.2	0.03
Dietary AGE intake (kU/day)	13823 (10840 to 20441)	19074 (13372 to 27340)	<0.0001	11940 (8787 to 15833)	14697 (9427 to 19071)	0.03
Energy intake (kcal/kg/day)	20.9 (16.6 to 27.3)†	30.1 (24.9 to 35.9)	<0.0001	17.9 (13.5 to 21.7)	18.9 (15.1 to 26.9)	0.053
Protein intake (g/kg/day)	0.7 (0.6 to 1.1)	1.1 (0.8 to 1.2)	<0.0001	0.8 (0.6 to 1.0)	0.8 (0.6 to 1.0)	0.9
Fat intake (g/day)	52.2 (41.1 to 69.8)†	83.5 (67.3 to 98.7)	<0.0001	44.8 (33.1 to 59.2)	49.2 (34.3 to 67.6)	0.09
Dry weight (kg)	60.9 (54.9 to 71.8)	61.4 (56.2 to 70.5)	0.8	66.4 (56.7 to 79.5)	66.8 (55.9 to 79.4)	0.4
Body mass index (kg/m^2)	22.1 (19.8 to 25.1)†	23.0 (20.4 to 24.8)	0.8	25.4 (20.5 to 28.1)	25.0 (20.6 to 29.1)	0.4
MAMC (cm^2)	23.1 (22.3 to 24.5)	23.6 (20.9 to 25.8)	0.3	24.0 (20.8 to 26.6)	24.1 (22.0 to 26.8)	0.2
Triceps skinfold thickness (mm)	12.9 (8.3 to 15.9)	13.0 (9.0 to 17.0)	0.1	14.6 (10.5 to 18.9)	15.6 (10.6 to 20.0)	0.4
Handgrip strength (kg)	15.2 (10.4 to 22.3)	16.7 (10.6 to 24.7)	0.8	17.3 (12.2 to 25.6)	18.3 (12.4 to 26.3)	0.053
SGA score	4.0 (3.25 to 5.0)	5.0 (5.0 to 6.0)	<0.0001	5.0 (3.0 to 5.0)	5.0 (3.0 to 7.0)	<0.0001

AGE, advanced glycation end-products; AU, arbitrary units; IQR, interquartile range; kU, kilounits; MAMC, mid-arm muscle circumference; SGA, subjective global assessment.

† p<0.05 Intervention vs. control at baseline. P-values in columns are for comparison of baseline and 6 month data within each group.

Figure 1

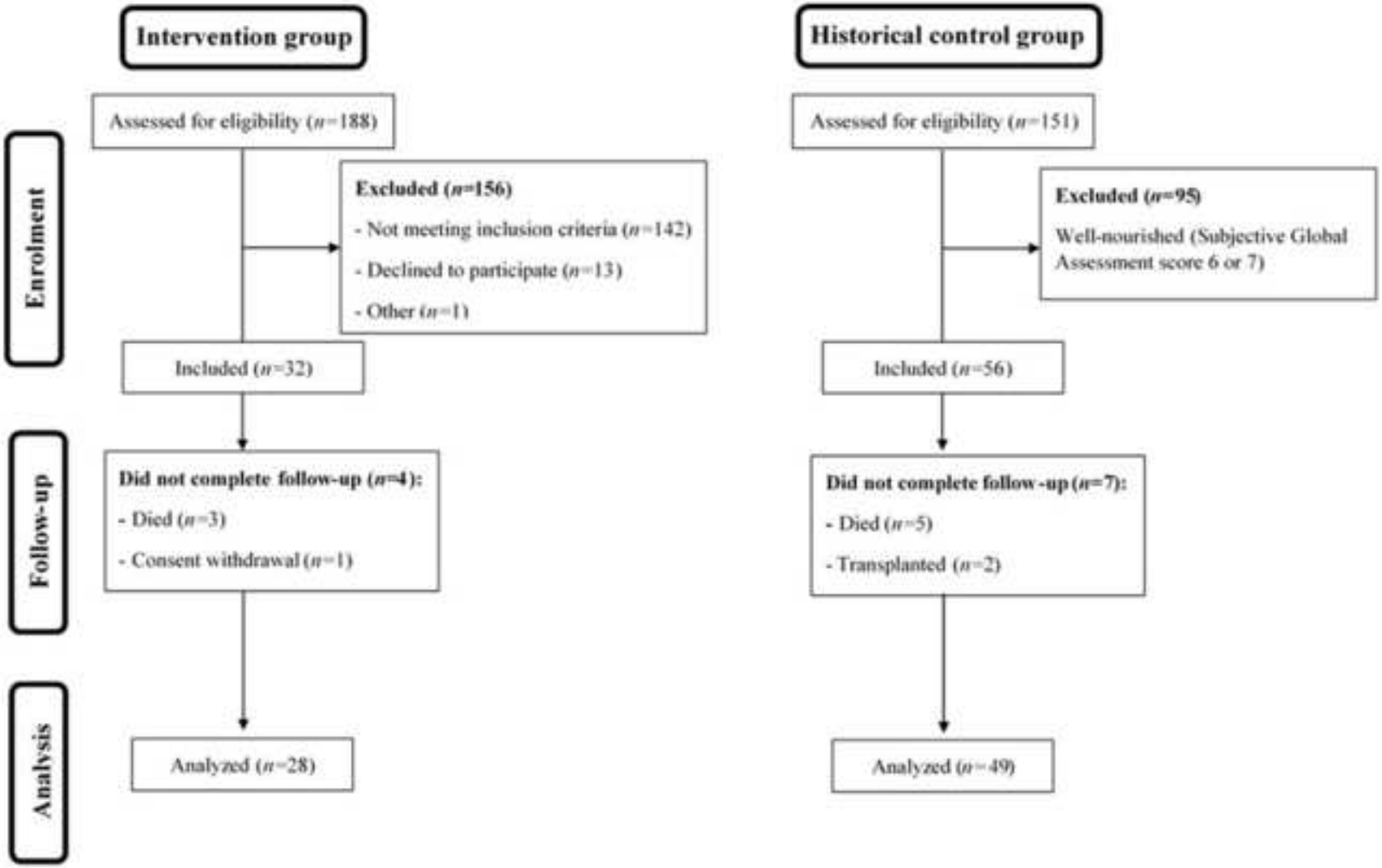

Figure 2