Universidade Federal do Rio Grande do Sul

Faculdade de Medicina

Programa de Pesquisa e Pós-Graduação em Ciências Médicas: Endocrinologia

INTERVENÇÕES NUTRICIONAIS NO PÓS-TRANSPLANTE RENAL:

Revisão Sistematizada de Escopo e Ensaio Clínico Randomizado Avaliando o Efeito de uma Dieta Hiperproteica e de Baixo Índice Glicêmico em Pacientes Transplantados Renais

Tese de Doutorado

Elis Forcellini Pedrollo

Porto Alegre, 2019.

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Orientadora: Profa. Dra. Cristiane Bauermann Leitão.
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“A vida é fugaz. As ideias, a inspiração

e o amor, duradouros”.

Chris Anderson.

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SUMÁRIO

LISTA DE ABREVIAÇÕES

ABTO - Associação Brasileira de Transplante de Órgãos

AHA - *American Heart Association*

BMI - *Body Mass Index*

CAPES - Coordenação de Aperfeiçoamento do Pessoal de Ensino Superior

CARI - *Caring for Australians with Renal Impairment*

CONSORT - *Consolidated Standards of Reporting Trials*

CHO - *Carbohydrates*

CKD - *Chronic kidney disease*

DG - *Diet group*

DPP – *Diabetes Prevention Program*

DXA - *Dual-energy x-ray absorptiometry*

eGFR - *Estimated glomerular filtration rate*

FAO - *Food and Agriculture Organization*

FIPE - Fundo de Incentivo ao Ensino e Pesquisa

GEE - *Generalized Estimated Equations*

GLP-1- *Glucagon-like peptide-1*

HbA1c – *Glycated haemoglobin*

HCPA – Hospital de Clínicas de Porto Alegre

HDL-c *High density lipoprotein cholesterol*

Hs-CRP - *High sensitive C reactive protein*

KDIGO - *Kidney Disease Improving Global Outcomes*

INTENT - *Intensive Nutrition Interventions on Weight Gain After Kidney Transplant*

IG - *Intervention group*

CG - *Control group*

cG - *Compliance group*

LDL-c – *Low density lipoprotein cholesterol*

AHEAD - *Action for Health in Diabetes*

MDRD - *Modification of Diet in Renal Disease*

MUFAs – *Monounsaturated fatty acids*

nPNA - *Nitrogen protein appearance*

PA – *Physical activity*

POUNDS - *Preventive Obesity Using Novel Dietary Strategies*

PRISMA - *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

PROSPERO - *International Prospective Register of Systematic Reviews*

PUFAs - *Polyunsaturated fatty acids*

PTDM - *Post-Transplant Diabetes Mellitus*

RCT - *Randomized clinical trial*

RMR – *Resting metabolic rate*

SFA – *Saturated fatty acids*

SG – *Study group*

SPIRIT - *Standard Protocol Items: Recommendations for Interventional Trials*

TC – *Total cholesterol*

TEI – *Total energy Intake*

TFA – *Trans fatty acids*

TGL – *Triglycerides*

UAE – *Urinary albumin excretion*

USDA – *United States Department of Agriculture*

VAS – *Visual Analogue Scale*

V1-V8 – *Clinical visits*

WC – *Waist circumference*

w-3 – *Omega 3*

w-6 – *Omega 6*

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RESUMO

O transplante renal é a melhor terapia de substituição renal atualmente disponível para pacientes com doença renal crônica em estágio avançado. Quando comparado à diálise, mostra claros benefícios, em especial no que se refere à qualidade de vida do paciente e sua sobrevida.

Entretanto, o ganho de peso excessivo e a obesidade – condições extremamente comuns nesses pacientes – são consideráveis fatores de risco para perda de enxerto e doenças cardiovasculares, principal causa de óbito nesse meio. As possíveis causas envolvidas no ganho de peso após o transplante renal incluem a imunossupressão e a mudança de restrições alimentares pelas quais o paciente é exposto, uma vez que durante a diálise, a dieta é muito mais restritiva.

Estudos realizados na população em geral, mostram benefícios de intervenções intensivas que atuem no estilo de vida e na dieta dos pacientes com o objetivo de perda de peso. Nesse contexto, a escolha por dietas compostas por alto teor de proteína e baixo índice glicêmico tem mostrado resultados interessantes sobre saciedade e emagrecimento.

Uma vez que no âmbito do transplante renal, a literatura carece de esclarecimentos nesse sentido, realizou-se uma revisão de escopo sistematizada para verificar o que se tem disponível sobre o tema em questão e executou-se um ensaio clínico randomizado com o objetivo de atuar na prevenção do ganho de peso desses pacientes um ano após o transplante.

Capítulo 1

Introdução

De acordo com a Associação Brasileira de Transplante de Órgãos (ABTO), foram realizados no país um total de 5.923 transplantes renais no ano de 2018. [1]. O transplante renal é a melhor terapia de substituição renal atualmente disponível e, quando comparado à diálise, mostra benefícios significativos, especialmente no que se refere à qualidade de vida do paciente e à sobrevida do mesmo [2–4]. Entretanto, apesar do aumento da sobrevida em relação aos pacientes em diálise, os receptores de transplante renal continuam a apresentar aumento de mortalidade quando comparados à população geral [5], fato esse que está intrinsecamente vinculado ao desenvolvimento de doença cardiovascular [6,7].

O ganho de peso excessivo, a obesidade e o diabetes são importantes fatores de risco para doenças cardiovasculares em pacientes transplantados renais. Diversos estudos mostram que esses fatores podem estar associados com o aumento do risco de mortalidade, eventos cardiovasculares e perda do enxerto renal [8-12]. A obesidade pré-transplante [13] e a presença de síndrome metabólica após o transplante [14] foram estudadas em duas meta-análises recentes do nosso grupo de pesquisa e foram associados com piores desfechos pós-transplante renal.

Pacientes submetidos a transplante renal comumente ganham peso no primeiro ano após o transplante. Estima-se que ocorra uma média de ganho de peso entre 10-35% neste período [15-17]. O aumento de peso excessivo nesse primeiro ano é fator de risco primordial para o desenvolvimento de síndrome metabólica e diabetes melito pós-transplante [20-22]. As possíveis causas para

o ganho de peso após o transplante renal incluem o regime imunossupressor (alta doses de corticosteroides) e a mudança de restrições alimentares pelas quais o paciente passa, uma vez que durante a diálise, a dieta é muito mais restrita [23,24]. Após do transplante, o paciente passa a ter orientações dietéticas mais abrangentes do que no período dialítico, no que se refere tanto aos alimentos, quanto às opções de bebidas, o que pode ocasionar uma maior ingestão energética. Além disso, a melhor qualidade de vida e mudanças no apetite decorrentes da normalização da função renal também podem desempenhar um papel no aumento de peso [11,23, 24].

Receptores de transplante renal obesos tem, além do risco aumentado de perda do enxerto, maior risco de mortalidade nos doze meses que sucedem o transplante, quando comparados a pacientes com peso normal [25]. O ganho de peso representa um fator de risco para desfechos negativos potencialmente modificáveis, e que deve, portanto, ser alvo de intervenção terapêutica [26].

Contudo, não há diretrizes específicas que abordem intervenções clínicas sobre a prevenção do ganho de peso e obesidade pós-transplante, provavelmente devido à falta de ensaios clínicos randomizados acerca do tema [26]. Atualmente as recomendações são embasadas em estudos não randomizados, que suportam diferentes posicionamentos com relação a esse problema. A diretriz do *Caring for Australians with Renal Impairment (CARI)* [27], sugere que os pacientes devam ser encaminhados a nutricionista para prevenção do ganho de peso, e reforça ainda, que esse tratamento deva ter avaliações regulares e contínuas. Já as diretrizes do *Kidney Disease: Improving Global Outcomes (KDIGO)* [28] e da *United Kingdon Renal Association* [29] não tem uma postura tão rigorosa: sugerem que a obesidade seja avaliada a cada

consulta e que serviços que atuem no controle do peso devam estar disponíveis aos pacientes.

Revisões sistemáticas de ensaios clínicos randomizados mostraram que intervenções que atuaram na nutrição, atividade física e comportamento podem ser efetivas na redução do ganho de peso de pacientes obesos da população em geral, muito embora os resultados não sejam mantidos a longo prazo [30-32]. Estudos que realizaram intervenções com maior regularidade, tais como o acompanhamento quinzenal durante os três meses iniciais e seguiram o monitoramento dos pacientes por, no mínimo, um ano, foram os que obtiveram melhores benefícios [33,34].

Em pacientes transplantados renais, a literatura acerca de estudos que avaliaram os efeitos da intervenção nutricional com relação ao peso corporal nos doze meses que sucedem o transplante é escassa e possui resultados inconsistentes [35-37]. Além disso, a interpretação dos resultados desses estudos é limitada, tendo em vista o desenho dos mesmos: dois estudos não são randomizados [35,36] e o terceiro foi elaborado no intuito de avaliar o desfecho de dislipidemia [37]. Dessa maneira, faz-se de extrema importância a criação de estratégias de intervenções nutricionais que atuem visando à prevenção do ganho de peso através do acompanhamento nutricional pós-transplante.

Uma das abordagens frequentemente utilizadas com o objetivo de perda de peso é a redução do valor energético total da dieta, aumentando a sensação de saciedade e reduzindo a fome, através da adaptação de alguns alimentos [38]. No entanto, essa adaptação é muito complexa, uma vez que o apetite é controlado por fatores psicológicos e respostas fisiológicas relacionadas à composição, densidade energética e microestrutura dos grupos alimentares [39].

Nesse contexto, cabe ressaltar que alimentos integrais têm sido associados a níveis de saciedade aumentados [40-46] e a uma menor secreção de insulina, quando comparada à carboidratos refinados [44,46]. Já é bem sabido, também, que o total e o tipo de carboidrato determinam os níveis de glicose pós-prandial e modulam as respostas da insulina sobre a ingestão alimentar [47,48].

Uma dieta com baixo índice glicêmico, além de apresentar benefícios sobre o peso e a composição corporal, também melhora o controle da glicemia [49,50] e desempenha um papel protetor no desenvolvimento de doença arterial coronariana [51] e de síndrome metabólica [52]. Uma metanálise que avaliou o efeito de dieta com baixo índice glicêmico em pacientes que apresentavam sobrepeso e obesidade observou melhores resultados para aqueles pacientes submetidos à essa dieta [50]. Além disso, um estudo multicêntrico que avaliou 1.209 indivíduos com sobrepeso concluiu que uma dieta com leve redução no índice glicêmico combinada a um aumento moderado no aporte proteico, foi determinante na manutenção do processo de emagrecimento [53].

Com relação ao conteúdo proteico da dieta, sabe-se que alguns mecanismos são responsáveis pelo efeito benéfico da dieta hiperproteica sobre o controle do peso corporal, entre eles o efeito termogênico das proteínas, que é superior ao dos carboidratos e dos lipídeos e o seu maior efeito sacietógeno em comparação aos outros macronutrientes [54]. Ainda, há evidencias que suportam a ideia de que o aumento da saciedade seja parcialmente mediado por um efeito sinérgico de hormônios sacietógenos, como o *glucagon-like peptide-1* (GLP -1) e o neuropeptídio Y [55-57]. Por fim, durante o processo de emagrecimento, dietas com maior teor proteico, preservam a massa magra, que é o principal fator determinante do gasto energético em repouso e de gasto

energético total, impedindo assim uma redução excessiva do metabolismo basal [58]. Desta maneira, uma intervenção dietética que inclua os benefícios da dieta com baixo índice glicêmico e de um maior aporte proteico poderia prevenir o ganho de peso observado no primeiro ano após o transplante renal.

Um recente ensaio clínico randomizado, publicado em 2018, avaliou o efeito de uma intervenção nutricional em pacientes submetidos ao transplante renal [59]. Mesmo com a realização de doze consultas ao longo de um ano, os pacientes randomizados para a intervenção nutricional intensiva não apresentaram peso menor do que o grupo controle. No entanto, esse estudo apresenta algumas limitações, dentre as quais: o pequeno tamanho amostral e ausência de avaliação do perfil dietético do grupo controle.

Tendo em vista a escassez da literatura científica acerca desse tema, essa tese de doutorado tem os seguintes objetivos:

- Revisar sistematicamente a literatura existente e descrever os resultados dessa busca no formato de uma revisão de escopo (*scoping review)*, com a descrição detalhada dos estudos que avaliaram intervenções dietéticas no período pós-transplante renal e seus efeitos sobre o peso;

- Avaliar o efeito de uma intervenção nutricional intensiva, que inclui uma dieta hiperproteica e com baixo índice glicêmico, sobre o peso de pacientes submetidos ao transplante renal, por meio de um ensaio clínico randomizado.

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Capítulo 2

Revisão sistematizada de escopo

Artigo a ser submetido para publicação no periódico *Journal of Renal Nutrition*

What is known about Dietary Interventions and Body Weight Management after Kidney Transplantation? A Scoping Review

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Abstract

Objective: Although numerous studies report weight gain after kidney transplant, which is commonly related to poor outcomes, there are limited recommendations addressing dietary interventions on body weight management. The purpose of this review is to describe what has been published on the effect of dietary interventions on body weight after kidney transplantation.

Design: Scoping review.

Methods: This review was designed according to Joanna Briggs Institute recommendations for scoping reviews. MEDLINE, EMBASE and Clinicaltrials.gov were searched up to September 16, 2019. Studies that assessed the effect of dietary interventions on body weight after kidney transplantation were included. Two independent reviewers summarized the data.

Results: Out of 4.983 studies identified, 13 papers, including 503 patients, were included. The majority of them were published before 2010 and presented incomplete methodology descriptions. The most common reported interventions were nutritional counselling and dietary prescriptions according *American Heart Association's* (AHA) step 1 diet. Three studies were randomized clinical trials (RCT) and only two of them had body weight as the primary outcome. None of RCT demonstrated benefits from interventions. Body weight seems not to be affected by the majority of dietary manipulations.

Conclusion: This scoping review identified a scarcity of published data regarding the topic. Most of studies were not controlled and of poor methodological quality. Moreover, due to small sample sizes, the assessment of dietary interventions in these patients still lacks power for definitive conclusions. Prospective RCT should

be conducted in order to define which intervention might be effective in preventing weight gain or decreasing body weight after kidney transplant.

Keywords: kidney transplantation, dietary interventions, nutritional counselling and body weight.

Introduction

In individuals with end staged renal disease, kidney transplantation is undoubtedly the best alternative for renal replacement treatment when compared to dialysis [1,2]. Although patient and long-term allograft survival after transplant have improved, complications such as cardiovascular events, post-transplant diabetes mellitus (PTDM), metabolic syndrome and obesity [3-6] are very often observed in these patients and are commonly associated to delayed graft function and graft loss [7,8]. The observed body weight gain and increment in body fat are possibly related, among other causes, to immunosuppressive regimen, appetite restoration and modifications in nutritional recommendations after transplant, once during dialysis the diet prescribed is much more restrictive [9-11].

The first year after transplant is considered an important period, as both significant modifications on body weight [12-14] and increased incidence of PTDM [15] have been reported. Excessive weight gain after kidney transplant is a potentially modifiable risk factor for adverse outcomes, so nutritional and lifestyle interventions are desired. Despite this, there are scantly evidence regarding interventions in renal transplant recipients to promote weight loss or its maintenance [16-18].

The assessment of interventions on body weight management and the availability of dietary advices in renal transplant recipients may provide useful information to guide therapeutic practice [9]. We therefore performed a scoping review to evaluate all available dietary interventions focusing on body weight management after renal transplantation.

Methods

Study design

This scoping review was performed in according to scoping methods, following the search recommendation of the Joanna Briggs Institute [19] and the principles of Arksey and O'Malley's framework [20].This review was registered on *The International Prospective Register of Systematic Reviews* (PROSPERO) database identified as CRD42018103182. As recommended, the key phases of this scoping review are the following: identify the research question, identify the most relevant studies, develop an adequate search strategy, select the appropriate studies, describe the data and then collating, summarizing and reporting the results.

Identifying the Research Question

The present scoping review addresses the following question: "What is known in the scientific literature about dietary interventions on body weight management after kidney transplant?"

Search Strategy and Study Selection

Papers were searched systematically and identified by using Medical Subject Heading (MeSH) terms and searching MEDLINE (accessed by Pubmed), EMBASE, Clinicaltrials.gov, gray literature and hand searching (through reference lists of obtained articles) up to September 16, 2019. The Medline

strategy is presented on supplementary material, Text 1. All retrieved papers were evaluated regardless its language.

Eligibility Criteria

We included studies that evaluated the effect of dietary interventions on kidney transplant recipients, and reports results (numerical or descriptive) about body weight and/or body mass index (BMI). Articles were excluded if other organ transplants recipients besides renal transplantation (liver, pancreas, heart or multiorgan transplant recipients) were analyzed, as well as those reporting outcomes in the pediatric population. Replicated data and articles using data base populations were not considered, since these databases may share patients that have already been assessed in original reports.

Data Extraction

Two researchers (E.F.P. and C.C) assessed titles and abstracts of retrieve studies. Neither of them was blinded to article journals, institutions and authors. Abstract with unclear information concerning the eligibility criteria were retrieved for full-text assessment. Data extraction was performed separately by two reviewers. In case of persistent doubt or possible contrariety, a third reviewer assessed the papers (C.B.L). The following data were collected: author's name, year of publication, sample size, study design, type and duration of dietary intervention, number of nutritional visits, method of body composition assessment, results (body weight and/or BMI) and conclusions. The following

demographic and transplant related variables were also extracted: age, gender, ethnicity, time on dialysis, and donor type (living or deceased).

Results

Literature Search and Study Characteristics

The databases search identified 4.983 applicable citations. Initially, 60 duplicated studies were recognized and excluded from analysis. After that, 4.888 papers were removed by reading of titles and abstracts. The remaining 35 studies were chosen for full-text assessment, and 13 fulfilled all inclusion and exclusion criteria, providing data on 503 kidney transplant recipients. The study flowchart is described in Figure 1.

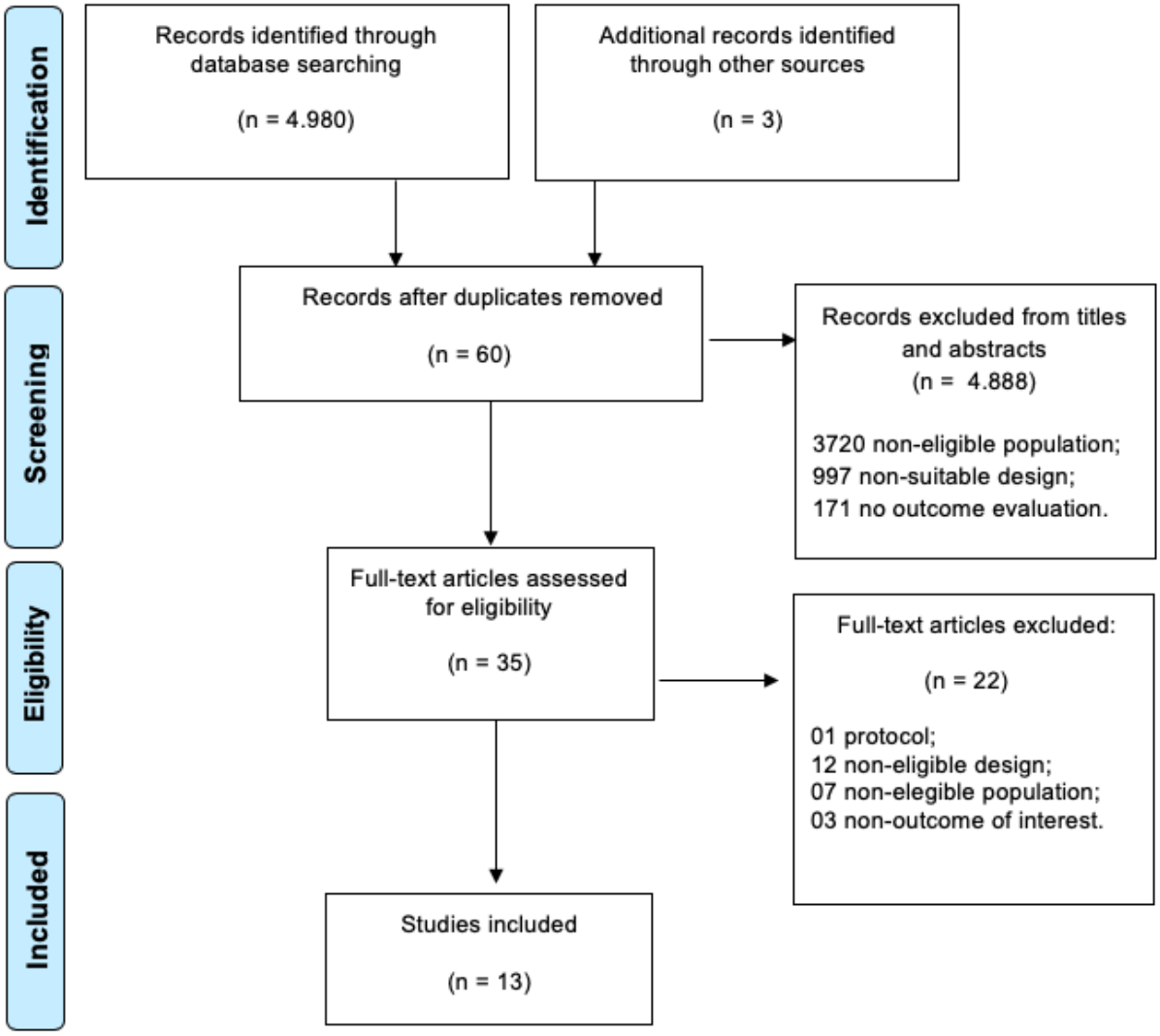

Figure 1 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Study general characteristics

The main characteristics of the 13 articles included are displayed in Table 1 and key outcomes and covariates in Table 2. All included studies were from single-centers. Only three studies were randomized clinical trials (RCT) [16, 21, 22] and one of them was designed as cross-over design [22]. The others 9 non-randomized intervention trials are not clear about the research design and

methods [17,18, 23-30]. One study, by the way, determined a ‘posteriori’ division of groups, after three months of diet prescription. That is, all patients received the same diet as intervention and three months later the degree of compliance to diet prescription was measured by food-frequency questionnaire. So, those patients who had 90% compatibility were considered as group diet. [17]. Also, it is important to emphasize that only two had body weight as a primary outcome [16,18] and only one was randomized [16].

Dietary intake was measured in different ways. Six studies used the 3-day dietary recall [16,25,26,27,28,29], one applied a detailed food-frequency questionnaire [17], another a dietary diary (weighting method) [24]. Also, one study used a 7-day estimated food record [21], another a dietary history method (once a week) [18] and another one, a daily self-report method [30]. Finally, two papers did not describe any dietary intake assessment method [22,23].

Body weight or BMI were presented in all studies, but body composition was analyzed only in five papers [16,17,24,25,28]. Two of them used dual-energy X-ray absorptiometry (DXA) [16,25], but one also associated skinfold method [16]. The others three used electrical bioimpedance, associated with skinfolds [24] and measurement of triceps skinfold [28].

Dietary interventions

Dietary interventions and study durations varied widely (Table 1). One RCT tested an individualized nutrition counseling associated with motivational interviewing techniques plus exercise counseling over one-year post transplant [16]. The other RCT used a lifestyle intervention (including a mediterranean style-

diet plus 150 minutes of physical activity per week) [21]. And the third, a randomized cross-over trial, a prescription of a high protein diet (2.0 g/kg/day versus a low protein diet (0.55 g/kg/day) [22].

Among non-randomized trials, Guida et al. prescribed a diet plan in according to guidelines of the *American Heart Association* (AHA) step one diet [31]. Dietary protein prescription was to 0.8 g/kg of ideal body weight/day and all patients were prescribed a low-salt diet, so that they should not exceed 1.5 g/day of sodium content [32]. Three studies also applied AHA step one diet as part of study intervention [27-29] and another used AHA step three diet [30].

Individualized nutrition counseling was applied in three studies as part of protocol [16, 18, 25], but only the RCT, previously cited, used motivational interviewing techniques [16]. Four studies advise for physical activity practice [17], exercise counseling [16], resistance training [27] and lifestyle intervention with multidisciplinary team [28] in addition to dietary prescriptions. Notably, some protocols were more specific on diet prescription: Apicella et al. prescribed a naturally enriched omega-3 (n-3) and low omega 6 (n-6) diet [29]; Cupisti et al. used a dietary substitution of 25g of animal protein with soy protein [30] and two others studies had an nutritional approach more focused in diet protein content, once renal function and transplant rejection were primary outcomes [22,24].

Body weight and BMI after interventions

The majority of studies reported no differences in body weight or BMI after dietary intervention [16,21,22,23,24,25,26,30]. Five of non-randomized studies reported loss of body weight in one group [17,18,27,28,29]. However, none of the

three RCT showed any advantage in weight loss [16,21,22]. The main results regarding body weight or BMI are described in table 2.

Table 1 - Study characteristics

Author, year	Sample (n)	Design	Intervention	Dietary visits (n)	Baseline time-point since Transplantation	Duration of follow up (months)	Primary outcome
Guida et al., 2007 [17]	46 (DG: 25; CG: 21)	Intervention trial	Dietary prescription according AHA step 1 diet plus 30min/day of PA (5-7 days/ week);	2	0 months	12 months	Body weight, serum lipids, glycemia.
Henggeler et al., 2018 [16]	37 (IG: 19; CG: 18)	RCT	Individualized nutrition counseling associated with motivational interviewing techniques plus exercise counseling;	IG: 12 CG: 4	0 months	12 months	Body weight
Apicella et al., 2012 [23]	49 (DG: 20; CG: 19)	Intervention trial	A diet naturally rich in n-3 (with no exogenous source) and low n-6 diet;	NA	NA	6 months	Metabolic and inflammatory markers
Bernardi et al., 2003 [24]	48 (cG: 30; CG: 18)	Intervention trial	Normocaloric diet and moderate intake of protein (0.8 g/kg), sodium (3 g/d), and lipids (< 30% of total energy).	Monthly for both groups	2 months post-transplantation	144 months	Renal function
Chadban et al., 2010 [25]	31	Pilot clinical trial	Progressive resistance training coupled with dietary advice.	NA	6- 8 weeks post-transplantation	6 months	Body composition, insulin resistance and PTDM
Cupisti et al., 2007 [26]	40 SG:20; CG: 20)	Intervention trial	Dietary substitution of 25 g of animal proteins with soy proteins.	NA	NA	5 weeks	Endothelium disfunction
Hines. et al.,2000 [27]	43 (GI: 13; GC: 30)	Prospective practice-based outcome study.	Individual assessment and counseling using AHA Guidelines (Step 1 diet).	NA	6.5 (±5.7) years	4.5 (±3.3) years	Serum lipids

Lopes et al. 1999 [28]	23	Intervention trial	Dietary intervention with the American Heart Association (AHA) Step One pattern.	6	39 (±30) months	6 months	Cholesterol Levels, body weight and body composition
Moore et al. 1990 [29]	17	Intervention trial	American Heart Association (AHA) Step One pattern	NA	Mean: 39,3 months	8 weeks	Serum lipid profile
Orazio et al. 2011 [21]	102 (IG: 56; CG: 46)	RCT	Lifestyle intervention (mediterranean style-diet plus 150 minutes of PA per week).	NA	6 months post-transplantation	2 years	Dietary intake, physical activity levels, cardiorespiratory fitness, and anthropometry.
Patel et al., 1998 [18]	33 (IG: 11; CG: 22)	Intervention trial	Individualized dietary advices	NA	Up to 4 months post-transplantation	Up to 8 months	Body weight
Salahudeen et al. 1992 [22]	14 (7/7)	RC cross-over trial	High protein diet (2.0g/kg)/day versus Low protein diet (0.55g/kg/day)	NA	77.4 (±14.2) months	11 days for each moment	Renal function
Sapan et al., 2009. [30]	20 (IG: 14; CG: 6)	Intervention trial	American Heart Association (AHA) Step three diet versus Regular diet (CG).	NA	IG: 22 months CG: 26 months	1 month	Serum lipids

DG: diet group; CG: control group; cG: compliant group IG: intervention group; SG: study group; AHA: American Heart Association; NA: not available; PTDM: Post Transplant Diabetes Mellitus. PA: physical activity. RCT: randomized clinical trial.

Table 2 - Key outcome measures and covariates

Author, year	Mean age (years)	Gender Male, n (%)	Dialysis duration (months)	Deceased donor, n (%)	Main results (Body weight and BMI)
Guida et al., 2007 [17]	DG: 40.2 (±11.5) CG: 41.5 (±8.2)	DG: 16 (64) CG: 14 (66.7)	DG: 35.5 (± 24.7) CG: 50.1 (± 35.2) months	64 (100)	Patients of DG showed a significant loss of body weight and BMI. Compliance to the diet related to sex (male better them female)
Henggeler et al., 2018 [16]	IG: 49.2 (±14.6) GC: 48.3 (±14.6)	IG:12 (67) CG:13 (72)	IG: 45.2 (± 33.2) CG 50.5 (± 45.2) months	IG: 11 (61) CG: 12 (67)	Weight increased between baseline, 6 and 12 months in both groups (GI: 4.16± 5.09; GC: 4.13±5.96).
Apicella et al., 2012 [23]	NA	NA	NA	NA	No significant modifications.
Bernardi et al., 2003 [24]	Women 41.45 (± 22.69) years Men 43.43 ±(12.42)	36 (75)	132.18 (± 66.5) months	NA	All patients have maintained or gained adequate nutritional status.
Chadban et al., 2010 [25]	NA	NA	NA	NA	There was no change in BMI.
Cupisti et al., 2007 [26]	SG:55 (± 11)	SG: 12 (60) CG: 12 (60)	NA	NA	Soy diet did not change weight or BMI.
Hines. et al.,2000 [27]	47 (± 12)	28 (65)	NA	NA	Mean weigh decreased significantly by 1.4kg during the study as well as BMI.
Lopes et al. 1999 [28]	42 (±14)	7 (30)	NA	NA	The mean weight loss was 3.2 ± 2.9 in overall population.
Moore et al. 1990 [29]	43.9 (±2.4)	7 (47)	NA	NA	The mean of weight loss was of 0.9kg in overall population
Orazio et al. 2011 [21]	IG: 54.9 (±9.9) CG: 54.7 (±11.8)	IG: 13 (59) CG: 29 (63)	NA	NA	No change in weight from baseline: IG: 1.31 kg (-1.58 ± 0.04) CG: 0.58 Kg (-0.70 ±3.00)
Patel et al., 1998 [18]	IG: 39 (±17) CG: 40 (±11)	IG: 9 (81.8) CG: 14 (63.6)	NA	NA	At one-year posttransplant, IG had a mean gain of 5.5kg compared to 11.8 in CG.
Salahudeen et al. 1992 [22]	37 (±4)	7 (50)	NA	NA	No differences in body weight was found.
Sapan et al., 2009. [30]	IG: 35.8 (±10.9) CG: 43.6 (±12.2)	IG: 8 (50) CG: 4 (66.7)	NA	NA	In any groups the body weight has not been changed more than 1% to 3% of baseline

DG: diet group; CG: control group; cG: compliant group IG: intervention group; NA: not available; SG: study group; BMI: body mass index.

Discussion

Even though weight gain is clearly a potential modifiable risk factor for adverse outcomes [7,8,13,14] after kidney transplant, this scoping review have shown that available scientific literature data presents paucity information regarding this topic. Furthermore, we must emphasize that there is considerable lack of high-quality evidence from intervention studies. As described here, only three studies had the recommend study design to evaluate efficacy of interventions, which is a RCT [16,21,22]. Among these three publications, only the one recently published has acceptable methodologic quality: is randomized and considers body weight as the primary outcome. The *Intensive Nutrition Interventions on Weight Gain After Kidney Transplantation* (INTENT) trial, is a single center New Zealand study with a single-blind design (investigators blinded to the group allocations). The authors reported no difference in body weight at 6 months and no additional benefits of intensive nutrition counselling in comparison with guidelines based standard-nutrition care. Of notice, this study has several limitations, such as the small sample size (only 37 patients) and the lack of dietary intake report of control group [16].

The majority of the studies are incomplete, lacking adequate methodological descriptions, and also, important clinical data are not available [23,24,25,27,29,30]. There are differences in baseline time point assessment from transplantation date. Although it is well-known that the first year after transplant is the phase of a major weight increment[13], only two studies in fact

assessed body weight of all participants during the first year posttransplant [16,17].

One study, at first look, seems to have a positive result: a decrease in body weight. But this study must be interpreted with caution. The authors report weight loss and decrease in fat mass in diet group and also, a better compliance in male participants, but in fact the division of groups (diet and control) was determined a 'posteriori' after three months of diet prescription in according to diet compliance. In other words, all the patients received the same diet intervention at baseline assessment, and the control group actually consists in not adherent patients [17].

Another non-randomized study concluded that an early intensive dietary advice could be effective in controlling body weight in 33 renal transplant recipients. In this study, the intervention group seems to respond positivity to individualized dietary advices, once the participants had a mean weight gain of 5.5 kg compared to 11.8 kg in control group. However, the control group was assessed at four years of transplant and the intervention, only two months after surgery [18]. This information is relevant, once changes in body weight can be quite dissimilar in different post-transplant phases, specially owing to immunosuppressive drugs well established adverse impact on body weight [13,14].

Lifestyle modifications, beyond dietary habits, such as physical activity have been suggested as potential targets to treat obesity [33]. Systematic reviews and RCT in general population have shown that interventions involving nutrition advices and physical activity can be effective in reducing weight in obese patients, although the benefits are not usually maintained over a long term follow up [33,34]. However, in the present review, the four studies analyzed (which

includes encouragement to physical activity or exercise) did not reported impact on body weight [16,17,21,25]. One of the RCT that applied a lifestyle intervention including regular consultations, using a mediterranean diet-style and a multidisciplinary team, conducted in patients with impaired glucose tolerance, did not find any significant changes on body weight and others metabolic parameters as well [21].

Still, high protein diets are known to be useful for body weight treatments in the general population [35,36], since protein exerts a better satiety impact than other macronutrients [37]. But, in renal transplant patients there is a considerable concern about high protein intake and kidney damage [24,38-40]. However, intriguingly, the three studies included in this review that focused in protein contents [22,24, 26] did not report significant differences in body weight in participants who were exposed to high protein intakes. Bernardi et al. assessed a low-protein, low lipid and low sodium diet in a 12-years follow up and reported a renal protective effect in this case, but no differences regard body weight was associated to the amounts of protein [24]. Salahuden et al. concluded that a very low protein diet reduces proteinuria, while a high protein one had no additional proteinuric effect and no difference regarding body weight was observed [22]. We must emphasize another important point regarding INTENT trial, the only RCT present in this review that has focused in weight loss as primary outcome: the intervention group presents a relative high protein intake over the study (1.3-1.4g/kg/day), but even so, any impact was observed on weight maintenance or loss. Besides, the researches have observed an average weight gain (4.6% of body weight in 6 months) [16]. To the better understand of this issue, two RCT with more representative samples are ongoing. One of them was designed to

prevent weight gain after kidney transplant through physical exercise and/ or diet in in 219 Dutch patients [43], and the other, an intensive nutrition intervention in 120 Brazilian patients, hopefully, will offer new important information on this topic [44].

This review demonstrated that available data on interventional studies to prevent body weight gain after renal transplantation are scarce and the majority of them published before 2000 [22,27-29]. However, it is determinative to encourage patients to adopt dietary prescription, once non-adherence to nutrition therapies in these patients is very often observed [45,46], comparable to that of chronic kidney disease (CKD) patients [47]. The lack of benefit of the tested interventions may be associated with reduced adherence to prescribed recommendations, as it is a commonplace among such individuals. The better understanding of reasons for non-adherence must be the key to determine alternatives in improving patient's compliance and so, optimize weight loss results [48,49].

A key strength of this paper is the applied methodology, once this is the first scoping review on this topic systematically performed. Moreover, it is important to emphasize the differences between systematic and scoping reviews. Systematic review is planned to answer a very specific research question, and so the articles included must have similarities among them. On contrast, scoping reviews presents a broader research question to determine the scope, diversity and nature of research activity in the specific field of renal transplant recipients and dietary interventions on body weight management. So that, the methods applied in this scoping review were very rigorous and clear, following a defined methodology [19,20,50] with systematic searches undertaken by two

independent reviewers. As the scoping study methodology attempt to find all relevant literature regardless of specific study design, its reach is comprehensive. However, since quality evaluation does not form part of the scoping methodology, differently from systematic reviews, this scoping review does not necessarily identify research gaps where the research itself is poor quality or determine whether particular studies provide robust findings [50]. The main limitations of this review are the heterogeneity of studies interventions included and the non-standardization of time from transplant to patient evaluation.

In conclusion, our results have shown the reality of scantly literature about dietary interventions in kidney transplant recipients and the poor quality of data available. The current small sample sizes of available studies still lacks power to firm conclusion of the effects of dietary interventions in these patients. Lastly, prospective RCT should be conducted - specially at the early phases of post transplantation period - in order to define which kind of approaches on body weight management would be effective, perhaps involving not only dietary and physical activity, but also psychological and/or behaviors interventions, such as cognitive behavior therapy, may be options.

Pratical Application

Renal transplant recipiets usually gain excessive weight after transplant, but it is unknown whether and what approachs envolving dietary interventions are able to avoid it. In this scoping review, the purpouse is to shed light on this topic. As the available scientific evidence is scarcy, this review may help plannig

future randomized trials evaluation the effects of dietary aproaches on body weight of kidney transplant recipients.

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Conflit of Interest Statemant

The authors have no conflicts of interest to declare. The results presented in this systematic scoping review have not been published previously.

Supplementary Data

Text 1 – Search strategy.

"Transplantation"[Mesh]

Transplantations

Recipient, Transplant

Transplant Recipient

Transplant Recipients

Recipients, Transplant

"Organ Transplantation"[Mesh]

Transplantation, Organ

Organ Transplantations

Transplantations, Organ

Grafting, Organ

Graftings, Organ

Organ Grafting

Organ Graftings

"transplantation" [Subheading]

grafting

grafts

"Transplantation, Heterotopic"[Mesh]

Heterotopic Transplantation

Heterotopic Transplantations

Transplantations, Heterotopic

"Kidney Transplantation"[Mesh]

Transplantation, Renal

Renal Transplantation

Renal Transplantations

Transplantations, Renal

Grafting, Kidney

Kidney Grafting

Transplantation, Kidney

Kidney Transplantations

Transplantations, Kidney

AND

(“Diet Therapy”[Mesh] OR “Diet” OR “Therapy” OR “Nutrition” OR “Intervention” “Nutritional intervention”).

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Capítulo 3

Protocolo do Ensaio Clínico Randomizado

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Effect of an Intensive Nutrition Intervention of a High Protein and Low Glycemic-Index Diet on Weight of Kidney Transplant Recipients: Study Protocol for a Randomized Clinical Trial

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Abstract

Background: Excessive weight gain is a commonly observed within the first year after kidney transplantation and it is associated with negative outcomes, such as graft loss and cardiovascular events. The purpose of this study is to evaluate the effect of a high protein and low glycemic index diet in preventing weight gain after kidney transplantation.

Methods: We designed a prospective, single-center, open-label, randomized controlled study to compare the efficacy of a high protein (1.3 – 1.4 g/kg/day) and low-glycemic index diet versus a conventional diet (0.8 – 1.0 g/kg/day of protein) in preventing weight gain after kidney transplantation. A total of 120 eligible patients with 2 months after transplantation will be recruited. Patients with estimated glomerular filtration rate through Modification of Diet of Renal Disease (MDRD) formula <30 mL/min/1,73m² or urinary albumin excretion >300 mg/24h will be excluded. Patients diets will be distributed through simple sequential randomization. Patients will be followed for 12 months with 9 clinic appointments with a dietitian and the evaluations will include nutritional assessment (anthropometrics, body composition and resting metabolic rate) and laboratory tests. The primary outcome is weight maintenance or body weight gain under 5% after 12 months. Secondary outcomes include body composition, resting metabolic rate, satiety sensation, kidney function and other metabolic parameters.

Discussion: Diets with higher protein content and lower glycemic index may lead to weight loss because of higher satiety sensation. However, there is a concern about the association of high protein intake and kidney damage. Nevertheless, there are few evidences on the impact of high protein intake on long-term kidney

function outcomes. Therefore, we design a study to test if a high protein diet with low-glycemic index will be an effective and safe nutritional intervention to prevent weight gain in kidney transplant patients.

Trial Registration: ClinicalTrials.gov identifier: NCT02883777 (date of registration: August 3, 2016).

Background

Weight gain after kidney transplantation is very often observed and it has been reported between 10 to 35 per cent, mainly during the first year after transplant [1-4]. Post-transplant overweight and obesity may lead to negative post-transplant outcomes, such as graft loss and cardiovascular events [5,6]. In addition, weight gain during the first year post-transplantation appears to be a risk factor for the development of new-onset diabetes and metabolic syndrome [7-9]. The main factors implied in the weight gain in this population are the immunosuppressive regimen, the cessation of dietary restrictions associated with dialysis, consequent appetite restoration and improvements in quality of life [10,11].

Data on nutritional management to prevent weight gain after transplantation is scarce [12-17]. Moreover, the evidence assessing protein requirements in kidney transplant patients is also limited [15,18]. High protein intake in the early period post-transplant is recommended to match protein catabolism, but there is no evidence available regarding long term protein requirements of stable renal transplanted recipients [18].

A high-protein diet is known to be effective for body weight loss and subsequent weight maintenance in general population [19-22]. Protein generally exerts a better satiety effect than carbohydrates and lipids [23 -25]. During the process of weight loss, a high protein diet preserves lean body tissue, which is the major determinant of resting and 24 hours energy expenditure, which in turn, prevents a greater reduction in energy expenditure [23] usually observed in individuals undergoing a weight reduction program. Besides, it is well known that

a diet with low glycemic index (GI) is determinant of postprandial metabolic responses to food intake and also may have beneficial effects on body weight and body composition [26-28]. Laresen et al. have shown that a dietary plan with moderately high protein associated with a slightly reduced GI leads to weight loss maintenance in overweight adults who had lost at least 8% of body weight [29]. In this context, we designed a randomized clinical trial in order to evaluate the effect of a high protein and low GI diet in preventing weight gain after kidney transplantation.

Methods

Study design and centers

This is a prospective, single-center, open-label, randomized clinical trial that will include an interventional group (high protein and low GI diet) and a control group (usual diet) patients that will undergo kidney transplant at Hospital de Clínicas de Porto Alegre, Brazil. The present protocol was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline, completing the SPIRIT checklist, and constructing a flow diagram in order to optimize the quality of reporting [30] (Fig 1 and Additional file 1).

Inclusion and exclusion criteria

The study will include kidney transplant recipients who agree to participate in the study protocol and provide written informed consent. The exclusion criteria will be the following: patients younger than 18 years old, prior transplant, multiple organ transplant, type 1 diabetes mellitus, current cancer, women in pregnancy

or lactation period, recipients of kidney from living donors, patients with urinary albumin excretion >300 mg/24h or estimated glomerular filtration rate through Modification of Diet of Renal Disease (MDRD) formula <30 mL/min/1,73m² and/or anticipated difficulty of adherence (for example, due to any kind of cognitive deficits or dementia).

Sample size

Sample size calculations were carried out in WINPEPI 11.20 (Brixton Health, Israel), based on data from Souza et al [31]. To find out a difference of 5% in body weight between groups one year after the transplant, considering a standard deviation of 8.8%, a significance level of $\alpha \leq 0.05$ and a statistical power of 80%, the minimum sample size will be 98 patients. But foreseeing possible dropouts, we will include 120 patients (60 randomized to each group).

Study Intervention

Patients will be randomized to: 1) intervention group, which will receive a high protein diet (1.3 – 1.4 g/kg/day) with low GI and 2) control group that will receive a conventional diet that provides approximately 0.8 – 1.0 g/kg of protein intake. All the patients will be followed for 12 months with 9 clinic appointments made by a researcher dietitian. The evaluations will include nutritional assessment (anthropometrics, body composition and resting metabolic rate) and laboratory tests.

Randomization

The randomization will be performed through a simple sequential randomization plan generated online, using the randomization.com website [32] by another researcher (CCF).

Blinding

In this clinical trial, blinding of patients and dietitians is not possible, because of evident differences between the intervention and control group.

Data collection and timeline

Follow-up evaluation and data collection will be undertaken over two years and six months at the Clinical Research Center of the hospital, Porto Alegre, Brazil, by trial personnel. All research tests will be assessed at the same day of protocol laboratory tests.

Adherence and acceptability

In order to assess diet compliance and safety issues, all participants will collect 24-h urine samples to measure albumin, protein, creatinine and urea excretion every three months. During the first semester, the subjects will have a monthly nutritional visit and during the second semester, patients will be seen at month 9th and month 12th after randomization.

	Enrolment	Baseline	Post-allocation							
TIMEPOINT*	$-t_0$	$-t_1$	$-t_2$	$-t_3$	$-t_4$	$-t_5$	$-t_6$	$-t_7$	$-t_8$	$-t_9$
Eligibility screen	X	X	X	X	X	X	X	X	X	X
Allocation	X									
Informed consent	X									
Randomization		X								
INTERVENTIONS:										
Nutrition Intervention (only intervention group)			X	X	X	X	X	X	X	X
ASSESSMENTS:										
Anthropometry (body weight and circumferences)		X	X	X	X	X	X	X	X	X
Bioelectrical Impedance		X			X			X	X	X
Indirect Calorimetry		X						X		
Laboratory tests	X	X	X	X	X	X	X	X	X	X
Visual Analogue Scale		X						X		
24 hours dietary recall		X	X	X	X	X	X	X	X	X

Figure 1 - SPIRIT Diagram. Timepoint of the protocol; $-t_0$ (enrolment); $-t_1$ (baseline); $-t_2$ $-t_3$, t_4, $-t_5$ $-t_6$, $-t_7$ (first semester monthly appointments); $-t_8$ (9^{th} month); $-t_9$ (12^{th} month).

Study protocol

Kidney transplant recipients who meet the inclusion criteria and are eligible will be invited to participate in this study, two months after the transplant surgery. Patients will be randomized to intervention group or control group. Intervention group will receive a high protein (1.3 – 1.4 g/kg/day) and low-GI diet (preference for foods with a glycemic index ≤55 %, with a daily glycemic load of ≤80 g) and control group will receive a conventional diet (0.8 – 1.0 g/kg/day of protein). The

protein requirement will be reevaluated 6 months after the baseline. For patients that have lost or gained more than 5% of body weight, the diet will be recalculated. Intervention and control groups will receive energy-matched diets.

Demographic and clinical data will be assessed at first visit. Nutritional assessment will comprise: a) anthropometric measurements: body weight, height [(with calculated body mass index (BMI) (kg/m^2)] and waist circumference (measured midway between the lowest rib margin and the iliac crest, with flexible, no stretched fiberglass tape) and will be performed in each 9 visits; b) body fat mass (%): measured by bioelectrical impedance analyzer (*In Body 230 – GE Health Care*), assessed every three months; and c) resting metabolic rate: evaluated by indirect calorimetry (*Meta Check 7100 – Metabolic Rate Analysis System – KOOR*) at baseline and 6 months later. All the nutritional measurements will be performed with the patient fasting, wearing light clothing, without contact with metals and without shoes.

Biochemical assessment will include serum and urine creatinine (monthly), fasting glycaemia, cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, glycated hemoglobin and uric acid (each three months), high-sensitivity C- reactive protein (hs-CRP), (baseline and at 6th month) and 24-h urine test with albumin, protein, creatinine and urea excretion (every three months).

The diet prescription will be calculated using a nutritional software (*Nutribase 2007 Clinical Manager software version 7.14*). GI will be estimated as proposed by the Food and Agriculture Organization (FAO) [33] by using the international table – United States Departament of Agriculture (USDA) table [34], with glucose as the standard food [35] and considering a daily glycemic load of

≤80g. It will be considered 1.3 – 1.4 g/kg/day of protein. Energy intake will be assessed by a 24-h recall in 9 visits by the research dietitian. Diet composition also will be analyzed using nutritional table by the software *Nutribase 2007 Clinical Manager software version 7.14* and will be made in each visit.

Two months after transplantation, patients are invited to participate in the study protocol and are randomized to intervention or control group. Intervention group receives the study diet and the control group receives the conventional diet. Both groups visit the center once a month in the first 6 months. After that, other two visits are schedule (9^{th} and 12^{th} month). In each visit, both groups are submitted to research anthropometric tests and the 24-h recall diet filled. Besides the intervention diet prescription after randomization, the research dietitian reinforces diet adherence at each visit, but only for intervention group. The standard diet adherence reinforcements are more sporadic for control group (three to four visits schedule per year) with the standard dietitian of the hospital. Thus, intervention group receive 8 diet reinforcements and control group, 3 to 4 during the study protocol.

Food intake and adherence to the prescribed diet will be assessed by 24-h recall. An experienced registered dietitian will implement the recall during a face-to-face interview. To assure accurate answers, a photographic album of food portions and household measures will be increase the precision of the amount of food consumed. A total of nine records over one year will be available for each included patient. Besides, the study protocol also includes the collection of urinary urea excretion, and add this to the calculation for protein equivalent of total nitrogen appearance (nPNA), as a measure of dietary protein intake adherence.

Satiety levels will be assessed twice through a visual analogue scale (VAS) of appetite [36]. This scale will be answered by each patient at home in a casual day 2 hours after three main meals: breakfast, lunch and dinner at baseline and 6 months later.

Primary outcome

The primary outcome will be weight maintenance and weigh gain under 5% of body weight.

Secondary outcomes

The secondary outcomes will consist of:

a) *Body Composition*

   Assessed each three months by using bioelectrical impedance analyzer (patients with 12 h fasting).

b) *Resting Metabolic Rate*

   Evaluated by indirect calorimetry at baseline and 6 months later (patients with 12 h fasting).

c) *Satiety*

   Evaluated twice (baseline and six months later) by visual analogue scale and it will be answered 2 hours after three main meals (breakfast, lunch and dinner).

d) *Kidney Function*

   Assessed by serum creatinine through estimated glomerular filtration rate (MDRD formula) and 24-h urine test with albumin and protein (every three months).

e) *Glycated hemoglobin*

Evaluated each three months.

f) Lipid Profile

Evaluated each three months by total cholesterol, HDL- cholesterol and triglycerides (with 12 h fasting) laboratory tests.

g) Inflammation

Assessed through hs-CRP at baseline and 6 months later.

Statistical analyses

Continuous variables with normal distribution will be expressed as mean ± standard deviation. Shapiro-Wilk test will be used for normality assessment; asymmetrically distributed continuous variables will be expressed as median and interquartile range; and categorical variables will be expressed as absolute and relative frequencies. For between-group comparisons, Student's *t*-test will be used for normally distributed variables, and the Mann–Whitney *U* test for asymmetrically distributed variables. A paired *t*-test will be used for within-group analysis of body weight and body composition. The Chi-square or Fisher's exact tests will be used to evaluate associations between categorical variables. The generalized estimating equations test with Bonferroni adjustment will be used for comparison between variables during the study period. The significance level will be set lower than 5%, and all data will be analyzed in SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Discussion

To the best of our knowledge, this is the first randomized clinical trial that will evaluate the impact of a high protein and low GI diet in the weight maintenance or weight gain lower than 5% of body weight after kidney transplantation. Furthermore, this study will evaluate other relevant parameters related to metabolic outcomes, since we hypothesized that this dietetic intervention may be able to improve body composition, resting metabolic rate, satiety, inflammation, lipid and glycemic profile.

Importantly, there is still concern related to high protein intake and kidney damage, based on some previous studies that showed an association of high protein intake with worsening of renal function [37 – 40]. However, there are scarcity data on the impact of protein intake on long-term outcomes in kidney transplant recipients [40- 43]. Bernardi et al. evaluated a low protein, low lipid and low sodium diet in a 12 years follow up study and showed a kidney protective effect of this diet [40], but the interpretation of the results are limited and controversial. Van den Berg et al. [41] studied the association of protein intake with blood pressure, proteinuria, and creatinine clearance in a cross-sectional study with 625 renal transplant recipients, and no deleterious effects of the diet were identified. Interestingly, in a cohort of 940 kidney transplant recipients, a higher protein intake was associated with protection for mortality and graft failure [42]. These results were confirmed in a more recent cohort of 604 kidney transplant recipients with 7 years of follow up [43]. Said et al. have shown that a high protein intake was associated with improvements in muscle mass and with

reduced risk of mortality and graft failure [43], suggesting that a relatively high protein intake may be beneficial to kidney transplant recipients.

Other studies evaluating the impact of dietary interventions in kidney transplanted recipients show conflicting results, mainly limited by the study design [12-14]. Thus, due to lack of high quality evidence data on this issue, there is no guidelines recommendation for a specific nutritional intervention to manage weight gain and obesity after kidney transplantation [44-46].

Since it is not possible to blind participants and researchers involved in this study, there are possible risks of bias. In order to diminish these risks, we will be evaluating standard measurements of weight and others anthropometric and laboratory tests. Besides, to reduce the potential for confounding due to measurement variability, a single investigator will perform all the measurements using the same instruments throughout the study and the same dietitian will perform the nutrition intervention protocol.

Trial status

The trial is ongoing. Forty patients have started the study protocol and additional patients are being recruited.

List of Abbreviations

BMI, body mass index; CONSORT, consolidated standards of reporting trials; FAO, food and agriculture organization; GI, glycemic index; MDRD, modification of diet of renal disease; SPIRIT, standard protocol items: recommendations for

interventional trials; United States department of agriculture, USDA;VAS, visual analogue scale.

Declarations

Ethics and approval and consent to participate

All procedures will be conducted in accordance with the ethical standards for human subject research set forth in the Declaration of Helsinki. Written informed consent will be obtained from all patients to be included in this clinical trial by main researcher (EFP), who will have access to the final trial database. The research project was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (registration number 16–0121) and is registered in the ClinicalTrials.gov database under identification number NCT02883777. Personal information about potential and enrolled patients will be maintained in a database in order to protect patients confidentially. Investigators will communicate trials results to participants, healthcare professionals and other relevant groups via publication.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

No competing interests to report for any authors or trial staff member.

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Authors' contributions

EFP conceived the study, participated in the design of the study, writing of protocol and prepared the final version of the manuscript. She is responsible for recruitment, data collection and nutritional evaluation. LCS, JMF and JRB will conduct the data collection and nutritional evaluation. EFP, BBN, LCS, JMF, JRB CCF, RCM, ACB, GCS and CBL conceived the study and drafted this manuscript. CCF is responsible for the randomization. EFP, BBN and CBL will participate in the data analysis. All authors read and approved the final manuscript.

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Aditional File 1.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Capítulo 4

Ensaio Clínico Randomizado

Artigo a ser submetido para publicação no Periódico *British Journal of Nutrition*

Effect of an Intensive Nutrition Intervention of a High Protein and Low Glycemic-Index Diet on Weight of Kidney Transplant Recipients: a Randomized Clinical Trial

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Abstract

Background: Exceeding weight gain is often observed within the first year post kidney transplant and it is associated with poor outcomes, such as cardiovascular events and graft loss. The purpose of this study is to evaluate the effect of a high protein and low glycemic index diet in preventing weight gain after kidney transplantation.

Methods: We designed a prospective, single-center, open-label, randomized controlled study to compare the efficacy of a high protein (1.3 – 1.4 g/kg/day) and low-glycemic index diet versus a conventional diet (0.8 – 1.0 g/kg/day of protein and no recommendations on glycemic index) in preventing weight gain after kidney transplant. A total of 120 patients with 2 months after transplantation were evaluated: 60 for intervention group (IG) and 60 for control group (CG). Participants with estimated glomerular filtration rate through Modification of Diet of Renal Disease (MDRD) formula <30 mL/min/1,73m² or urinary albumin excretion >300 mg/24 h were excluded. Patients were followed for 12 months with 9 clinic visits with a dietitian and the evaluations included nutritional assessment and laboratory tests. The primary outcome is weight maintenance or body weight gain under 5% after 12 months.

Results: Ninety-nine participants completed the protocol (82.5%). There were no differences in total energy intake, carbohydrates and total fats. IG increased protein intake to 1.38 ± 0.56 g/kg/day and decreased the glycemic load to 87.27 ± 4.54 g/day, while CG presented a dietary intake of 1.19 ± 0.43 g/kg/day and a

glycemic load of 115.60 ± 7.01 g/day. Total fiber intake was greater and trans-fat was lower in IG than in CG. Dietetic cholesterol increased in IG over time and was significantly different between groups. Overall, patients had an increase in body weight over time, with a mean increment of 4.1 ± 5.5 kg (5.75% of body weight). There were no differences in changes of body weight, body mass index, body composition and others laboratory parameters between groups. Glomerular filtration rate improved overtime in both groups, and no differences between groups were observed. For 24-h proteinuria and albuminuria, a similar raise was observed in both groups.

Conclusion: An intensive nutritional strategy and the implementation of a high protein and low glycemic-index diet in kidney transplant recipients did not impact on weight loss one year after transplant. Our findings suggest that other interventions might be added to dietary manipulation in order to improve patients body weight outcomes after transplant, perhaps cognitive behavior therapy plus pharmacotherapy. Howerver these approaches should be tested in prospective randomized controlled trials.

Trial Registration: ClinicalTrials.gov identifier: NCT02883777 (date of registration: August 3, 2016).

Keywords: Kidney Transplantation, Nutrition Intervention, High Protein Diet, Low-Glycemic Index Diet, Weight.

Background

Body weight gain during the first year post kidney transplantation is a risk factor for adverse metabolic consequences, such as posttransplant diabetes and metabolic syndrome, both conditions clearly associated with negative transplant-related outcomes [1-6]. Transplanted subjects gain an average of 10-35% of body weight, and the main reasons for such increment may be related to direct effects of immunosuppressive drugs on appetite and metabolic disarrangements, appetite restoration after uremia resolution and end of dietary restrictions imposed during dialysis [7-11].

Dietary recommendations to prevent weight gain after renal transplantation are scanty [12-18] and mostly based on specialist opinions, as only one randomized clinical trial evaluating the effects of nutritional interventions on body weight has been recently published [12]. A review, that summarized the evidence-based guidelines for dietary management in kidney transplant recipients, concluded that there is no grade I or II scientific evidence for a specific dietary recommendation in kidney transplant recipients [19]. Also, there are no guidelines addressing clinical interventions to prevent weight gain and obesity for this particular population, [20], and the current recommendations are based on non-randomized studies and include broadly and non-specific statements.

The Caring for Australians with Renal Impairment (CARI) guidelines [21] suggests that all transplant patients should be referred to a dietitian for weight gain prevention and the nutritional management must include regular and ongoing evaluations. *The Kidney Disease: Improving Global Outcomes* (KDIGO)

[22] and *United Kingdom Renal Association* [23] guidelines are not so strict: they suggest that obese patients should be evaluated at each visit and weight-management facilities should be available for referral. It is important to emphasize that the KDIGO workgroup developed a clinical practice guideline focused on prevention of post kidney transplant complications, and dietary recommendations for kidney transplant recipients were not mentioned [22].

Studies from the general population suggest that diets with higher protein content and lower glycemic index may lead to sustain weight loss, as they are associated with higher satiety sensation [24-2]. However, the prescription of high protein diets to kidney transplant recipients may not be well accepted by clinicians due to concerns on the possible association of high protein intake and kidney damage [18,33,34]. Regardless, there are few evidences on the impact of high protein intake on long-term kidney function outcomes [20].

Therefore, we design the present study to evaluate if a nutritional intensive intervention based on the prescription of a high protein and low-glycemic index diet would be an effective and safe intervention to prevent weight gain in kidney transplant subjects.

Methods

Study design

This is a prospective, single-center, open-label, randomized clinical trial that includes an interventional (high protein and low glycemic-index diet) and a control group (usual diet). Included subjects are patients that underwent kidney transplant at Hospital de Clínicas de Porto Alegre, Brazil from January 2016 to March 2018. The trial was approved by the local Research Ethics Committee and

it is registered in the ClinicalTrials.Gov database under identification number: NCT02883777. Detailed methodology has been previously published as a protocol [35].

Inclusion and exclusion criteria

The study included kidney transplant recipients who agreed to participate in the study protocol and provide written informed consent. The exclusion criteria were the following: patients younger than 18 years old, prior transplant, multiple organ transplant, type 1 diabetes mellitus, current cancer, women in pregnancy or lactation period, recipients of kidney from living donors, patients with urinary albumin excretion >300 mg/24h or estimated glomerular filtration rate by Modification of Diet of Renal Disease (MDRD) formula <30 mL/min/1,73m² and/or anticipated difficulty of adherence (for example, due to cognitive deficits or dementia).

Sample size

Sample size calculations were carried out in WINPEPI 11.20 (Brixton Health, Israel). We based the calculation on weight gain values reported by Souza and colleagues [36] from our transplant center, which reported an average weight gain of 2.9 kg ± 5.6 kg at one year after transplantation. For a significance level of $\alpha \leq 0.05$ and a statistical power of 80%, with a standard deviation of 5% of body weight the minimum sample size was 98 patients. Foreseeing possible dropouts, we included 120 patients (60 randomized to each group).

Study Intervention

Patients were randomized to intervention group (IG) and control group (CG). All patients were evaluated in 9 visits during a follow-up of 12 months. The evaluations included nutritional assessment (anthropometrics, body composition and resting metabolic rate) and laboratory tests.

Randomization

The randomization was performed through a simple sequential randomization plan generated online, using the randomization.com website [37] by a researcher not involved on study conduction.

Blinding

In this clinical trial, blinding of patients and dietitians were not possible, because of evident differences between the intervention and control group.

Data collection and timeline

Follow-up evaluation and data collection were undertaken over three years at the Clinical Research Center of the hospital, Porto Alegre, Brazil, by trial personnel. All research procedures were performed at the same day of protocol laboratory tests.

Adherence

In order to assess diet compliance, three different measurements were applied:

1) Measurement of reported dietary intake in 24-hour (R24-h) dietary recall over nine visits: baseline, visit 1 (V1), visit 2 (V2), visit 3 (V3), visit 4, (V4) visit 5 (V5), visit 6 (V6), visit 7 (V7) and visit 8 (V8), with daily glycemic load calculations at three moments (baseline, V3 and V6).
2) Collection of 24-hour urinary urea excretion to calculate the protein nitrogen appearance (nPNA) as a measure to estimate protein intake [urinary urea/2 + 0.031g/kg x 6.25] [38] at baseline, V3, V6, V7 and V8.
3) Goldberg and Black cut-offs were used to identify diet reports of poor validity [total energy intake assessed by 24-h recall /resting metabolic rate obtained by indirect calorimetry] at baseline and V6. Only patients with values between 0.76 and 1.24 were classified as acceptable reporting [39].

Safety

In order to assess diet safety, 24-hour urine samples were collected and proteinuria and albumin excretion (UAE) were measured to evaluate kidney injury. Besides, kidney function was assessed by serum creatinine, and glomerular filtration rate (eGFR) was estimated by MDRD formula.

Study protocol

Two months after the transplant surgery, kidney transplant recipients who meet the inclusion criteria and are eligible were invited to participate. Patients were them randomized for IG or CG.

Both groups were assessed at baseline, and them, patients visit the center once a month for the first 6 months (V1-A6). After that, another two visits were scheduled at months 9 (V7) and 12 (V8) as it is illustrated in figure 1. At each visit, both groups were submitted to the research protocol (laboratory exams and anthropometry). IG received the prescription of a high protein and low-glycemic index diet, along with individualized nutrition counselling delivered by a research dietitian at each visit during whole follow-up. In contrast, in CG, the nutrition appointments were made according hospital dietitian availability (≤ three visits of nutritional counselling during the one year follow-up). CG participants did not receive any further dietary counselling during schedule research visits. Thus, the intervention group received eight nutritional reinforcements and the CG, only three.

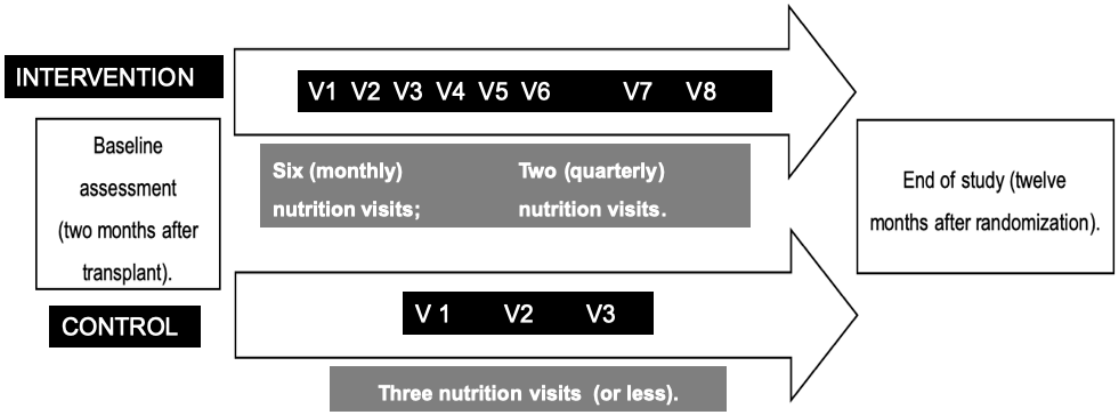

Figure 1 - Study logistic

Intervention: V1 – V6, six monthly visits; V7 and V8, quarterly visits;
Control: V1 – V3, Three nutrition visits.

Demographic and clinical data were assessed at first visit. Nutritional assessment comprised: a) anthropometric measurements: body weight, height [(with calculation of body mass index (BMI) (kg/m²)] and waist circumference (measured midway between the lowest rib margin and the iliac crest, with flexible, no stretched fiberglass tape) and were performed in each visit; b) body fat mass (%): measured by bioelectrical impedance analyzer (*In Body 230 – GE Health Care*), assessed every three months; and c) resting metabolic rate: evaluated by indirect calorimetry (*Meta Check 7100 – Metabolic Rate Analysis System – KOOR*) at baseline and 6 months later. All the anthropometric measurements were performed with the patient fasting, wearing light clothing, without contact with metals and without shoes.

Biochemical assessment included serum creatinine, fasting glycaemia, glycated hemoglobin (HbA1c), total cholesterol, HDL-cholesterol, triglycerides, and uric acid (each three months), high-sensitivity C- reactive protein, (baseline

and at 6th month) and 24-h urine sample for albumin, protein, creatinine and urea excretion (every three months).

Dietary prescription

Both groups received energy-matched diets, but IG group received a high protein (1.3 – 1.4 g/kg/day) and low-GI diet (preference for foods with glycemic index < 55%, with a daily glycemic load of <80 g) and CG received a conventional diet (0.8 – 1.0 g/kg/day of protein) with no recommendation regarding food GI. In case of patients who had gained or lost more than 5% of body weight, the diets were recalculated. The diet prescription was calculated using a nutritional software (*Nutribase 2007 Clinical Manager software version 7.14*). GI were estimated as proposed by the Food and Agriculture Organization (FAO) [40] by using the international table – United States Department of Agriculture (USDA) table [41], with glucose as the standard food [42]. Energy intake was assessed by a 24-h recall in 9 visits by the research dietitian. Diet composition also was analyzed using nutritional table by the software *Nutribase 2007 Clinical Manager software version 7.14* and was made in each visit. Satiety levels were assessed twice through a visual analogue scale (VAS) of appetite [43].

Primary outcome

The primary outcome was body weight maintenance or weigh gain under 5% of body weight.

Secondary outcomes

The secondary outcomes were: body composition, glycemic parameters, lipid profile, inflammation status and kidney function.

Statistical analyses

Shapiro-Wilk test was used for normality assessment. Continuous variables with normal distribution were expressed as mean ± standard deviation, while asymmetrically distributed variables were expressed as median and interquartile range. Categorical variables were expressed as absolute and relative frequencies. For between-group comparisons, Student's *t*-test was used for normally distributed variables, and the Mann–Whitney *U* test for asymmetrically distributed variables. A paired *t*-test was used for within-group analysis of body weight and body composition. The Chi-square or Fisher's exact tests were used to evaluate associations between categorical variables. The generalized estimating equations (GEE) test with Bonferroni adjustment were applied for comparison between variables during the study period. Energy and nutrient intake data were adjusted before analyses for energy intake according the residual method. The significance level will be set lower than 5%, and all data was analyzed in Statistical Package for Social Sciences (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Included subjects had a mean age of 49 ± 13 years-old, were predominantly men (62%), had the main following etiologies for renal failure: hypertension (15%), diabetes (13%), glomerulonephritis (12%) and polycystic kidney disease (12%) and were on dialyses for a mean duration of 1.8 (1.0 - 3.2) years. Baseline characteristics are presented in table 1, and clinical and laboratory variables were similar in both groups, with the exception of higher frequency of African decedents in CG. Also, there were no differences in anthropometric and metabolic measures between groups at baseline (Table 2). Although not statistically different, all four participants diagnosed as underweight were randomized to CG. From the one-hundred-twenty subjects included, ninety-nine participants completed the protocol (82.5%) as demonstrated in study flow chart (figure 2). Dropout rates were similar between groups.

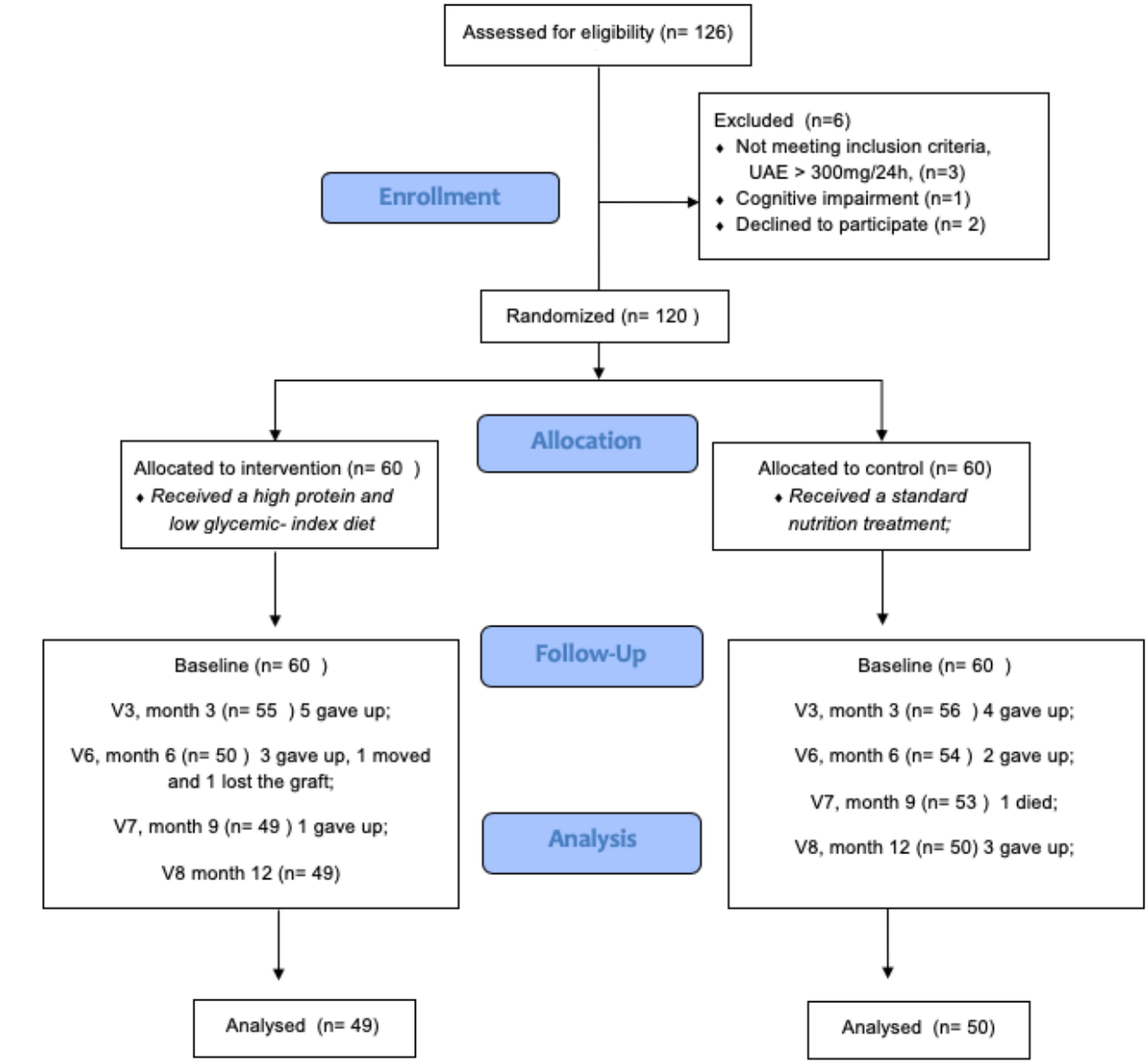

Figure 2 - Consolidated Standards of Reporting Trials (CONSORT) flow diagram

UAE: urinary albumin excretion; V1, visit 1 moth after randomization V3, visit 3 moths after randomization, V6, visit 6 moths after randomization, V7, visit 9 moths after randomization, V8, visit 12 moths after randomization.

Table 1 - Baseline characteristics between groups

	Intervention (n=60)	**Control (n=60)**	**P value**
Age, years	50.5 ± 12.1	48.5 ±14.6	0.422
Male gender, n (%)	34 (57)	41 (68)	0.258
White ethnicity, n (%)	51 (86)	41 (68)	0.032
Hypertension, n (%)	45 (76)	49 (82)	0.619
Diabetes mellitus prior transplant, n (%)	17 (28)	12 (20)	0.394
Primary kidney disease, n (%)			
Unknown	20 (33)	26 (43)	
Hypertension	10 (17)	8 (13)	
Diabetes mellitus	10 (17)	6 (10)	
Glomerulonephritis	9 (15)	6 (10)	0.668
Polycystic kidney disease	6 (10)	9 (15)	
Others	5 (8.3)	5 (8)	
Renal replacement therapy, n (%)			
Hemodialysis	53 (88)	55 (91)	
Peritoneal dialysis	2 (3)	4 (8)	0.258
Hemodialysis and peritoneal dialysis	5 (8)	1 (2)	
Dialysis duration (years)	1.8 (1.0 -3.0)	1.7 (1.1- 4.3)	0.709
Delayed graft function, n (%)	29 (49.2)	31 (51.7)	0.928

Values are expressed in mean ± SD, n (%) or median (interquartile range).

Table 2 - Baseline anthropometric and metabolic characteristics between groups

	Intervention (n=60)	Control (n=60)	P value
Body weight (kg)	72.3 ± 1.7	72 ± 1.9	0.917
BMI (kg/m^2)	26.7 ± 0.5	26.2 ± 0.6	0.524
Body fat (%)	30.4 ± 1.1	27.6 ± 1.3	0,099
Lean mass (kg)	27.7 ± 0.7	28.3 ± 0.8	0.589
Waist circunference (cm)	96.8 ±1.7	94.7 ± 1.8	0.067
Nutritional status , n (%)			
Underweight	0 (0)	4 (6.7)	
Eutrophia	25 (41.7)	21 (35)	0.064
Overweight	24 (40)	17 (18.3)	
Obesity,	11 (18.3)	18 (30)	
Resting metabolic rate (Kcal)	1490.8 ± 66.7	1432.1 ± 49.4	0.482
Fasting plasma glucose (mg/dL)	97 (88.2 - 115)	95.25 (85.1 - 106.3)	0.224
HbA1c (%)	5.8 (5-7)	5.5 (5-6.2)	0.345
eGFR (<60 mL/min/1.73m²)	37 (78.7)	38 (82.6)	0.832
Total Cholesterol (mg/dL)	201.1 (± 5.4)	193.5 (± 5.3)	0.315
HDL-C (mg/dL)	52 (39-70)	47.5 (120.5-251.25)	0.324
Triglycerides (mg/dL)	183 (118.5 - 262.5)	164 (120.5 - 251.2)	0.775
Uric acid (mg/dL)	5.80 (5-6.7)	6.05 (5 -7.1)	0.472
hsCRP (mg/dL)	1.52 (0.7 – 4.6)	0.73 (2.04 - 4.4)	0.348
24-h urinary protein excretion (mg/dL)	148 (102 - 204)	150 (99 - 182)	0.671
24-h urinary albumin excretion (mg/dL)	16.8 (7.2- 40.1)	18.9 (8.3 -55)	0.431
24-h urinary urea excretion (mg/dL)	23.4 (16.9 - 29.9)	23.3 (18.7-28.2)	0.796
24-h urinary creatinine excretion (mg/dL)	1086.25 (± 487.8)	1192.31 (± 401.1)	0.216
Activity level (low), n (%)	47 (78.3)	47 (78.3)	1

Values are expressed in mean ± SD, n (%) or median (interquartile range).

eGFR: estimated glomerular filtration rate; hsCRP: high-sensitivity C-reactive protein; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycated haemoglobin; BMI: body mass index;.
Values expressed in mean ± standard error

Adherence

At the baseline assessment, both groups presented a high protein intake. In IG, the mean protein intake was 1.13 ± 0.43, with 36% of patients ingesting more than 1.3 g/kg (Table 1, Sup. file). In CG, protein intake was 1.15 ± 0.48 and 44.% had a dietary protein intake over 1.3 g/kg/d (Table 2, Sup. file). Moreover, both groups presented a high daily glycemic load intake as well (IG: 113.18 ± 6.98; CG: 121 ± 5.39 g). As prescribed, IG increased protein intake to 1.38 ± 0.56 g/kg/day and decreased the glycemic load to 87.27 ± 4.54 g/day, while CG had a protein to 1.19 ± 0.43 g/kg/day and a glycemic load of 115.60 ± 7.01 g/day. Besides, more individuals reached the goal of a daily glycemic load <80 g and >1.3 g/kg in IG (Table 3, Sup. file) than in CG. No correlation between protein obtained by 24h dietary recall and the nPNA as a measure of dietary protein intake was observed ($p = 0.148$).

In according with The Goldberg and Black cut-offs [38,39], at baseline assessment, 36% of patients from IG and 40% from CG were classified as acceptable reporting. Six months later, 52% of patients were classified as acceptable reporting in IG and 44% in CG. No statistical differences were observed in these parameters overtime or between groups [p (group): 0.201; p (time): 0.081; p (group x time): 0.375].

According to dietary report analyses, there were no differences in total energy intake, carbohydrates, net carbs, total fats, saturated and monounsaturated fats, polyunsaturated fatty acids (PUFAS), omega-3 (w-3) fatty acids, omega-6 (w-6) fatty acids overtime or between groups. Notably, total fiber intake was greater and trans-fat was lower in IG than in CG, as well as dietetic cholesterol increased in IG over time and was significantly different between groups (Table 4, Sup. file).

Body weight and anthropometric measurements

Patients had an increase in body weight over time, with a mean increment of 4.1 ± 5.5 kg (5.75% of body weight). There were no differences in changes of body weight (figure 3) and BMI between groups throughout one year of follow up. The same patterns were observed for waist circumference, body fat and resting metabolic rate (Figure 3). The satiety scale was not included in analysis as subjects had a lower capability for both understanding and filling it, resulting in low credibility of results.

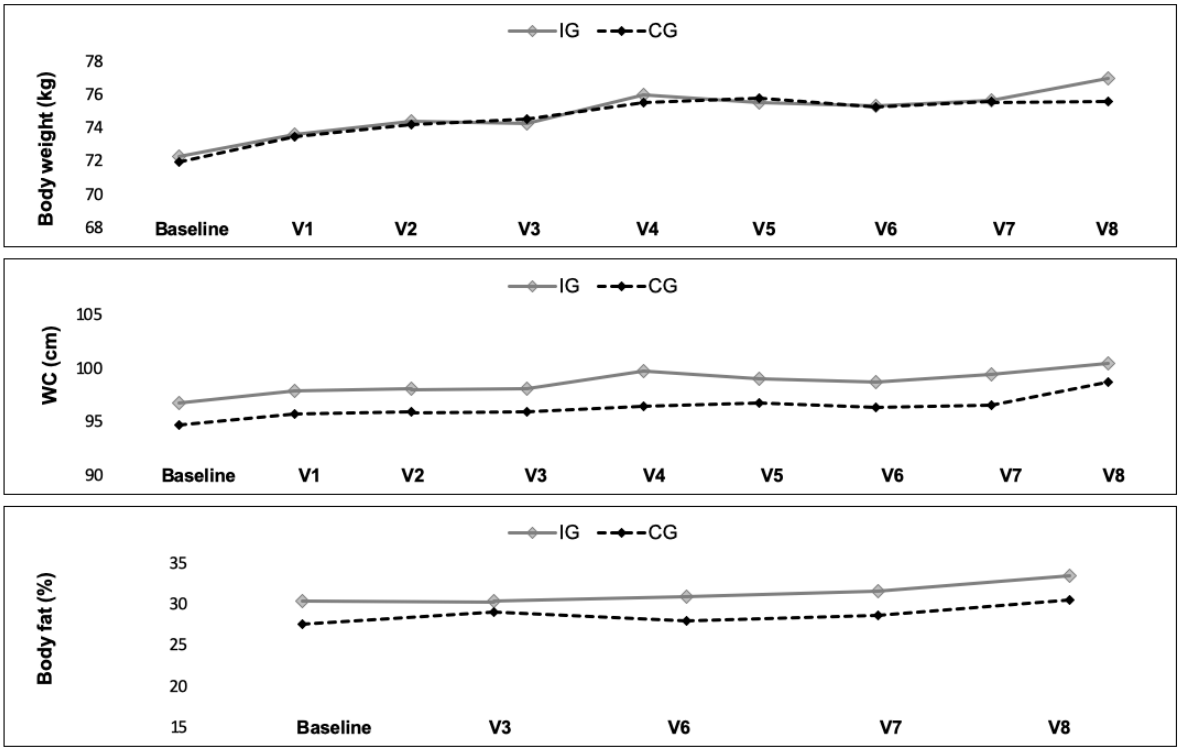

Figure 3 - Anthropometric parameters

V3, visit 3 moths after randomization, V6, visit 6 moths after randomization, V7, visit 9 moths after randomization, V8, visit 12 moths after randomization;

Body weight: P (group):0.931; P (time) < 0.001; P (group x time: 0.904).
WC: P (group):0.407; P (time) < 0.001; P (group x time: 0.832).
Body fat: P (group):0.331; P (time): 0.001; P (group x time: 0.487).

Metabolic and inflammatory variables

Glycemic parameters, measured as fasting plasma glucose and HbA1c, were similar between groups (Figure 4), even that subjects from IG reported lower glycemic load intake at V3 and V6. Also the incidence of posttransplant diabetes was similar between groups (GI: 19.5% (8/41) vs. 10.4% (5/48), p 0.363).

Serum lipids improved overtime. A decrease was observed in total cholesterol (TC), HDL-c and triglycerides (TGL) (p <0.001) in both groups, but no differences or interaction were observed between them (Figure 4). Low density lipoprotein – cholesterol (LDL-c) (p: 0.730; p: 0.358; p: 0.372), uric acid and hs-CRP were stable during the study in both groups (Sup. file).

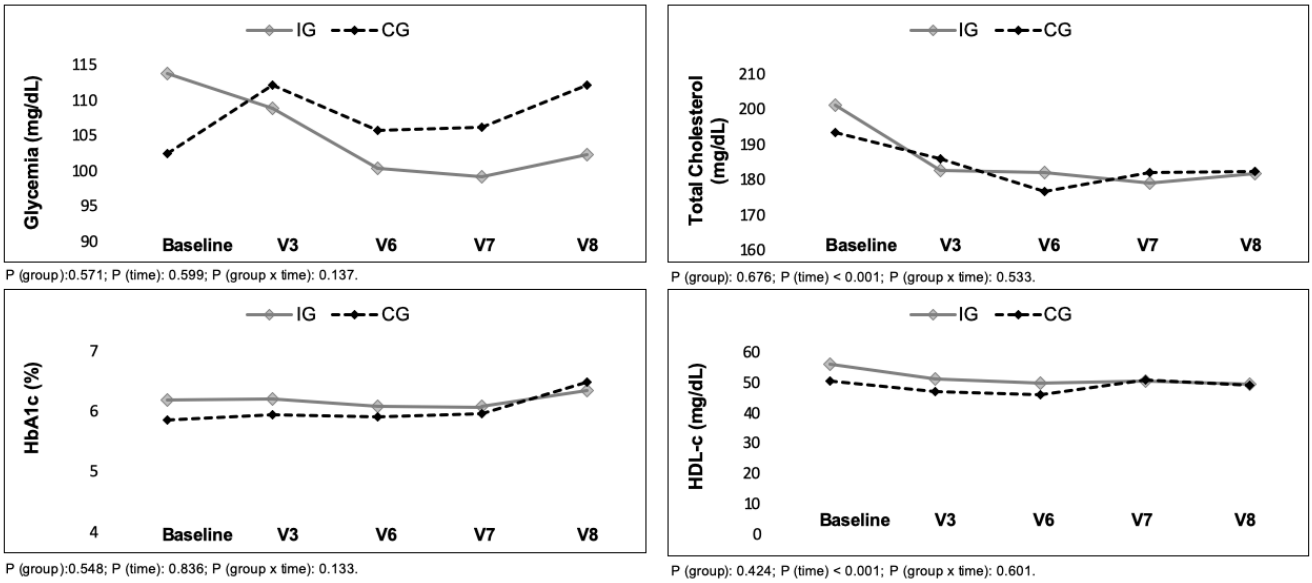

Figure 4 - Glycemic and Lipid parameters

V3, visit 3 moths after randomization, V6, visit 6 moths after randomization, V7, visit 9 moths after randomization, V8, visit 12 moths after randomization;
Glycemia: P (group):0.571; P (time): 0.599; P (group x time): 0.137.
HbA1c: P (group):0.548; P (time): 0.836; P (group x time): 0.133.
Total cholesterol: P (group): 0.676; P (time) < 0.001; P (group x time): 0.533
HDL-c: P (group): 0.424; P (time) < 0.001; P (group x time): 0.601.

Safety monitoring

Renal function, assessed by serum creatinine and eGFR, improved overtime, and no differences between groups were observed (Figure 5). For 24-h proteinuria and 24-h albuminuria, a similar raise was observed in both groups.

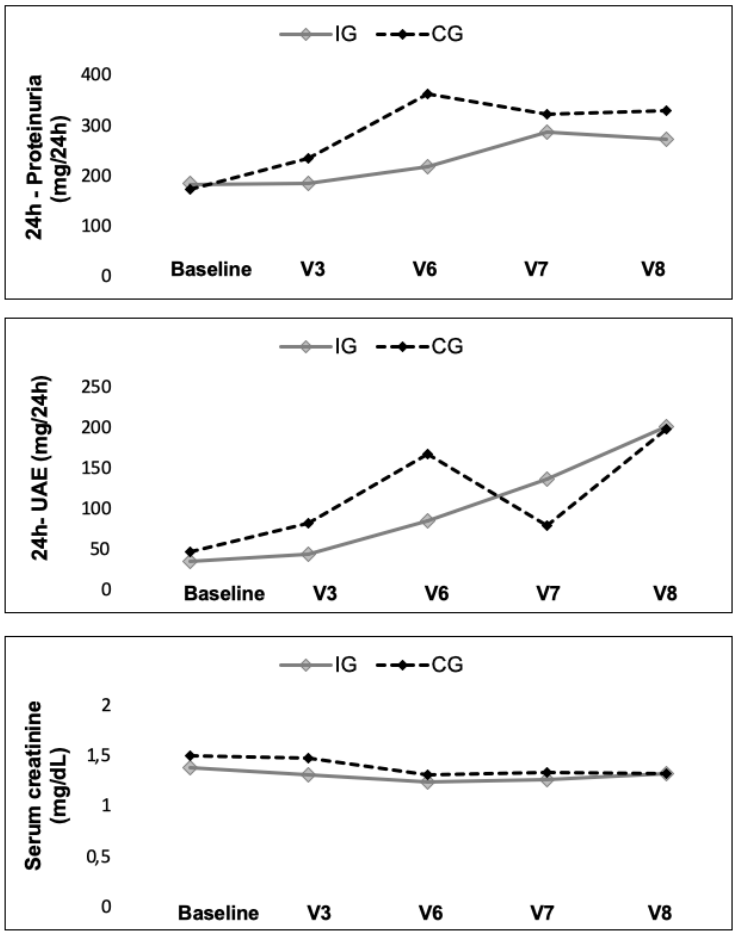

Figure 5 - Safety parameters

V3, visit 3 moths after randomization, V6, visit 6 moths after randomization, V7, visit 9 moths after randomization, V8, visit 12 moths after randomization;24h – Proteinuria P (group):0.549; P (time): 0.006; P (group x time): 0.242. 24h – UEA: P (group):0.096; P (time) < 0.001; P (group x time) < 0.001. Serum Creatinine: P (group):0.375; P (time) < 0.001; P (group x time): 0.242.

Discussion

In this sample of kidney transplant recipients, an intensive nutritional intervention based on the prescription of a high protein and low glycemic index diet was not capable to prevent body weight gain in the first year post-transplantation. Both groups gained an expressive amount of kilograms (IG: 5.39% $\pm$ 7.95; CG: 6.09% $\pm$ 7.51), even though IG proved to adhere to prescribed diet modifications. The others metabolic parameters, including biochemical tests such as glycemia, HbA1c, serum lipids, triglycerides, renal parameters were not different between groups as well.

This study is the first randomized trial testing the impact of a high protein and low glycemic-index diet on kidney transplant recipients. We have hypothesize that it would improve satiety and would help patients to decrease calorie intake, however, our hypothesis was not confirmed. Furthermore, it was not possible to measure the satiety parameter, once patients had difficulties in filling the satiety scale at home, and so we did not consider a reliable data to be considered for analysis.

In fact is that in present trial the total energy intake between groups was matched, and some robust studies have shown that what really results in weight loss is a reduced-calorie diet, regardless of which difference in macronutrient is prescribed [44-46]. The *Preventive Obesity Using Novel Dietary Strategies* (POUNDS) Lost Study, the largest study examining macronutrient composition and body weight loss, randomized patients to one of four diets, with 80% of patients providing data on body weight over two years. The diets were: (a) 20% fat; 15% protein; (b) 20% fat; 25% protein; (c) 40% fat; 15% protein; or (d) 40% fat; 25% protein. In authors conclusions, the weight loss was similar for all different dietary approaches, independently of macronutrients composition.

However, those who achieved the largest increase in protein intake lost the largest amount of weight [47].

The data from this paper are resembling with the recommendations of the *American College of Cardiology/American Heart Association/Obesity Society Guideline for the Management of Overweight and Obesity in Adults*, which recommends that "*a variety of dietary approaches can produce weight loss in overweight and obese adults, and that the choice should be based on the patient's preferences and health status*" [48]. So that, perhaps a personalized dietary treatment for each kidney transplant recipient, which considers patients preferences along with behavior approaches might be considered for future studies. Behavioral modifications have been reported as a fundamental part of weight-loss programs. Consolidated trials, such as The *Look Action for Health in Diabetes* (AHEAD*) trial* and the *Diabetes Prevention Program* (DPP)*,* support the efficacy of these approaches. Such studies are the gold standard and are remarkable for emphasizing individualizing therapy frequency of contact, and long-term interventions for maintaining weight loss [49-51].

The evidence assessing dietary interventions in renal transplant patients is quite limited, once there are few studies and the methodology is doubtful [13-18]. One recent randomized clinical trial performed an intensive nutrition intervention to avoid excess weight gain one year after transplant, but both intervention and control groups increased body weight similarly. Besides, this study had some important limitations, such as small sample (only thirty seven patients and eleven withdraws) and also the dietary intake of control group was not estimated [12]. Another randomized trial, which assessed a dietetic advice for modification of cardiovascular risk factors, resulted in healthier eating habits, however overall there was no differences in weight loss [52].

There are so many reasons that might be associated to the difficulty in obtain positive results when we test nutritional strategies to improve body weight

in this population of patients. First, the changes regarding dietary restrictions from dialysis to the more liberal prescriptions in the post-transplant period, along with appetite improvement cannot be underestimated. Second, the well-known side effects of immunosuppressive drugs on appetite and metabolism. And third, it is important to lay emphasis on main etiologies for renal failure in these patients: hypertension and diabetes, both conditions probably associated with previous non-healthy nutrition behavior and classically related to a poor adherence and compliance to medical and nutritional recommendations [7,49,53]. In general, weight loss in diabetic patients is challenging and patients with diabetes consistently lose less weight with a given treatment than those who do not have diabetes [54]. This is particularly notable in some obesity trials, in which body weight losses are very often reported to be 25% lower in patients with obesity and diabetes than in patients with obesity but without diabetes [54].

Besides, for this research subjects were systematically invited to undergo on dietary restrictions, so they did not spontaneously seek for nutritional recommendations. It may perhaps to impact in less valorization of treatment as reported in healthy population previously [55]. It was observed a withdraw of 17.5% in the present trial (eleven patients in IG and ten in CG), which characterizes somehow the lack of interest of these patients in dietary treatments. Therefore, it is possible to consider that in kidney transplant recipients, only dietary treatment would not lead to sufficient weight loss and health improvements, as shown by us and by an another randomized trial recently published [12]. Hence, obesity pharmacotherapy could be a valuable option for treatment when indicated. Numerous studies have shown the benefit of combining cognitive behavior therapy and pharmacotherapy to dietary recommendations on weight and glycemic outcomes [49, 54].

Interestingly, despite the concerns related to high protein diets and kidney damage, renal function parameters were similar in both groups, and an

increment in eGFR was observed. Albuminuria and proteinuria were not different between groups, but both increased during the follow-up, as expected post-transplant [56]. Interestingly, three observational studies in renal transplantation did not find any association of high protein intake and kidney damage [57-59]. Notably, one of them, that analyzed 904 patients, suggests a protection of high protein intake and graft failure and mortality [59]. The other, with 604 patients and seven years of follow up, reported that patients with greater protein intake improved body composition with greater lean mass, and again, had reduced risk for graft failure and mortality [58].

The main limitations of the present study are the single-center and open-label design. Moreover, once it was performed in a public hospital in Brazil and the participation was voluntary, many patients had poor conditions to buy prescribed dietary items, so that it could be a possible barrier to better adherence. Also, we had used a 24-h dietary recall for estimate food intake, which certainly might reflect some specific dietary intake one day before visit and exams. But as we had a considerable number of 24h dietary recall per patient (nine in total), we believe the these registries reflects a mean of dietary intake of the whole period of follow up.

In conclusion, an intensive strategy and the implementation of a high protein and low glycemic-index diet in kidney transplant recipients did not impact in weight loss one year after transplant. Our findings suggest that perhaps another interventions should be added to the dietary recommendations, such as behavior therapy plus pharmacotherapy, to optimize weigh loss in these patients. However, such combined interventions must be tested in prospective randomized controlled trials.

The authors have no conflicts of interest to declare and would like to acknowledge the Coordenação de Aperfeiçoamento de Pessoal de Nível

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EFP was responsible for trial design, data acquisition, analysis, interpretation and drafting of the manuscript. CC contributed to data acquisition analysis and interpretation of data. BBN contributed to study design, interpretation and drafting of the manuscript. JCMF, JRB and GSG contributed to data acquisition and interpretation. ACB and RCM contributed to study design, and data interpretation. CBL and GCS contributed to study design, data analysis interpretation and drafting of the manuscript. All authors have read and approved the final manuscript. EFP is the one responsible for this RCT and, as such, had full access to all the data in the study and take responsibility for the integrity of the data report and the accuracy of the data analysis.

Supplemental file

Supplementary Table 1 - Dietary protein Intake (g/kg/day)

Group	Baseline	V3	V6	V7	V8	P		
						Groups	Time	Group x Time
IG	1.13 ± 0.43	1.29 ± 0.44	1.28 ± 0.40	1.34 ± 0.40	1.38 ±0.56	0.04	0.09	0.279
CG	1.15 ± 0.48	1.13 ± 0.38	1.20 ± 0.52	1.22 ± 0.35	1.19 ± 0.43			

Values expressed in mean and standard deviation. IG, intervention group; CG, control group.
V3, three months visit, V6, six months visit, V7, nine months visit; V8, twelve months visit.

Supplementary Table 2 - Adherence protein intake >1.3g/kg/day

Group	Baseline	V3	V6	V7	V8	P		
						Groups	Time	Group x Time
IG								
n	21	20	16	21	22			
(%)	(36)	(37)	(33.3)	(44.7)	(47.8)			
						0.483	0.401	0.202
CG								
n	26	17	18	21	14			
(%)	(44.1)	(30.9)	(34)	(42)	(28)			

IG, intervention group; CG, control group.
V3, three months visit, V6, six months visit, V7, nine months visit; V8, twelve months visit.

Supplementary Table 3 - Adherence by daily glycemic load

Group	Baseline	V3	V6	P		
				Group	Time	Group x Time
IG						
Daily GL(g)						
(mean, DP)	113.18 ± 6.98	91.52 ± 6.21	87.27 ± 4.54			
≤ 80 (n,%)	15 (25)	26 (49.1)	22(42,3)			
> 80 (n,%)	45 (75)	27 (50.9)	30 (57.7)			
				0.001	<0.001	0.160
CG						
Daily GL (g)						
(mean, DP)	121.68 ± 5.39	108.87 ± 5.67	115.60 ± 7.01			
≤ 80 (n,%)	7 (11,7)	15 (27,8)	9 (18)			
> 80 (n,%)	53 (88,3)	39 (72,2)	41 (82)			

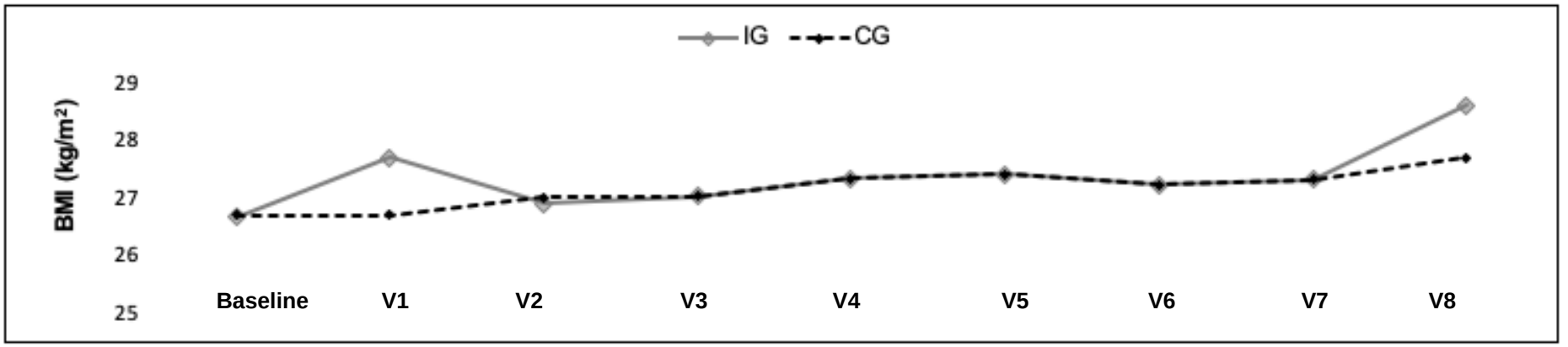
Values expressed in mean and standard deviation. IG, intervention group; CG, control group, GL, glycemic load. V3, three months visit, V6, six months visit, V7, nine months visit; V8, twelve months visit.

Table 4. - Dietary intake of energy and nutrients

		TEI (Kcal)	P value	Protein (g)	P value	CHO (g)	P value	Total fiber (g)	P value	Total fats (g)	P value	TC (mg)	P value
	Baseline	1859.03±82.87		83.09 ± 3.22		210.87 ± 7.07		17.66 ± 1.16		69.24 ± 2.49		245.55 ± 27.10	
	V3	1669.47 ±75.57		95.26 ± 3.21		196.11 ± 7.21		22.96 ± 1.61		66.19 ± 2.43		368.69 ± 52.45	
IG	V6	1581.29 ±63.65		94.66 ± 3.21		189.56 ± 5.62		22.35 ± 1.27		66.42 ± 1.81		368.66 ± 46.74	
	V7	1593.16 ±83.83	0.480	98.90 ± 3.21	0.002	188.21 ± 6.99	0.113	20.43 ± 1.49	0.243	65.52 ± 2.1	0.512	459.75 ± 62.93	<0.001
	V8	1954.9 ±171.59	0.003	96.99 ± 4.41	0.009	175.18 ± 18.84	0.043	24.61 ± 2.86	0.146	58.09 ± 6.56	0.419	432.03 ± 59.16	0.037
	Baseline	1869.58 ±68.61	0.244	84.48 ± 3.14	0.286	208.54 ± 7.97	0.534	21.94 ± 4.13	0.013	67.41 ± 3.20	0.772	239.97 ± 30.24	0.017
	V3	1764.04 ±80.93		83.89 ± 2.95		200.59 ± 6.84		19.24 ± 2.69		68.78 ± 2.96		214.80 ± 19.00	
CG	V6	1802.07 ±87.63		86.38 ± 3.54		205.34 ± 9.91		18.24 ± 3.23		66.89 ± 3.13		263.29 ± 25.39	
	V7	1719.38 ±76.61		90.03 ± 2.69		198.49 ± 6.06		14.62 ± 2.12		65.39 ± 2.15		241.93 ± 26.63	
	V8	1793.98 ±71.20		87.10 ± 3.40		206.64 ± 8.22		17.66 ± 2.58		64.98 ± 2.45		261.33 ± 42.85	

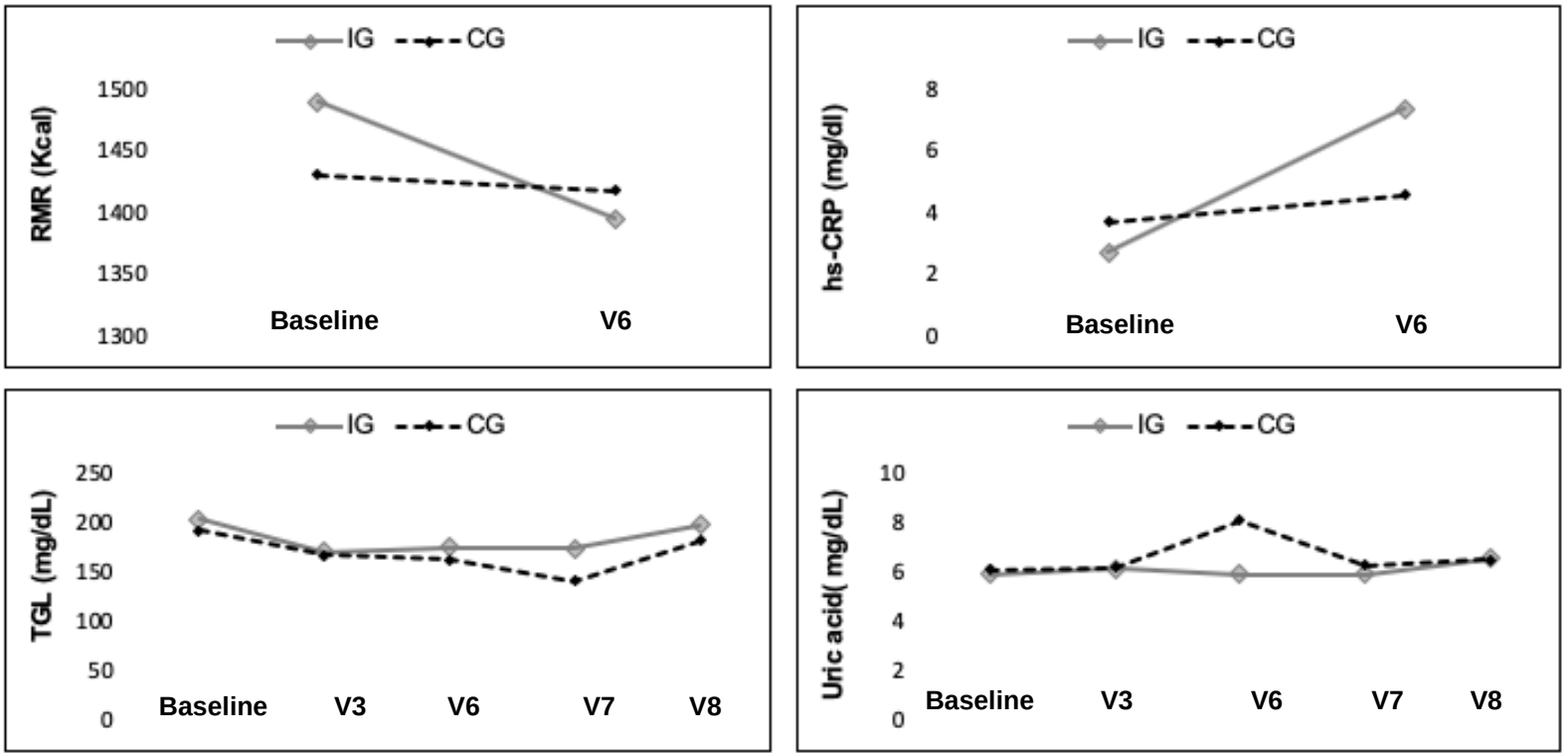
		SFA (g)	P value	MUFAs (g)	P value	PUFAs (g)	P value	TFA (g)	P value	w-3 (mg)	P value	w-6 (mg)	P value
	Baseline	20.63 ± 0.96		25.45 ± 1.35		15.87 ± 0.99		0.44 ± 0.14		1.61 ± 0.20		21.23 ± 10.24	
	V3	19.22 ± 1.01		23.68 ± 1.24		16.08 ± 0.92		0.36 ± 0.17		1.91 ± 0.25		27.46 ± 13.6	
IG	V6	20.24 ± 0.83		23.35 ± 0.94		14.86 ± 0.71		0.23 ± 0.06		1.56 ± 0.16		22.67 ± 7.05	
	A7	21.12 ± 1.16	0.796	21.9 ± 0.87	0.983	14.07 ± 0.72	0.188	0.29 ± 0.09	0.149	1.43 ± 0.14	0.477	26.38 ± 11.59	0.166
	V8	17.42 ± 2.18	0.671	19.93 ± 2.38	0.014	13.31 ± 1.77	0.100	0.09 ± 0.05	0.088	1.76 ± 0.16	0.361	24.52 ± 10.57	0.051
	Baseline	19.26 ± 1.22	0.427	24.25 ± 1.54	0.927	16.49 ± 0.86	0.825	0.17 ± 0.08	0.008	1.5 ± 0.12	0.122	12.20 ± 1.20	0.612
	V3	20.68 ± 1.06		23.07 ± 1.38		16.67 ± 1.45		0.35 ± 0.11		1.44 ± 0.09		14.59 ± 1.33	
CG	V6	20.45 ± 1.19		23.54 ± 1.44		16.04 ± 1.17		0.21 ± 0.06		1.76 ± 0.17		12.38 ± 1.95	
	V7	19.79 ± 0.92		22.05 ± 1.03		14.6 ± 0.83		0.59 ± 0.14		1.57 ± 0.14		13.28 ± 1.56	
	V8	19.62 ± 0.89		21.54 ± 1.31		16.16 ± 0.91		0.76 ± 0.27		1.49 ± 0.08		13.55 ± 1.38	

IG, intervention group; CG, control group; V3, three months visit, V6, six months visit, V7, nine months visit; V8, twelve months visit.
TEI, total energy intake; CHO, carbohydrates; TC, total cholesterol; SFA, saturated fatty acids, MUFAs, monounsaturated fatty acids; PUFAs, Polyunsaturated fatty acids, TFA, trans fatty acids; ω−3, omega-3 fatty acids; ω−6, omega-6 fatty acids. Order of *P value: group, time and group x time.*



Supplementary Figure 1 - Body mass Index (BMI) parameters: P (group): 0.536; P(time): <0.001; P(group x time): 0.959.

V1, one month visit; V2, two months visit; V3, three months visit, V4, four months visit; V5, five months visit; V6, six months visit, V7, nine months visit; V8, twelve months visit.



Supplementary Figure 2 - Metabolic parameters

RMR: P (group): 0.785; P(time): <0.320; P(group x time): 0.271; **Hs-CRP:** P (group): 0.246; P(time): 0.060; P(group x time): 0.589; **TGL:** P (group): 0.416; P(time): <0.001; P(group x time): 0.784; **Uric acid:** P (group): 0.506; P(time): 0.057; P(group x time): 0.895; V3, three months visit, V6, six months visit, V7, nine months visit; V8, twelve months visit.

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Capítulo 5

Considerações finais

Há essencialmente dois pontos a serem considerados a partir dos dados expostos nesta tese. O fato de que a literatura, em termos de intervenção dietética e ganho de peso em pacientes receptores de transplante renal, é realmente escassa e questionável, em função da metodologia com limitações e amostras pequenas [1-3]. E, em segundo lugar, o fato de que os resultados do ensaio clínico randomizado aqui apresentado, a partir de uma intervenção nutricional intensiva com base em dieta hiperproteica e de baixo índice glicêmico, não demonstraram ser efetivos no manejo terapêutico do ganho de peso após o transplante. Ainda, é importante salientar que a exposição dos indivíduos a uma dieta hiperproteica não representou qualquer risco do ponto de vista de segurança renal.

Portanto, propõe-se o desenvolvimento de novos ensaios clínicos que atuem de forma integrativa no manejo desta condição clínica, mas que considerem ainda, outras ferramentas complementares de tratamento, como por exemplo: tratamento nutricional em conjunto com terapia cognitivo comportamental [4-5], e possivelmente, o uso de fármacos antiobesidade adequados que otimizem o processo de emagrecimento destes pacientes parecem alternativas a serem consideradas [6].

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