Universidade Federal do Rio Grande do Sul
Faculdade de Medicina
Doutorado em Endocrinologia pelo Programa de Pós-graduação em Ciências Médicas: Endocrinologia

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Perfil glicêmico em pacientes com fibrose cística e intervenção nutricional na fase de pré-diabetes

Porto Alegre
2021

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CIP - Catalogação na Publicação

Eccel Prates Freiberg, Raquel
Perfil glicêmico em pacientes com fibrose cística e intervenção nutricional na fase de pré-diabetes / Raquel Eccel Prates Freiberg. -- 2021.
57 f.
Orientadora: Ticiana da Costa Rodrigues.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Porto Alegre, BR-RS, 2021.

1. diabetes. 2. fibrose cística. 3. dieta de baixo índice glicêmico. I. da Costa Rodrigues, Ticiana, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

FOLHA DE APROVAÇÃO

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Orientadora: Dra. Ticiana da Costa Rodrigues

Aprovada em: Porto Alegre,2 de fevereiro de 2021.

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DEDICATÓRIA

Dedico este trabalho ao meu marido, Victor, meu
grande incentivador, e à minha filha Martina,
motivo de todo meu esforço.

AGRADECIMENTOS

Gostaria de agradecer, primeiramente, à minha família, principalmente aos avós que destinaram seu tempo ajudando para que eu pudesse me dedicar aos estudos.

Ao meu marido que sempre possibilitou e incentivou que esse sonho acontecesse.

Aos meus colegas do grupo de pesquisa pelas trocas, sugestões e apoio nos momentos difíceis.

Aos professores pneumologistas do ambulatório de fibroce cística, pela oportunidade de realização de trabalho e compartilhamento de conhecimento.

À minha orientadora, que ao longo dos anos foi mais que uma professora, soube ver não só o conhecimento técnico, mas dificuldades emocionais que envolvem o trabalho do aluno.

Obrigada a todos.

RESUMO

A fibrose cística (FC) é uma doença genética autossômica recessiva. A patologia pulmonar é a característica central da FC, levando a várias consequências como a desnutrição e baixa massa óssea. O diabetes relacionado à fibrose cística (DRFC) é a comorbidade mais prevalente nestes pacientes e com alto índice de mortalidade. Objetivos: Avaliar o impacto das alterações glicêmicas no estado nutricional e declínio da função pulmonar de pacientes com FC que acompanham no Serviço de Pneumologia do Hospital de Clínicas de Porto Alegre (HCPA). Como segundo objetivo, avaliar a resposta glicêmica após aconselhamento nutricional atráves de uma dieta de baixo índice glicêmico em pacientes com pré-diabetes e FC. Métodos: esta defesa se divide em três capítulos: referencial téorico sobre o tema, um artigo de corte retrospectivo com todos os pacientes com FC em seguimento no HCPA, um segundo artigo realizado como um ensaio clínico randomizado (ECR). Resultados: No estudo retrospectivo, avaliamos um total de 175 pacientes, 59% apresentavam estado glicêmico alterado (classificados por qualquer alteração glicêmica). Estas alterações foram associadas com a piora da função pulmonar quando divididas pelos tercis da capacidade vital forçada (CVF) menor tercil <62%, status glicêmico alterado [n = 41 (71.9%); p = 0.03)], hemoglobina glicada (HbA1c) [n = 35 (68.6%); p = 0.01] DM [n = 13 (22.8%); p = 0.01]. Para a volume expiratório em 1 segundo (VEF1) menor tercil <56%, status glicêmico alterado [n = 37 (66.1%); p = 0.001] HbA1c [n = 31 (64.6%, p = 0.001)]. No ECR foram avaliados 22 pacientes, encontramos uma associação do maior consumo de fibras e melhor controle glicêmico no grupo que recebeu a intervenção (n=10) e isso foi associado com melhor função pulmonar nestes pacientes. VEF1% diferença (IC95%) pré e pós-intervenção -0,90(-4,05 a 2,25) p=0,57 e -5,18(-9,94 a -0,42) p=0,03 e CVF% (IC95%) -3,26(-7,80 a 1,28) p=0,15 e -6,2(10,2 a -2,21) p=0,002.
Conclusão: As alterações glicêmicas estão associadas à piora da função pulmonar, bem como ao baixo peso. Uma dieta de baixo índice glicêmico com maior consumo de fibras pode ter efeito no controle da glicemia e estar associada com melhores desfechos pulmonares.

Palavras-chave: diabetes relacionada a fibrose cística, desnutrição, intervenção nutricional.

ABSTRACT

Cystic fibrosis (CF) is an autosomal recessive genetic disease. Pulmonary pathology is the central feature of CF, leading to several consequences such as malnutrition and low bone mass. Diabetes related to cystic fibrosis (CFRD) is the most prevalent comorbidity in these patients and has a high mortality rate. Objectives: To assess the impact of glycemic changes on nutritional status and decline in lung function in CF patients who are followed up at the Pulmonology Service of Hospital de Clínicas de Porto Alegre (HCPA). As a second objective, to evaluate the glycemic response after nutritional counseling through a low glycemic index diet in patients with pre-diabetes and CF. Methods: this defense is divided into three chapters: theoretical framework on the topic, a retrospective article with all CF patients being followed up at HCPA, a second article carried out as a randomized clinical trial (RCT). Results: In the retrospective study, we evaluated a total of 175 patients, 59% had an altered glycemic status (classified by any glycemic alteration). These changes were associated with worsening lung function when divided by the tertiles of the forced vital capacity (FVC) lower tertile <62% altered glycemic status [n = 41 (71.9%); p = 0.03)], glycated hemoglobin (HbA1c) [n = 35 (68.6%); p = 0.01] DM [n = 13 (22.8%); p = 0.01]. For 1-second expiratory volume (FEV1) lower tertile <56%, altered glycemic status [n = 37 (66.1%); p = 0.001] HbA1c [n = 31 (64.6%, p = 0.001)]. In the RCT 22 patients were evaluated, we found an association of higher fiber consumption and better glycemic control in the group that received the intervention (n = 10) and this was associated with better lung function in these patients. FEV1% difference (95% CI) before and after intervention -0.90 (-4.05 to 2.25) p = 0.57 and -5.18 (-9.94 to -0.42) p = 0, 03 and FVC% (95% CI) -3.26 (-7.80 to 1.28) p = 0.15 and -6.2 (10.2 to -2.21) p = 0.002.
Conclusion: Glycemic changes are associated with worsening lung function, as well as with low weight. A low glycemic index diet with higher fiber consumption can have an effect on glycemic control and be associated with better pulmonary outcomes.

Keywords: diabetes related to cystic fibrosis, malnutrition, nutritional intervention.

SUMÁRIO

1 REFERENCIAL TEÓRICO

A fibrose cística (FC) é uma doença genética autossômica recessiva, afetando aproximadamente 1 a cada 2.500 nascidos vivos. Atualmente quase 70.000 pessoas vivem com FC no mundo (1). No Brasil, estima-se que a incidência de fibrose cística seja de 1 a cada 10 mil nascidos vivos segundo dados do Ministério da Saúde, porém, apresenta diferenças regionais, com valores mais elevados nos estados da região Sul (2). Segundo registro brasileiro de 2017 o país conta com 5.138 mil casos de FC (2). A doença surge de mutações na proteína do gene CFTR (gene regulador da condutância transmembrana da fibrose cística) que está localizado no braço longo do cromossomo 7 e é responsável pelo controle do canal de sódio e íons de cloreto nas membranas celulares (3). Se caracteriza pela presença de secreções mucosas espessas e pegajosas em vários órgãos produtores de mucina, sendo esta a base patogênica da doença.

A patologia pulmonar é a característica central da FC, mas vários outros órgãos são frequentemente acometidos como o sistema gastrointestinal, o pâncreas (exócrino e endócrino) e o sistema reprodutivo, levando a várias consequências da doença como a desnutrição e a baixa massa óssea, entre várias outras (4).

Desde a descoberta do gene CFTR em 1989, foram identificadas 2.000 variantes diferentes, das quais aproximadamente 440 são causadoras de doenças. As mutações do CFTR são categorizadas em 5 grupos, dependendo da quantidade de proteína presente na membrana da superfície celular e o grau de funcionalidade (5). Em termos gerais, as mutações de classe I estão associadas a fenótipos mais graves e classe V mutações com fenótipos mais suaves. A mutação delta F508 é responsável por aproximadamente 90% da prevalência de mutações CFTR causadoras de doenças em populações caucasianas e é caracterizado por uma deleção de fenilalanina na posição 508 (6) .

Nas últimas décadas os avanços no diagnóstico e as estratégias terapêuticas desenvolvidas têm elevado a expectativa de vida da doença que nos anos 60 não passavam de apenas 4 anos de idade (7). Dados *Cystic Fibrosis Foundation Patient Registry* de 2019 mostram que a idade mediana de sobrevida atual é de 39,6 anos(8). O aumento da longevidade na FC resultou em uma maior proporção de problemas médicos relacionados com a idade e com a progressão da doença, modificando as necessidades na assistência da saúde destes pacientes.

1.1 ASPECTOS NUTRICIONAIS E RECOMENDAÇÕES

Deficiências nutricionais na FC constituem um dos mais graves e difíceis desafios do tratamento (9). A má absorção dos nutrientes é predominantemente ocasionada pela disfunção pré-epitelial e decorre da rejeição de nutrientes não hidrolisados no lúmen intestinal pela insuficiente secreção pancreática (10). A piora no estado nutricional pode manifestar-se por diversas formas, entre as quais as mais comuns são: parada do crescimento, emagrecimento acentuado, deficiências nutricionais específicas, puberdade retardada e grande comprometimento da função pulmonar (11).

A meta do tratamento nutricional é alcançar o peso ideal para a altura, aumentar e equilibrar a ingestão energética, reduzir a má absorção e a má digestão e controlar a ingestão de vitaminas e minerais (12). Para tanto, o cuidado nutricional adequado deve incluir: terapia de reposição enzimática, dietas hiperenergéticas e hiperlipídicas, bem como a suplementação de micronutrientes (13). O tratamento nutricional deverá ser estabelecido após a avaliação antropométrica para avaliação do estado nutricional do paciente e de hábitos alimentares através de registros e recordatórios alimentar realizada por nutricionista experiente no acompanhamento e tratamento destes pacientes (2).

Com relação às necessidades energéticas, para compensar as carências comuns aos pacientes com fibrose cística, o tratamento nutricional deve incluir uma recomendação de ingestão que atinja 120% a 150% das necessidades diárias recomendadas (RDA) para energia (14). Em relação aos macronutrientes, a recomendação de lipídeos deve corresponder a 40% da distribuição diária do valor energético total (VET), enquanto as proteínas devem suprir 20% e os carboidratos em torno de 40% a 50% do VET (15). A suplementação de vitaminas e minerais faz parte da terapia nutricional. As vitaminas hidrossolúveis são bem absorvidas nos pacientes com FC, já as lipossolúveis não, devido à má absorção de gorduras (16). Estes pacientes estão mais suscetíveis a deficiências de vitaminas liposolúveis A e D, tendo uma recomendação de suplementação de 4.000 a 10.000UI diárias para vitamina A e de 400 a 2000UI para vitamina D (16)(17). A intervenção nutricional deve ser a princípio com alimentos de alta densidade calórica. Entretanto, existem pacientes que, mesmo com o uso destes alimentos e da reposição enzimática correta, não conseguem manter um bom estado nutricional. Nestes casos, é necessária a introdução de suplementos energéticos administrados por via oral, enteral ou mesmo por ostomia(18).

Em relação ao impacto da intervenção nutricional precoce em pacientes com DRFC os estudos ainda são limitados (19)(20). O uso de nutrição enteral de baixo índice glicêmico (IG)

através de fórmulas tem demonstrado efeito na melhora da homeostase glicêmica (21). Em pacientes com DM 2 ou em outras formas do diabetes, dietas com baixo IG apresentam grande potencial no controle da glicemia e fazem parte das recomendações nutricionais (22). Em uma revisão sistemática em 2012, foi encontrado apenas dois estudos que avaliaram os efeitos do baixo IG da dieta no controle da glicemia e qualidade de vida em pacientes com FC (23). Recentemente um ensaio clínico randomizado associou o uso de dietas de baixo IG em crianças e adolescentes com melhora da glicemia e desfecho pulmonar (24).

1.2 DIABETES RELACIONADA À FIBROSE CÍSTICA

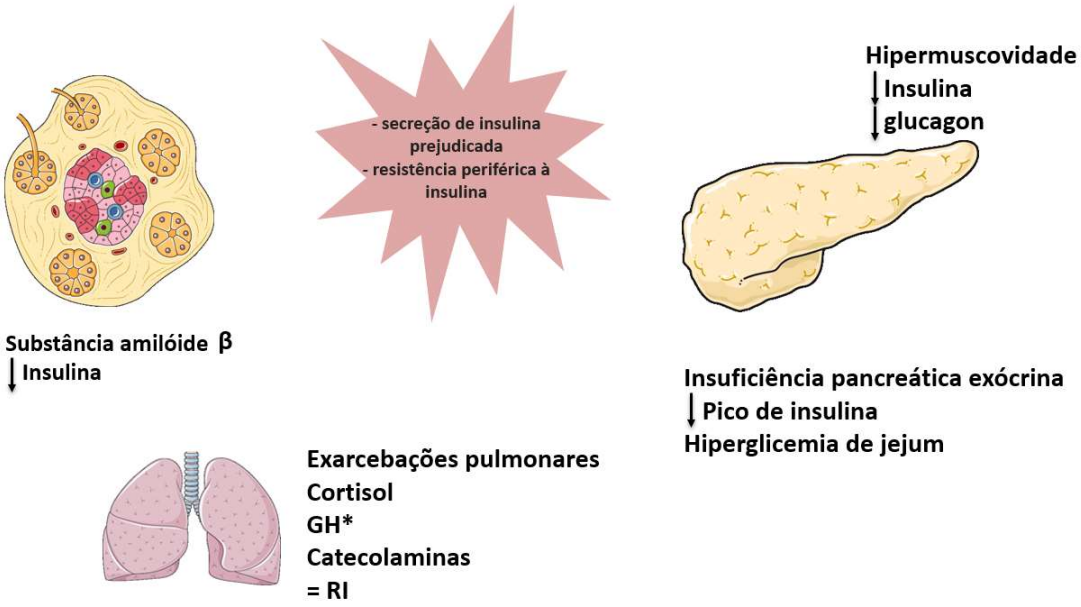
O diabetes relacionado à FC (DRFC) é a comorbidade mais comum desenvolvida pelos pacientes com FC, acometendo cerca de 35-40% dos pacientes adultos com FC (25)(2). Sua patogênese está associada à fibrose e à destruição pancreática, sendo mais frequente em indivíduos que apresentam insuficiência pancreática exócrina (26).

O DRFC está associado à diminuição da função pulmonar causada em parte pelo aumento da colonização dos pulmões por bactérias como *Pseudomonas aeruginosa* e *Staphylococcus aureus*. Pacientes com DRFC demonstraram ter até o dobro das exacerbações pulmonares em comparação com pacientes sem diabetes e FC(8).

Níveis elevados de glicose induzem acidificação líquida da superfície das vias aéreas nos deficientes em CFTR. Isso resulta em um aumento na produção de lactato e é ainda mais exacerbado pela colonização por P. aeruginosa (27).

O DRFC compartilha características clínicas do diabetes melito tipo 1 e tipo 2 (DM1 e DM2, respectivamente), mas é considerada uma classificação distinta de diabetes. Consistente com DM1, os pacientes são deficientes em insulina, magros e adolescentes ou adultos jovens no momento do diagnóstico; no entanto, DRFC não é uma condição auto-imune. Apresenta modesta resistência à ação da insulina, o que é comum ao DM2 (25).

Figura 1 - Fisiopatologia do DRFC



Nota: GH hormônio do crescimento. RI: resistência a insulina.

Fonte: Elaborada pela autora

Os distúrbios da glicose em pacientes com FC geralmente se iniciam com uma hiperglicemia pós-prandial, seguida por intolerância à glicose oral sem hiperglicemia em jejum e, finalmente, diabetes com hiperglicemia em jejum, tanto que se utiliza estas classificações na FC (28). A deficiência de insulina e a hiperglicemia resultantes, pioram o estado nutricional destes pacientes. Há uma perda de massa magra corporal devido ao estado catabólico causado pela deficiência de insulina, o que leva a um consumo de gordura e proteínas e afeta também a função pulmonar (12). A deficiência de insulina promove uma deterioração clínica nessa população e não somente um metabolismo anormal da glicose (29). A terapia com insulina nestes pacientes parece estar associada a melhora do estado nutricional e consequente função pulmonar e diminuição de mortalidade (30), contudo, não existe consenso de qual melhor momento para iniciar o uso de insulina.

A *American Diabetes Association* recomenda o controle glicêmico por meio da coleta de glicemia ao acaso, principalmente após as refeições, glicemia de jejum e complementação com o teste de tolerância oral à glicose (TTOG) (14).

A triagem sistemática para o DRFC é recomendada principalmente após os 10 anos de idade(2) . Os valores de diagnóstico são: para hemoglobina glicada (HbA1c) ≥6,5%, glicemia de jejum ≥ 126 mg/dL, TTG ≥200mg/dL em 120 minutos ou glicemia ao acaso ≥200mg/dL (14).

A hiperglicemia de jejum pode estar presente o tempo todo (DRFC crônica) ou somente em situações de descompensação aguda (DRFC intermitente), como em infecções e exacerbação pulmonar, ocasionando flutuações glicêmicas (31).

Tabela 1 - Valores de referência para diagnóstico do DRFC

TESTE	GLICOSE	DIAGNÓSTICO	CONDUTA
Glicemia capilar ao acaso (qualquer horário)	<200mg/dL	Inespecífico	TTOG anual a partir dos 10 anos ou se sintomas
	≥200mg/dL	Risco DRFC	TTOG
Glicemia de jejum	<100mg/dL	Normal	TTOG anual a partir dos 10 anos ou se sintomas
	100-125mg/dL	Gliemia de jejum alterada	TTOG
	≥126mg/dL	DRFC	Insulina
TTOG	120min. < 140md/dL	Normal	TTOG anual a partir dos 10 anos ou se sintomas
	120min. 140-199mg/dL	Intolerância a glicose	TTOG anual a partir dos 10 anos ou se sintomas
	Tempos intermediários (30, 60,90) >200mg/dL	Glicemia indeterminada (risco para DRFC)	TTOG anual a partir dos 10 anos ou se sintomas
	120min. ≥140mg/dL	DRFC	Insulinoterapia

Fonte: Adaptada de *Cystic Fibrosis Foundation* 2015

1.3 TRATAMENTO DO DIABETES RELACIONADA À FIBROSE CÍSTICA

A terapia com insulina é o tratamento mais comumente usado para DRFC. Estudos demonstram que os pacientes com FC se beneficiam do tratamento com insulina, para manutenção de peso e com melhores desfechos pulmonares e mortalidade (32)(33). Porém não há resultados consistentes que o tratamento também deve ser feito para aqueles com outras desordens glicêmicas. Sabe-se do efeito negativo da fase pré-diabética e da piora na função pulmonar nesses pacientes, por isso sugere-se o início precoce da insulina devido seus efeitos anabólicos(34). Entretanto, o momento preciso não está completamente definido.

As diretrizes da *Cystic Fibrosis Foundation* (CFF) recomendam a insulina como o tratamento de escolha, com base em evidências apoiadas pela observação de tendências crescentes de deficiência de insulina ao longo do tempo de evolução da doença (35). Porém sabe-se que a deficiência de insulina raramente é absoluta, pois a cetoacidose é uma complicação muito incomum na FC(36). O aumento da resistência à insulina foi ainda correlacionado ao desenvolvimento progressivo de tolerância à glicose diminuída observada na

FC(37). A implicação de uma diminuição relativa na liberação de insulina pancreática e um aumento na resistência à insulina ao metabolismo da glicose pelo corpo sugerem papéis potenciais para medicamentos hipoglicêmicos de liberação de insulina oral e as classes mais novas de medicamentos injetáveis e sensibilizantes à insulina orais (38).

Ensaios clínicos demonstram que o uso de pelo 0,5UI de insulina de ação rápida tem efeitos no aumento do IMC e melhora no declínio da função pulomonar (30)(39). Porém ainda não é conclusivo os efeitos da insulina antes da detecção do diabetes em pacientes com FC.

2 JUSTIFICATIVA

Devido ao escasso número de evidências que suportem o uso da dieta de baixo índice glicêmico na resposta glicêmica e outros desfechos em pacientes com FC, se torna necessário mais estudos consistentes e bem delineados que possam embasar o manejo dietético nestes pacientes.

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CAPÍTULO I - ARTIGO 1

Artigo formatado de acordo com as normas da Revista Jornal Brasileiro de Pneumologia

Impact of glycemic alteration and nutritional status on lung function in patients with cystic fibrosis

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Funding Sources

This work was funded by the Conselho Nacional de Desenvolvimento Científico e tecnológico (CNPq), Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre (FIPE) and CAPES-PROEX. Rodrigues TC is recipient of PQ scholarship from CNPq and Freiberg RE was recipient of scholarship from CAPES.

Abstract

Introduction: Optimization of glycemic control is known to improve clinical status and lung function in patients with CFRD as well as reduce mortality. Objectives: To evaluate the impact of glycemic changes on the nutritional status and decline in lung function of CF patients. Methods: This was a retrospective cohort study of CF patients that used spirometry, blood glucose, and anthropometric data. Results: We evaluated a total of 175 patients, 59% had an altered glycemic status. Changes in glycemia were more prevalent in the first tertiles of lung function for FVC (tertile <62%), altered glycemic status [n = 41 (71.9%); p = 0.03)], alterations in glycated hemoglobin levels [n = 35 (68.6%); p = 0.01] and diagnosis of DM [n = 13 (22.8%); p = 0.01]. As for FEV1 (tertile <56%), altered glycemic status [n = 37 (66.1%); p = 0.001] and altered glycated hemoglobin values [n = 31 (64.6%, p = 0.001)] were significantly correlated, and diagnosis of DM [n = 10 (17.9%); p = 0.44] was not significant. Conclusion: Increased blood glucose levels are related to worse pulmonary outcomes as well as low weight.

Key words: diabetes, cystic fibrosis, glycemic change, underweight

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disease characterized by great phenotypic variability (1). It ranges from mild forms with later diagnosis to severe forms with repercussions in multiple organs from the early stages of life. The main clinical manifestations are respiratory, which are responsible for 90% of the morbidity and mortality of CF (1) (2). CF survival has increased significantly in the last 30 years due to therapeutic advances (3) that include periodic assessment of pulmonary function, early detection of changes in the airways, and appropriate treatment methods (4).

With greater longevity, other complications arise, such as the alteration of carbohydrate metabolism in the form of glucose intolerance, which evolves to diabetes that is related to cystic fibrosis (CFRD) (5). Approximately 20% of adolescents and up to 40% of adults develop CFRD (6). The presence of glycemic alterations worsens nutrition and lung function, even in the pre-diabetes stage (7). The pathophysiology of CFRD is complex and includes the loss of pancreatic islet cells, leading to insulin and glucagon deficiencies associated with fluctuations in insulin resistance due to chronic inflammation and infection (7)(8). CFRD is typically diagnosed in late adolescence or early adulthood (9). Thus, every patient with CF over 10 years of age must annually undergo the oral glucose tolerance test (OGTT), with fasting blood glucose collection 8 h and 2 h after ingesting 75 g of glucose (10)(11).

The combination of diabetes and CF worsens clinical outcomes when compared to patients with CF and diabetes alone (12). Optimization of glycemic control is known to improve clinical status, lung function, and reduce mortality (4). Insulin therapy is the proposed treatment for CFRD, but its role in pre-diabetes is quite controversial, and there is disagreement about the ideal time to start it in these situations (13)(14). High caloric intake is recognized as a necessary therapy for nutritional treatment of CF due to increased energy expenditure, malabsorption, risk

of malnutrition, and abnormalities of the digestive tract and liver disease (15). Maintaining a good nutritional and glycemic balance, as well as improving clinical performance in order to increase the survival of CF patients is a major challenge in any CF treatment center.

The aim of this study was to evaluate the impact of glycemic changes on the nutritional status and decline in lung function of CF patients treated at a referral center for the treatment of CF in southern Brazil.

METHODS

Study population

This is a retrospective cohort study in which data were collected from CF patients treated at the Adult and Pediatric Cystic Fibrosis Outpatient Clinic of Hospital de Clínicas de Porto Alegre (Reference Center for the Treatment of Disease in southern Brazil, HCPA) during the period from 2015 to 2019. All patients diagnosed with CF, as confirmed by sweat chlorine levels >60 mEq/L and/or genetic testing confirming two CF-causing mutations aged >4 years, were included. The study protocol was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre (no. 160206).

Clinical evaluation

Laboratory data were collected during the patients' annual check-ups, such as their fasting glucose, glycated hemoglobin (HbA1c), oral glucose tolerance test (at 0 and 2 hours) (OGTT), and serum C-reactive protein (CRP) levels, as well as their spirometry lung function data related to these laboratory tests.

Spirometry was routinely performed at the Pulmonary Physiology Unit of HCPA using a computerized spirometer (Jaeger-v 4.31; Würzburg, Germany) according to the Pulmonary Function Testing Guidelines of the Brazilian Society of Pulmonology and Phthisiology (16).

Both forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were included for analysis and are presented as percentages of the predicted values.

Diagnostic criteria for glycemic status

Patients were classified according to their glycemic status according to the any of the following blood glucose values: Altered — Hb1Ac values between 5.7%–6.4%, or fasting glucose level between 100–125 mg/dl, or OGTT between 140–199 mg/dl after 2 hours of overload of 75 g of glucose. Diabetes — patients with HbA1c values greater than or equal to 6.5%, or fasting glucose greater than or equal to 126 mg/dl, or OGTT greater than or equal to 200 mg/dl in 2 hours at more than one moment, or patients with established diseases (diagnosis) that are receiving insulin treatment (10).

Nutritional assessment

The anthropometric data collected were as follows: weight (kg), measured without shoes and with minimal clothing on a platform-type anthropometric scale (Filizola, São Paulo, Brazil), and height (cm), measured with a stadiometer attached to the scale, with the head position adjusted. BMI (body mass index), were calculated using their weight divided by their height squared, per the criteria of the ESPEN reference values for patients with CF (17). Pediatric patients with a low BMI were considered to have a BMI value below -2 standard deviations of the z-score, and adults were considered to have a low weight when their BMI was ≤ 22 kg/m^2 for women and ≤ 23 kg/m^2 for men.

Statistical analysis

The data were presented as absolute and relative frequencies (n [%]), along with the means, standard deviations (mean ± SD), or median and interquartile ranges, according to the

distribution of the variable. Pearson or Spearman correlation coefficients were used to describe the correlation between the glycemic parameters, lung function, and other variables. A Chi-square test was used to stratify the lung function tertiles associated with blood glucose values as well as lung function and low weight. A generalized linear model (GLM) with a gamma regression was used for the multiple comparisons, and the Tukey test was used for the post-hoc analysis. All analyses were performed using SPSS Statistics 18.0 (SPSS Inc., Chicago, IL).

RESULTS

A total of 175 CF patients were analyzed; Table 1 describes the baseline characteristics of all patients in the sample. The mean age was 22.1 ± 9.9 years, with 62.3% (n = 109) being female patients. Regarding nutritional status, 10.7% (n = 6) of children and 49.5% (n = 86) of adults were classified as underweight. The mean fasting glucose was 91 mg/dL (IIQ 84–102 mg/dL); 13.1% (n = 23) of the patients had a diagnosis of DM and 59.4% (n = 104) had altered glycemic status. The mean pulmonary function as a percentage of the predicted value was FVC 70.5% ± 17.4% and FEV1 63.9% ± 20.8%. A total of 60.4% (99 of 110) of the patients had a genotype with the F5 delta allele 08, and 56.9% (n = 99) had bacterial colonization by *Pseudomonas aeruginosa*.

We found a negative correlation of lung function (translated using FEV1% values) with age and fasting blood glucose levels (r = -0.223, p = 0.003; and -0.152, p = 0.045, respectively). FVC was negatively correlated with fasting blood glucose (r = -0.177, p = 0.019) and glycated hemoglobin (r = -0.179, p = 0.027); FEV1% was positively correlated (r = 0.280, p = 0.036; r = 0.210, p = 0.022) with BMI values in children and adults, respectively (Table 2).

We stratified lung function in tertiles and observed an association between lower tertiles (worse lung function) and higher blood glucose levels. The first tertile for FVC was considered <62%, the second tertile was between 62-78% and the third tertile was >78%. For FEV1, the

first tertile was considered <56%, the second tertile was between 56-75% and the third tertile was >75%. Changes in glycemia were more prevalent in the first tertiles of lung function for FVC (tertile <62%), altered glycemic status [n = 41 (71.9%); p = 0.03)], alterations in glycated hemoglobin levels [n = 35 (68.6%); p = 0.01] and diagnosis of DM [n = 13 (22.8%); p = 0.01]. As for FEV1 (tertile <56%), altered glycemic status [n = 37 (66.1%); p = 0.001] and altered glycated hemoglobin values [n = 31 (64.6%, p = 0.001)] were significantly associated, and diagnosis of DM [n = 10 (17.9%); p = 0.44] was not significant. (Tables 3 and 4).

We performed multiple regression analyses using FVC and FEV1% as dependent variables and adjusted for co-factors, the results of which are shown in Table 5. There was an association between FEV1 in the lowest tertile (<75%) with altered glycemic status even after adjusting for age, sex, and low weight [1.52 (95% CI 1.19–1.93); p = 0.001] and the same was seen for FVC in the lowest tertile (<78%) with the same adjustments [1.25 (95% CI 1.02–1.55) p = 0.03]. FVC was also associated with DM even after all adjustments [1.33 (95% CI 1.11–1.59); p = 0.002].

Figure 1 shows the association of low weight with the CVF% tertiles; 24.6% of patients with low weight were surveyed in the lowest tertile (<62%, p = 0.014) and 26.8% were in the FEV1% tertile (<56%, p = 0.010), as shown in Figure 2. Figures 3 and 4 illustrate the patients' glycemic status and lung function, showing 71.9% with altered glycemic status and altered in the lowest FVC tertile (<62%), and 66.1% without lower tertile of FEV1 (<56%).

DISCUSSION

Our study found an association between changes in blood glucose level, both for fasting glucose and after 2 hours, and worsening lung function. These associations remained independent even after adjusting for other variables that have a negative relationship with declines in lung function, such as age and sex. The patients defined as having altered glycemic

status were in the worst FEV1% and FVC% tertiles, and this was also observed for patients with low weight.

Studies that evaluate glucose metabolism and lung function have shown that patients with pre-diabetes and diabetes have worse pulmonary outcomes and a higher risk of mortality (18)(3). Patients with HbA1c ≥8.0% have a 2.4 times greater risk of pulmonary impairments than those with HbA1c ≥6.9%, even after adjustments (18). According to our results, patients with HbA1c ≥6.7% were in the worst tertiles of lung function. Chan et al. evaluated multiple blood glucose measurements through continuous glucose monitoring and monitoring of the declines in FEV1% and FVC%; the worsening measures were correlated with the same glucose maximums of >200 mg/dL/day (8).

CF patients are at an increased risk of developing sarcopenia, which is related to a worse disease prognosis and worsening lung function (19). In our results, we found an association between low weight (BMI and z-scores) with worse pulmonary function values. Pereira et al. found a strong association between predicted FEV1% and BMI ($R= 0.59$, $p = 0.001$), the decrease of 1.0 point in the BMI among patients showed a decrease of 11% in the predicted FEV1% (20).

Our comparative and retrospective data did not allow us to assess the glucose behavior of these patients over time, since glycemic fluctuation is a characteristic of CF patients. To assess nutritional status, we used weight and height as the basis, which is the fastest and easiest method available at our service center. However, for a better assessment of body composition and to determine associations with pulmonary outcomes, it would be more appropriate to use fat percentage and lean mass data.

Our findings agree with those already identified in the literature; increased blood glucose levels are related to worse pulmonary outcomes as well as low weight, therefore, our

results reinforce the impact of glycemic control in FC patients. More studies are needed evaluating the best moment and how to treat these patients to change outcomes and life time.

Table 1. Clinical and nutritional characteristics of the sample

Variables	**n=175**
Age (years)	22.1 (± 9.9)
Female patients - n (%)	109 (62.3)
Adults – BMI (kg/m²) (n=119; 68%)	21.4 (± 2.8)
Children (z-score BMI) (n=56; 32%)	-0.48 ± 1.23
Underweight n (%)	28 (16.0)
Children	6 (10.7)
Adults	86 (49.1)
Fasting blood glucose mg/dl	91 (84-102)*
Glycated hemoglobin % (n=153)	6,1 (± 1.3)
Glycemic status changed n (%)	104 (59.4%)
Diabetes - n (%)	23 (13.1%)
FEV1 (%)	63.9 (± 20.8)
FEV1 (L)	2.04 (± 1.00)
FVC (%)	70.5 (± 17.4)
FVC (L)	2.70 (± 1.12)
Chronic bacterial infection - n (%)**	
Pseudomonas aeruginosa	99 (56.9)
Staphylococcus aureus	71 (40.8)
Achromobacter	12 (6.9)
Genotype with an allele ΔF508 n=110 n (%)	99 (60.4)

BMI, body mass index; FEV1, forced expiratory volume in the first minute; FVC, forced vital capacity; glycemic status: any value changed to fasting glucose (> or equal to 100 mg/dl), HbA1c (greater than or equal to 5.7%) or oral glucose tolerance test (2h after greater than 140 mg/dl). Analyses are expressed as means ± SD and *interquartile ranges. **Multiple answer question.

Table 2. Correlations between sample characteristics and lung function

Variables	FEV1 (%)		FVC (%)	
	r	p	r	p
Age	-0.223	**0.003**	-0.064	0.399
BMI z-score	0.280	**0.036**	0.218	0.106
BMI	0.210	**0.022**	0.178	**0.053**
Fasting blood glucose*	-0.152	**0.045**	-0.177	**0.019**
Glycated hemoglobin	-0.109	0.178	-0.179	**0.027**

BMI: body mass index. FEV1, forced expiratory volume in the first minute; FVC, forced vital capacity. *Spearman's correlation coefficient

Table 3. Stratification by the means of the FVC tertiles and the changes in blood glucose

Variables	CVF% Tertiles			p
	<62 n (%)	62-78 n (%)	>78 n (%)	
Glycemic status change				**0.037**
Change	41 (71.9)*	37 (57.8)	26 (48.1)	
Glycated hemoglobin change				**0.010**
Yes	35 (68.6)*	31 (56.4)	18 (38.3)	
Fasting blood glucose change				**0.034**
Yes	19 (33.3)	22 (34.4)	8 (14.8)	
Diabetes diagnosis				**0.012**
Yes	13 (22.8)*	8 (12.5)	2 (3.7)	

Note: *Statistically significant association based on the residual test adjusted to a 5% significance level. Glucose status: any value changed to fasting glucose, HbA1c, or oral glucose tolerance test. FVC, forced vital capacity.

Table 4. Stratification by the means of the FEV1 tertiles and the changes in blood glucose

Variables	VEF1% Tertiles			p
	<56 n (%)	56-75 n (%)	>75 n (%)	
Glycemic status change				**0.001**
Change	37 (66.1)	45 (71.4)*	22 (39.3)	
Glycated hemoglobin change				**0.001**
Yes	31 (64.6)	37 (66.1)*	16 (32.7)	
Fasting blood glucose change				**0.014**
Yes	17 (30.4)	24 (38.1)*	8 (14.3)	
Diabetes diagnosis				0.448
Yes	10 (17.9)	7 (11.1)	6 (10.7)	

Note: *statistically significant association based on testing the residues, adjusted to a 5% significance level. Glucose status: any value changed to fasting glucose, HbA1c, or oral glucose tolerance test. FEV1, forced expiratory volume in the first minute.

Table 5. Lung function regression analysis with glycemic changes*

Variables	FEV1 <75 %		FVC <78%	
	PR (CI 95%)	p	PR (CI 95%)	p
Glycemic status change (dysglycemia)				
Model 1 – without adjustment	1.51 (1.19 – 1.93)	**0.001**	1.24 (0.99 – 1.54)	**0.055**
Model 2 – adjusted for age and sex	1.51 (1.18 – 1.93)	**0.001**	1.25 (1.01 – 1.55)	0.045
Model 3 –adjusted for model 2 and underweight	1.52 (1.19 – 1.93)	**0.001**	1.25 (1.02 – 1.55)	0.036
Diabetes + glycemic status change				
Model 1 – without adjustment	1.14 (0.92 – 1.40)	0.236	1.15 (0,94 - 1,41)	0.163
Model 2 – adjusted for age and sex	1.14 (0.93 – 1.41)	0.210	1.14 (0,94 - 1,40)	0.187
Model 3 – adjusted for model 2 and underweight	1.12 (0.91 – 1.38)	0.277	1.12 (0,92 - 1,36)	0.270
Diabetes				
Model 1 – without adjustment	1.10 (0.84 – 1.44)	0.478	1.39 (1,17 - 1,65)	**<0.001**
Model 2 – adjusted for age and sex	1.11 (0.84 – 1.46)	0.460	1.36 (1,14 - 1,62)	0.001
Model 3 – adjusted for model 2 and underweight	1.09 (0.83 – 1.43)	0.560	1.33 (1,11 - 1,59)	0.002
Underweight				
Model 1 – without adjustment	1.26 (1.02 – 1.55)	**0.032**	1.30 (1.07 – 1.57)	0.007
Model 2 – adjusted for age and sex	1.28 (1.03 – 1.57)	**0.024**	1.33 (1.10 – 1.60)	0.003
Model 3 – adjusted for model 2 and glycemic status change	1.10 (0.81 – 1.48)	0.555	1.27 (0.99 – 1.64)	0.063

Note: *Poisson univariate regression. FEV1, forced expiratory volume in the first minute; FVC, forced vital capacity; DM, diabetes mellitus; PR, prevalence ratio; CI, confidence interval.

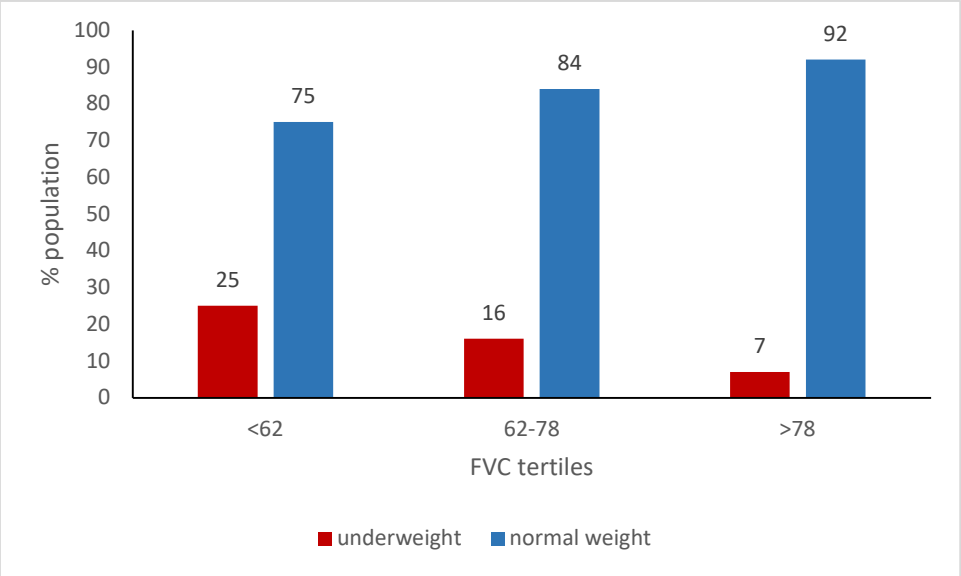

Figure 1. Association of low weight with FVC tertiles (linear trend chi-square: p = 0.014)

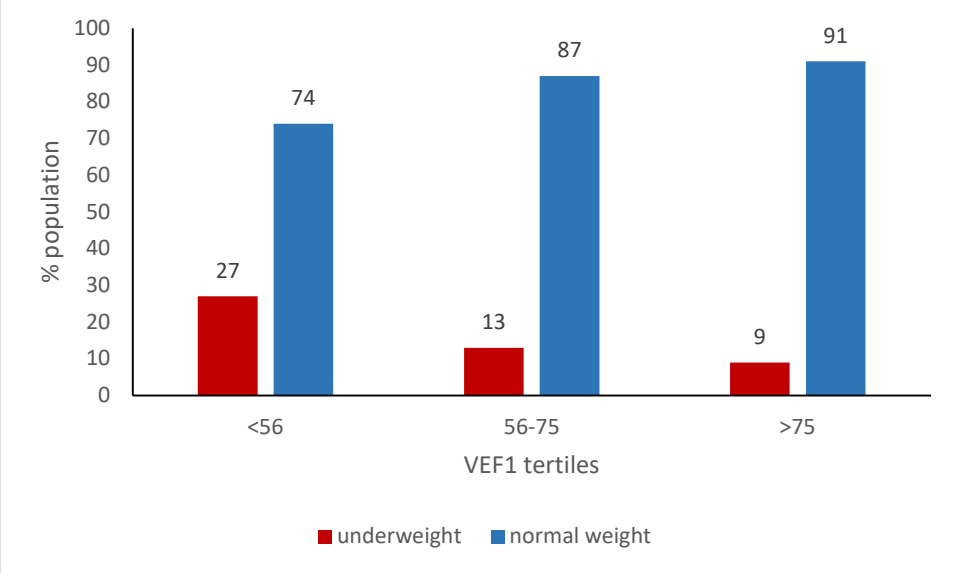

Figure 2. Association of low weight with FEV1 tertiles (linear trend chi-square: p = 0.010)

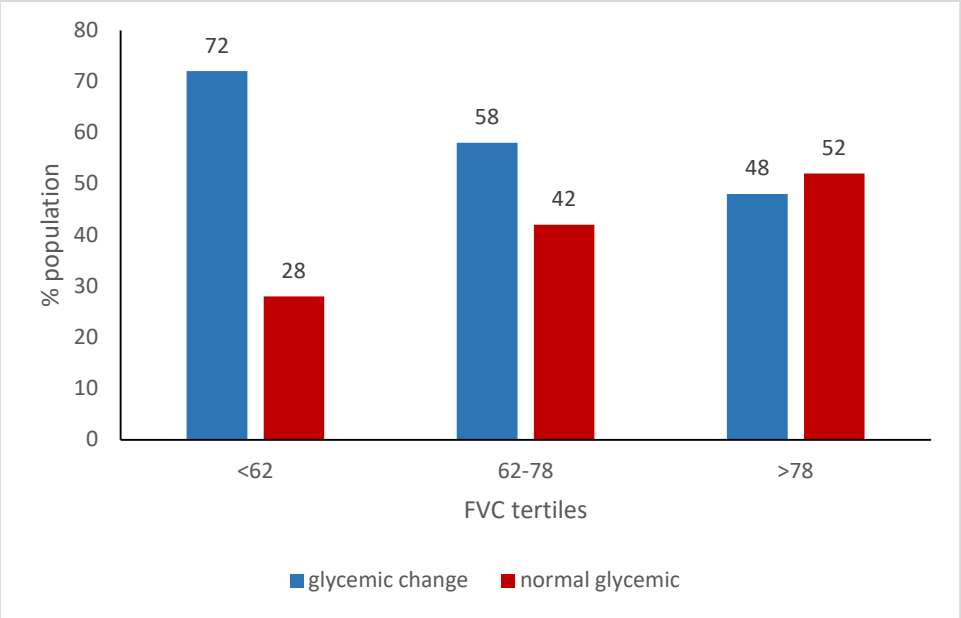

Figure 3. Association of glycemic status with CVF tertiles (linear trend chi-square: p = 0.011)

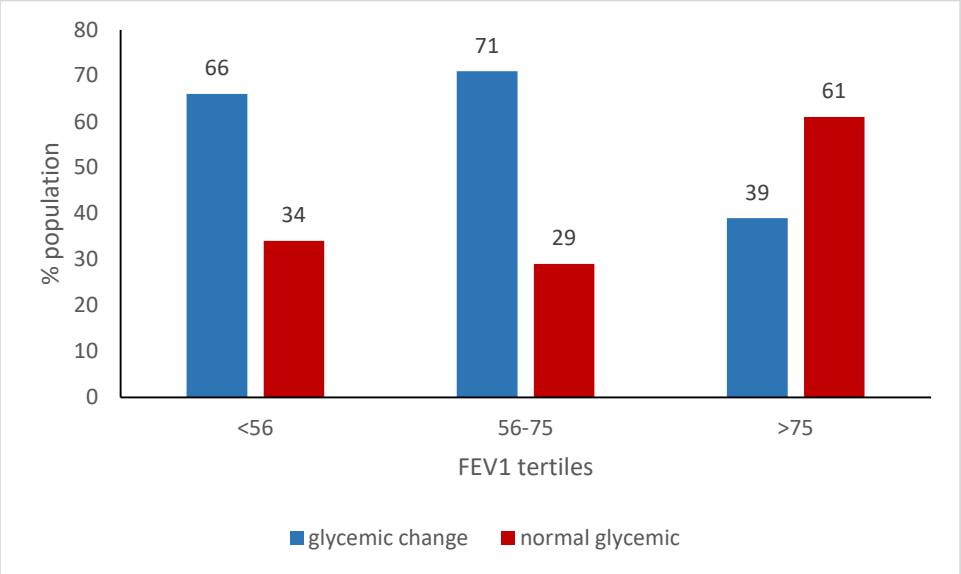

Figure 4. Association of glycemic status with VEF1 tertiles (linear trend chi-square: p = 0.004)

Author contributions

Design and planning of the study: REPF and TCR. Collection, analysis, and interpretation of the data: REPF and TCR. Preparation and/or review of the study: REPF, EP, PM, and TCR. Approval of the final version: REPF, EP, PM, and TCR. Public responsibility for the content of the article: REPF, EP, PM, and TCR.

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CAPÍTULO II - ARTIGO 2

Artigo formatado de acordo com as normas da Revista Journal of Cystic Fibrosis

A LOW-GLYCEMIC INDEX DIET IMPROVES GLYCEMIA IN PATIENTS WITH CYSTIC FIBROSIS IN THE PRE-DIABETIC PHASE: A RANDOMIZED CLINICAL TRIAL

A LOW-GLYCEMIC INDEX DIET IMPROVES GLYCEMIA IN PATIENTS WITH CYSTIC FIBROSIS

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Design and planning of the study:

REF, TCR. Collection, analysis, and interpretation of the data: REF, TCR. Preparation or review of the study: REF, EP, PM, TCR. Approval of the final version: REF, EP, PM, TCR. Public responsibility for the content of the article: REF, EP, PM, TCR

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ABSTRACT

Approximately 40% of cystic fibrosis (CF) adult patients develop CF-related diabetes (CFRD) which is associated associated with pulmonary function decline and increased mortality.. We assessed the glycemic response after nutritional counselling in favour of a low glycemic index diet in patients with CF in the pre-diabetic phase and evaluated the nutritional and pulmonary outcomes. **Methods**: We conducted a randomized clinical trial in CF adult patients with abnormal glucose tolerance using nutritional intervention for 12 weeks and evaluate glycemic, nutritional and pulmonary outcomes **Results**: Ten patients were included in the intervention group and 11 patients in the control group. The intervention group consumed more fibre [0.97g (95 % CI: 0.61 to 1.34) $p < 0.001$] and showed significant improvements in fasting glucose levels [-4.00 mg/dl (-7.49 to -0.510), $p = 0.025$], 2-hour glycaemic response in oral tolerance glucose test [-19.9 mg/dL (95 % CI: -33.6 to - 6.16) $p = 0.005$], and HbA1c levels [-0.34 % (95 % CI: -0.43 to -0.25). **Conclusion**: A diet with a low-glycemic nutritional index seems to have a positive effect on the glycemic status in CF patients in a pre-diabetic phase.

Keywords: cystic fibrosis, diet under glycaemic index, diabetes related to cystic fibrosis

Declarations of interest: none.

1 INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive, chronic, and progressive genetic disease [1]. It presents as an accumulation of thick mucus secretion that obstructs the ducts of exocrine glands, leading to the appearance of three basic characteristics: chronic obstructive pulmonary disease, high levels of electrolytes in sweat, pancreatic insufficiency with poor digestion/malabsorption, and consequent malnutrition. Respiratory and liver complications are the main causes of CF-related mortality and morbidity [2].

Nutritional deficiencies in patients with CF is one of the most serious and difficult treatment challenges. The goals of nutritional treatment are to attain the ideal weight for height, increase and balance the energy intake, reduce malabsorption and poor digestion, and control the intake of vitamins and minerals [3]. For this, adequate nutritional care must include enzyme replacement therapy, hyperenergetic and hyperlipidic diets, and micronutrient supplementation [4].

About 40% of adult patients develop CF-related diabetes (CFRD) that is associated with losses of lung function and increased mortality. Active systematic screening for the presence of CFRD is recommended mainly after 10 years of age in patients with CF [5]. Nutritional recommendations for CFRD are high-calorie diets that provide 110–140% of the recommended daily needs. This includes 40–50% complex chain carbohydrates; however, there is no restriction on simple sugars [6].

The pre-diabetic period in patients with CF is very heterogeneous, with descriptions of frequent fluctuations between euglycaemia and dysglycaemia over time before diabetes sets in [7]. However, there is no consensus on the institution of routine pharmacotherapy for individuals with glucose intolerance with or without fasting hyperglyceamia [8,9].

There is evidence supporting the implementation of specific diets in this pre-diabetic phase to improve blood glucose and lung function. The main objective of this study was to evaluate the glycaemic response after nutritional guidance in favour of a low-glycaemic index (GI) diet in patients with CF in the pre-diabetic phase and its repercussions on nutritional status and lung function through a randomized clinical trial.

2 MATERIALS AND METHODS

A 12-week-long open randomized clinical trial was performed on patients with CF at the Adult and Pediatric CF Outpatient Clinic of Hospital de Clínicas de Porto Alegre (HCPA). The recruitment and intervention period took place between 2016 and 2018. Patients who satisfied the inclusion criteria of the research and agreed to participate signed the free and informed consent form. The study protocol was approved by the Research Ethics Committee of the Research and Graduate Group of the Hospital de Clínicas de Porto Alegre (# 160206). In accordance with the principles of the Declaration of Helsinki.

2.1 Population

We included patients with CF confirmed by sweat chlorine levels > 60 mEq/L and/or genotypes with 2 CF-causing mutations, those aged over 18 years, those with stable lung disease in the last four weeks (without exacerbations in this period), and those who presented altered glycaemic values, without characterizing the presence of diabetes; that is, fasting blood glucose values between 100 and 125 mg/dl and/or glucose tolerance test (OGTT) with 2h blood glucose after 75g of glucose between 141 and 199 mg / dl at least two different times with an interval

of 3 months. The last OG0TT performed in the 3 months prior to inclusion in the study was used or, if there were none, the OGTT was repeated at the time of inclusion in the study.

For each patient, demographic data (age and sex) and information related to the status of the pulmonary infection were collected (chronic infection by bacteria was their persistence for at least six consecutive months, in at least three consecutive culture tests. oropharyngeal swab or sputum samples).

2.2 Intervention

The patients were randomized into 2 groups: control and intervention, and randomisation was performed using the website www.randomization.com, which generated a random list of patients. The patients in the intervention group received a booklet with specific nutritional guidelines regarding the quality of the foods they should consume, advising them to prioritise a diet richer in proteins of high biological value and preferably whole carbohydrates and avoiding foods rich in simple sugars, but maintaining the same caloric intake to avoid weight loss (Annex 1). The patients belonging to the control group were informed to follow their usual diets as directed by the CF team. The patients who met the inclusion criteria for the study were approached while they were waiting for consultation in the waiting in the waiting room of the CF outpatient clinic. Those who agreed to participate were then interviewed at appropriate locations. A 24-hour food recall (R24h) was applied during the interview to investigate the food consumption of the day before the interview.

2.3 Nutritional, clinical, and laboratory evaluations

Anthropometric data were collected at the first meeting and at the end of 12 weeks

period, including weight (kg), height (cm) and body mass index (BMI). The weight was measured using a platform-type antropometric scale (Filizola, Sao Paulo,Brasil) and the height usind the stadiometer attached to the scale. The BMI was calculated from the ratio weight (kg)/height2 (m2) using the ESPEN reference values for patients with cystic fibrosis [10]. Women with BMI $\leq$ 22 kg/m^2 and men with BMI $\leq$ 23 kg/m^2 were considered underweight. the laboratory methods used were fasting glucose (UV enzyme method-Hexokinase-COBAS c702), glycated haemoglobin (HbA1c-HPLC high performance liquid chromatography method-Variant II Turbo), OGTT (UV enzyme method-Hexokinase-COBAS c702), and insulin immunoassay method. These examinations were from the last evaluation consultation with a maximum interval of 3 months. The examinations were repeated at the end of 12 weeks. Lung function data were collected from patients on the day of the initial assessment and were repeated after 12 weeks. Pulmonary function examinations were performed by spirometry at the Pulmonary Physiology Unit of HCPA using a computerised spirometer (Jaeger-v 4.31; Würzburg; Germany) according to the Guidelines for Pulmonary Function Tests of the Brazilian Society of Pulmonology and Tisiology [11]. The spirometric parameters evaluated included forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). Spirometric data are presented as percentages of the predicted values. The study flowchart can be found in Annex 2.

2.4 Sample Calculation

A study that evaluated the glycemia through the OGTT and markers of oxidative stress in 31 patients with CF was used as a parameter for the calculation of the sample size. The main outcome of the study was to assess glucose intolerance before and after glycaemic overload [12]. To obtain a difference of 20 mg/dl (standard deviation of 18 mg/dl) in the OTTG and

considering a statistically significant $P < 0.05$, with $\beta = 20$ %, 10 patients would be needed in each study group, taking into account a 10 % margin for possible losses. Data were calculated using Winnepi v.11.43.

2.5 Analysis of results

Continuous variables were described as means and standard deviations and were compared between interest groups using Student's t-test for independent samples.

Categorical variables were described by absolute and relative frequencies, and the relationship between them was assessed using chi-square or Fisher's exact tests.

For simultaneous intra- and intergroup comparisons, the generalised estimation equation model complemented by the least significant difference test was used.

The level of significance was set at 5 %. The statistical program SPSS 21.0 (SPSS, Chicago) was used for the analysis. R24h was calculated using Nutribase software.

3 RESULTS

Twenty-one patients completed the study, of which 11 and 10 were in the control and intervention groups, respectively. Out of 28 eligible patients, 7 patients refused to participate.

Table 1 describes the baseline characteristics of the patients. There were no differences between the groups according to age (25.7 ± 10.3 and 26.6 ± 6.8 years, for intervention and control groups, respectively, $p = 0.807$), BMI (22.4 ± 3.6 vs. 21.0 ± 3.7 kg/m^2, $p = 0.335$), and pulmonary function, namely, FEV1 % predicted (71.8 ± 16.0 vs. 76.5 ± 21.5, $p = 0.544$) and FVC % predicted (72.4 ± 19.8 vs. 77.5 ± 17.8, $p = 0.711$). 32.9% demonstrated the presence of heterozygosis, having an allele mutated to ΔF508, being, therefore, heterozygous compounds;

and 23.4% presented homozygosity, with two alleles mutated for ΔF508. Bacterial colonization by *Pseudomonas aeruginosa* (70 % vs. 54.5 %) and *Staphylococcus aureus* (20 % vs. 45.5 %) showed no significant differences between the intervention and control groups.

Variable*	Intervention (n=10)	Control (n=11)	p
Age (years)	25.7 ± 10.3	26.6 ± 6.8	0.807
BMI (kg/m^2)	22.4 ± 3.6	21.0 ± 3.7	0.335
Weight	58.1 ± 11.4	58.0 ± 13.1	0.984
Gender			0.670
Female	6 (60.0)	5 (45.5)	
Male	4 (40.0)	6 (54.5)	
Civil stage			1.000
Single	8 (80.0)	8 (72.7)	
Married	2 (20.0)	3 (27.3)	
FEV_1 (% predict.)	71.8 ± 16.0	76.5 ± 21.5	0.544
FVC (% predict.)	72.4 ± 19.8	77.5 ± 17.8	0.711
Bacterial infection			0.313
Pseudomonas aeruginosa	7 (70.0)	6 (54.5)	
Stafilococus aureus	2(20.0)	5(45.5)	

Table 1. Sample characterization
* described as mean ± standard deviation or n (%). BMI: body mass index. FEV1: forced expiratory volume in the first second. FVC: forced vital capacity.

Table 2 describes the variations in weight and BMI at the beginning and end of the study, showing the differences between and within groups. At the end of the study, both the groups showed reductions in body weight [-0.54 kg (95 % CI -1.13 to 0.05) and -0.56 kg (95 % CI -1.16 to 0.05), p = 0.973] with consequent reductions in BMI [-0.46 kg/m^2 (-0.97 to 0.05) vs. -0.41kg/m^2 (-0.88 to 0.06), p = 0.898]; however, these results were not statistically significant.

Variable*	Intervention (n=10)	Control (n=11)	p
Weight (kg)			
Pre	58.1 ± 11.4	58.0 ± 13.1	0.984
Post	57.6 ± 11.2	57.5 ± 12.7	0.981
Difference (CI 95%)	-0.54 (-1.13 - 0.05)	-0.56 (-1.16 to 0.05)	0.973
P	0.073	0,071	
BMI (kg/m^2)			
Pre	22.4 ± 3.6	21.0 ± 3.7	0.335
Post	22.0 ± 3.4	20.6 ± 3.6	0.331
Difference (CI 95%)	-0.46 (-0.97 a 0.05)	-0.41 (-0.88 to 0.06)	0.898
P	0.078	0.084	
Protein (%)			
Pe	20.2 ± 4.1	22.4 ± 7.7	0.379
Post	20.2 ± 3.4	23.1 ± 7.2	0.190
Difference (CI 95%)	-0.09 (-0.88 to 0.69)	0.72 (-0.35 to 1.78)	0.235
P	0.818	0.191	
Carbohydrates (%)			
Pre	53.3 ± 6.7	54.3 ± 8.5	0.747
Post	53.7 ± 7.1	53.0 ± 7.3	0.814
Difference (CI 95%)	0.46 (-0.24 to 1.17)	-1,.5 (-2.33 to -0.17)	**0.009**
p	0.200	**0.023**	
Fibers (g)			
Pre	17.4 ± 12.3	23.9 ± 16.8	0.283
Post	18.4 ± 12.6	21.9 ± 15.1	0.542
Difference (CI 95%)	0.97 (0.61 to 1.34)	-2.02 (-3.36 to -0.69)	**<0.001**
p	**<0.001**	**0.003**	
Total lipids (%)			
Pre	26.5 ± 6.1	23.3 ± 8.6	0.290
Post	26.2 ± 6.7	23.8 ± 8.8	0.471
Difference (CI 95%)	-0,37 (-0.01 to 0.26)	0.54 (-0.20 to 1.29)	0.068
p	0.253	0.154	
MUFA (g)			
Pre	28.6 ± 15.4	26.7 ± 18.7	0.793
Post	38.1 ± 24.9	25.8 ± 15.7	0.160
Difference (CI 95%)	9.53 (0.48 to 18.6)	-0.91 (-4.43 to 2.61)	**0.015**
p	**0.039**	0.611	
PUFA (g)			
Pre	10.5 ± 11.2	10.3 ± 9.36	0.955
Post	7.28 ± 3.98	8.58 ± 8.14	0.621
Difference (CI 95%)	-3.26 (-9.85 to 3.32)	-1.72 (-3.88 to 0.43)	0.591
p	0.331	0.117	
SFA (g)			
Pre	23.1 ± 12.8	19.9 ± 12.7	0.547
Post	18.9 ± 9.11	20,7 ± 15.7	0.733
Difference (CI 95%)	-4.19 (-9.13 to 0.75)	0.80 (-3.26 to 4.87)	0.107
p	0.096	0.699	

Table 2. Comparison of anthropometric data and consumption of proteins, carbohydrates and fibers between the pre and post intervention groups.
* described as mean ± standard deviation or n (%). BMI: body mass index. MUFA: monounsaturated fatty acid. PUFA: polyunsaturated fatty acid. SFA: saturated fatty acid.

Regarding food consumption, protein and carbohydrate intakes were similar between the groups. However, the intervention group consumed more fibre after the intervention [0.97g (95 % CI: 0.61 to 1.34) $p < 0.001$] and monounsaturated fatty acids [9.53g (95% CI: 0.48 to

18.6) p = 0.015] than the control group (Table 2). Figure 1 illustrates the consumptions of the groups in relation to fibre intake. The main foods consumed and their GIs are described in Annex 3.

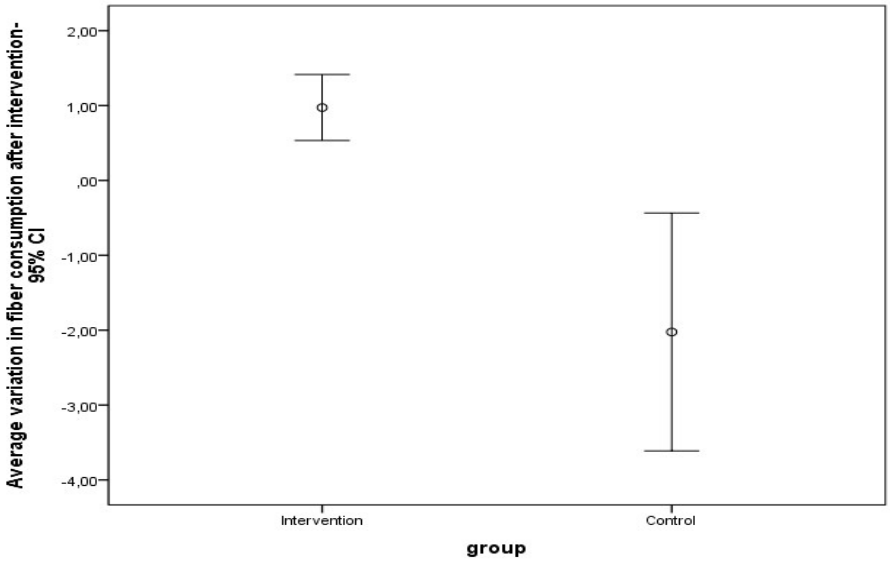

Figure 1 - Fibers consumption of the control and intervention groups before and after intervention.

Regarding the glycaemic profile, both groups showed similarities at baseline in terms of fasting blood glucose levels, glycaemic response in the OGTT, and HbA1c and insulin levels. At the end of the study, the intervention group showed significant improvements in fasting blood glucose levels [-4.00 mg/dl (-7.49 to -0.510), p = 0.025], 2-hour glycaemic response in the OGTT [-19.9 mg/dl (95 % CI: -33.6 to - 6.16), p = 0.005], and HbA1c [-0.34 % (95 % CI: -0.43 to -0.25) p = < 0.001] and insulin levels [-1.00 mg/dL (95 % CI: -1.55 to -0.45) p = < 0.001]. There were significant differences between the intervention and control groups in relation to fasting blood glucose (84.7 ± 10.4 vs. 96.0 ± 10.8, p = 0.010), 2-hour blood glucose in the OGTT (143.2 ± 22.2 vs. 166.9 ± 19.0, p = 0.006), and HbA1c (5.44 ± 0.67 vs. 6.27 ± 0.58, p = 0.001) and insulin levels (10.8 ± 6, 91 vs. 13.6 ± 9.03, p = 0.028) (Table 3).

Variable*	Intervention (n=10)	Control (n=11)	p
OGTT fasting (mg/dL)			
Pre	92.3 ± 10.2	95.8 ± 7.09	0.339
Post	88,3 ± 6.49	93.5 ± 7.16	0.064
Difference (CI 95%)	-4.00 (-7.49 to -0.51)	-2.27 (-4.26 a -0.29)	0.400
P	**0.025**	**0.025**	
OGTT 120 min (mg/dL)			
Pre	163.1 ± 34.5	173.3 ± 30.6	0.454
Post	143,2 ± 22.2	166.9 ± 19.0	**0.006**
Difference (CI 95%)	-19.9 (-33.6 to -6.16)	-6.36 (-15.1 a 2.34)	0.103
P	**0.005**	0.152	
HbA1c (%)			
Pre	5.78 ± 0.66	5.99 ± 0.76	0.474
Post	5,44 ± 0.67	6.27 ± 0.58	**0.001**
Difference (CI 95%)	-0.34 (-0,43 to -0.25)	0.28 (-0.07 a 0.63)	**0.001**
P	**<0.001**	0.114	
Fasting glucose (mg/dL)			
Pre	86.0 ± 13.5	95.1 ± 20.1	0.197
Post	84.7 ± 10.4	96.0 ± 10.8	**0.010**
Difference (CI 95%)	-1.30 (-3.65 to 1.05)	0.91 (-7.31 a 9.13)	0.612
P	0.279	0.828	
Insulin (mg/dL)			
Pre	11.8 ± 7.45	13.7 ± 9.65	0.590
Post	10.8 ± 6.91	13.6 ± 9.03	0.393
Difference (CI 95%)	-1.00 (-1.55 to -0.45)	-0.08 (-0.94 a 0.77)	**0.028**
p	**<0.001**	0.851	

Table 3. Comparison of the glycemic profile between the pre and post intervention groups
* Variable variables by mean ± standard deviation or, n (%) HbA1c: Glycated hemoglobin OGTT: oral glucose tolerance test.

Table 4 shows the declines in lung function that were observed in both groups; however, it was only significant in the control group (FEV1 % -5.18 [95 % CI -9.94 to -0.42] p = 0.033 and FVC % - 6.20 [95 % CI -10.2 to -2.21] p = 0.002).

Variable*	Intervention (n=10)	Control (n=11)	P
FEV_1 (% predict.)			
Pre	71.8 ± 16.0	76.5 ± 21.5	0.544
Post	70.9 ± 13.5	71.4 ± 15.0	0.937
Difference (CI 95%)	-0.90 (-4.05 to 2.25)	-5.18 (-9.94 a -0.42)	0.142
p	0.576	**0.033**	
FVC (% predict.)			
Pre	72.4 ± 19.8	77.5 ± 17.8	0.711
Post	69.1 ± 15.4	71.3 ± 15.6	0.543
Difference (CI 95%)	-3.26 (-7.80 to 1.28)	-6.20 (-10.2 a -2.21)	0.636
p	0.159	**0.002**	

Table 4. Comparison of lung function between the pre and post intervention groups
* described as mean ± standard deviation or n (%). FEV1: forced expiratory volume in the first second. FVC: forced vital capacity.

4 DISCUSSION

This randomized clinical trial was the first to show that patients with CF and glycemic alterations in the pre-diabetic phase respond favourably to nutritional guidance for improved glucose parameters. We observed an improvement in all the glycemic parameters evaluated as well as the insulin levels.

An ever-present concern in patients with CF is the body weight and nutritional status. A slight weight loss was observed without a change in the nutritional status of the patients. Regarding lung function, we did not observe differences between the groups at the end of the study despite the fact that the control group had a greater loss of function compared to its baseline (intra-group evaluation).

The consumption of fibre was higher in the intervention group, which suggests real changes in the eating habits of these patients, as indicated in our guidelines through the intake of complex carbohydrates, which have been well-described and studied in the literature for their important and favourable roles in the control of blood glucose [13]. Our patients in the intervention group showed significant improvements in the 2-hour blood glucose levels in the OGTT and in the HbA1c levels.

The low-GI dietary intervention had positive effects on insulin resistance and glycaemic control in other types of diabetes not associated with CF and is part of the recommendations of the American Diabetes Society [14].

A systematic review carried out in 2012 by Balzer et al. found only two studies that assessed the GI of foods and the glycaemic profiles of patients with CF [15]. Spotinik et al. examined the glycaemic response through low-GI enteral feeding in 19 adolescents (mean age, 13 years) with CF with glucose intolerance. The study compared the glycaemic load and the physiological response via the glucose curve to the enteral feeding formula with the OG TT

response. Numerical data are not provided by the authors because the data are in a graphical format [16]. The other was a pilot study that evaluated a sample of 13 patients with CF and glucose intolerance who received dietary guidance versus those who did not receive guidance. After a 12-month-long intervention, they showed glycaemic improvement and other outcomes such as those in oxidative markers; however, the study was not randomized and did not adequately describe the tools for dietary assessment [12].

More recently, a randomized clinical trial with 44 children and adolescents with CF evaluated the effect of a low-GI diet. The patients were randomized into two groups, one with a diet high in fat and calories and the other with the same diet, but with a low GI. Blood glucose levels before and after the intervention were found to be significantly lower after the consumption of a low-GI diet (a decrease of 10.95 ± 15.19 mg/dl $p = < 0.001$). Adherence to a low-GI diet seemed to be associated with improvements in the glycaemic status of these patients, which is in line with our findings [17].

Despite few studies on the subject, the available research corroborates our findings, suggesting the benefit of using a diet with a reduced GI in the management of patients with CF in the pre-diabetic phase. Since there is no consensus on the best management in relation to blood glucose fluctuations that are characteristic of the disease, some authors advocate insulin therapy in these patients, which is associated with improved nutritional status and lung function [8, 18].

A strength of this study is that it is a randomized clinical trial that evaluated dietary intervention in patients with CF at the critical moment of transition to established diabetes. The small sample size and the short follow-up period are relevant issues to be highlighted as possible limitations along with the lack of better tools for assessing adherence to the diet and the inclusion of other disease progression markers. However, nutritional intervention studies are always complex to carry out, especially in populations of clinically severe patients like those

with CF who demand several concomitant interventions and are highly susceptible to complications during their treatment.

In conclusion, nutritional guidance aimed at the consumption of complex carbohydrates and a low-GI index diet while preserving adequate caloric intake seems to have a positive effect on the glycaemic control in patients with CF in the pre-diabetic phase. Obviously, more studies with a larger sample sizes and follow-up periods are needed until a definitive indication of diet in this clinical setting is determined.

Acknowledgements

The author is grateful to professor and doctor Ticiana da Costa Rodrigues for the support and encouragement of this research. And the medical colleagues and teachers Elenara Procianoy, Paulo Dalcin and Paulo Maróstica, who helped by reviewing and adding knowledge to this article.

Funding Sources

This work was funded by the Conselho Nacional de Desenvolvimento Científico e tecnológico (CNPq), Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre (FIPE) and CAPES-PROEX. Rodrigues TC is recipient of PQ scholarship from CNPq and Freiberg RE was recipient of scholarship from CAPES.

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ANNEX 1

NUTRITION GUIDELINES AND HEALTHY FOOD FOR PATIENTS WITH CYSTIC FIBROSIS

Carbohydrates: starches, flours, sugars, potatoes

- Give preference to whole carbohydrates, brown rice, whole-grain bread, sweet potatoes, whole grain, whole grain cookies, granola, oats;
- Avoid sugared sweets, chocolates, milkshakes, breakfast cereal, soft drinks, candies, and sweets;
- Avoid natural watermelon, grape, and orange juice; prefer lemon and passion fruit; and,
- Replace refined sugar with brown or demerara sugar.

Proteins: meat, chicken, pork, egg, milk, cheese

- Prefer lean meats, rump, duckling, fillet, inside-leg portion;
- Avoid breaded preparations, nuggets, and fried foods;
- Eat fish once a week; and,
- Eat 1 scoop of beans or lentils daily;

General tips

- Include 3 servings of fruit daily between meals;
- Include 2 tablespoons of olive oil in the salad;
- Eat 4 to 5 servings of raw and cooked vegetables in the main meals;

- Drink 1.5 to 2 L of water; and,
- For snacks between meals, include 3 nuts from Pará.

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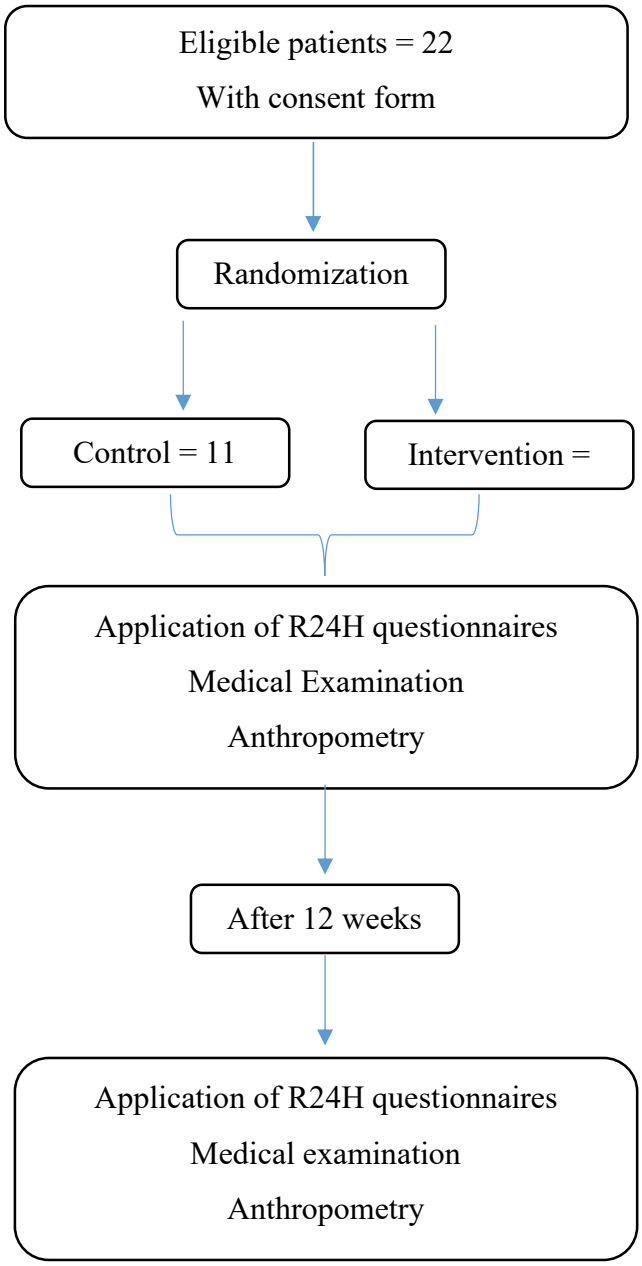
ANEXX 2

Flowchart



ANNEX 3

Main foods eaten by patients and their respective glycemic index

Foods	Glycemic index
Banana	52
Apple	38
Orange juice	50
Brown rice	40
Rice	69
Pasta	64
Potate	85
Beans	48
Yogurt	27
Fatty milk	27
Whole grain bread	67
Biscoito Craker	65
Bred	95
French bread	95
Ice cream	61

*Glycemic index at 100 grams
Source:Fostar-Powell et al. International table og glycemic index and glycemic load values, Am J Clin Nutri 2002;76:5-5