ADRIANA HAACK DE ARRUDA DUTRA

ASPECTOS EPIDEMIOLÓGICOS ,CLÍNICOS , NUTRICIONAIS E TRATAMENTO FARMACOLÓGICO DE PACIENTES COM FIBROSE CÍSTICA ATENDIDOS EM CENTRO DE REFERÊNCIA DO DISTRITO FEDERAL

BRASÍLIA,2014

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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

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Tese apresentada ao Curso de Pós-Graduação em Ciências da Saúde, Faculdade de Ciências da Saúde, Universidade de Brasília como requisito parcial à obtenção do título de Doutor em Ciências da Saúde.

Orientadora: Profª. Drª. Maria Rita C. Garbi Novaes

BRASÍLIA, DF

2014

ASPECTOS EPIDEMIOLÓGICOS, CLÍNICOS, NUTRICIONAIS E TRATAMENTO FARMACOLÓGICO DE PACIENTES COM FIBROSE CÍSTICA ATENDIDOS EM CENTRO DE REFERÊNCIA DO DISTRITO FEDERAL

Adriana Haack de Arruda Dutra

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FOLHA DE APROVAÇÃO

Adriana Haack de Arruda Dutra

Aspectos epidemiológicos, clínicos, nutricionais e tratamento farmacológico de pacientes com Fibrose Cística atendidos em Centro de Referência do Distrito Federal

Tese apresentada ao Curso de Pós-Graduação em Ciências da Saúde da Faculdade de Ciências da Saúde da Universidade de Brasília para obtenção do título de Doutor.
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Aprovada em: ____ de _____ de 2014.

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"Todos os homens, por natureza, desejam saber". (Aristóteles)

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Haack A. **Aspectos epidemiológicos, clínicos, nutricionais e tratamento farmacológico de pacientes com fibrose cística atendidos em centro de referência do Distrito Federal.** 2014. 176 folhas. Tese [Doutorado] – Programa de Pós- Graduação em Ciências da Saúde. Universidade de Brasília. Orientadora: Profª. Drª. Maria Rita Carvalho Garbi Novaes.

A fibrose cística é uma doença de herança autossômica recessiva, que atinge as glândulas exócrinas, envolve múltiplos órgãos como sistema digestório, respiratório e evolui de forma crônica e progressiva, inclusive com desnutrição grave. O objetivo do estudo foi avaliar e descrever aspectos epidemiológicos, clínico-nutricionais e farmacológicos de pacientes atendidos no ambulatório de fibrose cística em um centro de referência do Distrito Federal. O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Universidade de Brasília. Com os resultados obtidos, concluiu-se que práticas como atendimento multidisciplinar, intervenção clínico-nutricional e estímulo à atividade física devem ser incentivados nos pólos de atendimento e acompanhados para que a assistência seja precoce e a mais efetiva possível. Manifestações no trato digestório e respiratório podem comprometer o estado nutricional na fibrose cística. A suplementação enzimática e vitamínica, assim como, o uso de fármacos como antibióticos, mucolíticos entre outros são necessários para tratar e prevenir complicações. O estudo mostrou uma associação positiva entre o uso de suplementos - tipo e frequência, e a variável déficit nutricional. Alterações nas provas de função pulmonar também foram encontradas e foram associadas com medidas antropométricas como a circunferência de braço. O acesso aos suplementos, fármacos e a assistência clínica por meio de políticas públicas e financiamento pelas instituições governamentais, como programas domiciliares, podem contribuir para a menor morbidade e maior sobrevida dos fibrocísticos. O estudo não mostrou associação entre a *P. aeruginosa* e o estado nutricional, possivelmente pelo número de casos acometidos pela colonização das cepas mucóide e não mucóide. Modelos de serviço multiprofissional, baseados em triagem neonatal e no auxílio com fármacos, suplementos nutricionais, vitamínicos e enzimáticos devem ser estimulados e ampliados evitando-se quadros de exacerbação da doença que podem culminar com a necessidade de transplante e prejudicar a qualidade de vida de todos os envolvidos.

Palavras-chave: estado nutricional; fibrose cística; terapêutica; doença pulmonar.

ABSTRACT

Haack A. **Epidemiological, clinical, nutritional and pharmacological treatment of patients with cystic fibrosis treated in a referral center in the Federal District.** 2014. 176 pages. PhD [Dissertation] – Program in Health Sciences Brasília University. Advisor: Profª. Drª. Maria Rita Carvalho Garbi Novaes.

Cystic fibrosis is a genetic recessive disease that affects the exocrine glands and involves the digestive, respiratory and evolves from chronic and progressive manner, including severe malnutrition. The aim of the study was to assess and describe epidemiological, clinical and nutritional and pharmacological of clinical patients with cystic fibrosis in a reference center of the Federal District aspects. The study was approved by the Ethics Committee in Research of the University of Brasilia. With the obtained results, it was concluded that practices such as multidisciplinary care, clinical nutrition intervention and encouraging physical activity should be encouraged in centers of care and followed for that assistance is early and effective as possible. Manifestations in the digestive and respiratory tract may compromise the nutritional status in cystic fibrosis. The enzyme and vitamin supplementation, as well as the use of drugs such as antibiotics, mucolytics and others are required to treat and prevent complications. The study showed a positive association between the use of supplements - type and frequency, and variable nutritional deficit. Changes in pulmonary function were also found and were associated with anthropometric measurements such as arm circumference. Access to supplements, pharmaceuticals and clinical care through public policies and funding by government institutions such as residential programs, may contribute to lower morbidity and survival of cystic fibrosis patients. The study showed no association between *P. aeruginosa* and nutritional status, possibly by the number of cystic fibrosis patients affected by colonization of mucoid and non-mucoid strains. Multidisciplinary service models, based on neonatal screening and assistance with medications, nutritional, vitamin and enzyme supplements should be encouraged and extended frames avoiding exacerbation of the disease that can lead to the need for transplantation and impair the quality of life for all involved.

Keywords: nutritional status; cystic fibrosis; therapy; lung disease.

1 INTRODUÇÃO

A Fibrose Cística (FC) é considerada a doença de caráter hereditário letal mais comum na população branca. A mucoviscidose ou FC é uma doença de herança autossômica recessiva, que atinge as glândulas exócrinas, envolve múltiplos órgãos como sistema digestório, respiratório e evolui de forma crônica e progressiva, inclusive com desnutrição grave[1]. A tríade clássica, doença pulmonar crônica, diarréia crônica esteatorréica e dificuldade de ganho pôndero-estatural, acomete os fibrocísticos recém nascidos e também os adultos e as crianças pode estar presente precocemente nos recém-nascidos[2].

O objetivo geral do trabalho foi avaliar os aspectos epidemiológicos, clínicos-nutricionais e farmacológicos de pacientes atendidos no ambulatório de fibrose cística em um centro de referência em hospital público do Distrito Federal.

Os objetivos específicos foram:

- Descrever os aspectos socioeconômicos e demográficos dos pacientes com fibrose cística atendidos no ambulatório;

- Avaliar os aspectos clínicos, função pulmonar, prognóstico, e as características bioquímicas e metabólicas de pacientes com fibrose cística;

- Analisar o estado nutricional de pacientes com fibrose cística;

- Avaliar o uso de vitaminas lipossolúveis, enzimas e suplementos nutricionais de pacientes com fibrose cística;

- Analisar a fisiopatologia do sistema digestório e respiratório na Fibrose Cística e as drogas habitualmente utilizadas no seu tratamento;

-Analisar a função pulmonar e o exercício físico realizados entre os pacientes com Fibrose Cística.

Os experimentos deste trabalho foram conduzidos no período de 2009 a 2011 sendo que os resultados dos estudos foram apresentados na forma de artigos científicos.

Foram elaborados cinco artigos de revisão. O artigo **Segmento Clínico e Nutricional de Pacientes com Fibrose Cística** foi submetido ao periódico Científico, Revista Brasília Médica, indexado nas Bases Lilacs e Latindex Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs/Bireme) classificado pelo Programa da CAPES-Qualis Medicina II como B5, que realiza uma revisão da literatura sobre o tratamento farmacológico e clínico-nutricional, atualmente utilizado e discute os

resultados principais destes trabalhos de forma a contribuir no atendimento de pacientes com fibrose cística.

O segundo artigo de revisão intitulado **Multidisciplinary care in cystic fibrosis: a clinical-nutrition review** foi publicado na revista **Nutrición Hospitalaria 2012; 27(2): 362-371**, periódico indexado nas bases de dados Medline, Index Medicus, Embase, Excerpta Médica, Cancerlit, Toxline, Aidsline, Health Planning and Administration, Índice Médico Español (IME), Índice Bibliográfico Español en Ciencias de la Salud (IBECS), SENIOR), classificado pelo Programa da CAPES-Qualis Medicina II como B2. Este artigo descreve os principais aspectos da intervenção clínica e nutricional de pacientes com fibrose cística atendidos por equipe multidisciplinar.

O terceiro artigo de revisão **Pathophysiology of cystic fibrosis and drugs uses in associated digestive tract diseases** foi publicado no periódico **World Journal of Gastroenterology 2013; 19(46): 8552-8561**, periódico indexado nas bases de dados Current Contents/Clinical Medicine and Science Citation Index–Expanded, Index Medicus, MEDLINE and PubMed, PubMed central, Chemical Abstracts, EMBASE/Excerpta Medica, Abstracts Journals, Nature Clinical Practice Gastroenterology and Hepatology, classificado pelo Programa da CAPES- Qualis Medicina II como A2. Este artigo descreve a fisiopatologia e os mais importantes aspectos do tratamento com fármacos direcionados ao trato digestório dos fibrocísticos.

O quarto artigo de revisão **Pathophysiology of Cystic Fibrosis and drugs commonly used in respiratory manifestations: what should we know** foi submetido ao periodico **Revista de Investigación Clínica,** periódico indexado nas bases de dados LILACS, Artemisa, Index Medicus, Currents Contents, classificado pelo Programa da CAPES-Qualis Medicina II como B3 e aguarda resposta dos revisores. Este artigo descreve a fisiopatologia e os mais importantes aspectos do tratamento com fármacos direcionados ao trato respitatório dos fibrocísticos.

O quinto artigo de revisão **Exercício físico e Fibrose Cística: uma revisão bibliográfica** será publicado na revista **Comunicação em Ciências da Saúde 2013; 24(2) [no prelo]** periódico indexado na Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) do Centro Latino-Americano e do Caribe de Informação em Ciências da Saúde (Bireme), classificado pelo Programa da CAPES-Qualis Medicina II como B3. Este artigo realizar uma revisão da literatura sobre o exercício físico e fibrose cística.

Foram elaborados dois artigos originais que tratam do perfil socioeconômico, clínico e nutricional de pacientes fibrocísticos, além das avaliações das provas de função pulmonar e a presenção de colonização por *Pseudomonas aeruginosa* entre os fibrocísticos. O uso de suplementos nutricionais fornecidos por programa de atendimento domiciliar também foi descrito. São eles:

- **Cystic fibrosis patients assisted by a program nutrition therapy: assessment of the use of supplements in patients colonized and non colonized by *P. aeruginosa*** publicado na revista **Revista de Investigación Clínica 2014 [no prelo]** periódico indexado nas bases de dados LILACS, Artemisa, Index Medicus, Currents Contents, classificado pelo Programa da CAPES-Qualis Medicina II como B3.
- **Clinical and nutritional aspects of cystic fibrosis patients assisted by a home enteral nutrition program in Brazil** publicado na **Revista Chilena de Nutrición 2013; 40(2): 112-118** periódico indexado nas bases de dados LILACS-Literatura Latinoamericana y del Caribe en Ciencias de la Salud SciELO Chile-Scientific Electronic Library Online, classificado pelo Programa da CAPES-Qualis Medicina II como B3.

ARTIGO 1 – ARTIGO DE REVISÃO

Em português:

Segmento Clínico e Nutricional de Pacientes com Fibrose Cística, submetido ao periódico Científico, Revista Brasília Médica.

2 ARTIGO DE REVISÃO

SEGMENTO CLÍNICO E NUTRICIONAL DE PACIENTES COM FIBROSE CÍSTICA: EVIDÊNCIAS DA LITERATURA

CLINICAL AND NUTRITIONAL SEGMENT OF PATIENTS WITH CYSTIC FIBROSIS: LITERATURE EVIDENCE

Resumo

Introdução: Fibrose cística (FC) ou mucoviscidose é considerada a doença de caráter hereditário letal mais comum na população branca e no Brasil a incidência estimada é de 1/9.500 nascimentos. A sobrevida dos pacientes portadores de FC vem aumentando significativamente. Atualmente a sobrevida é de aproximadamente 35 anos em países europeus e norte-americanos. **Objetivo**: realizar uma revisão da literatura sobre o tratamento clínico e nutricional, utilizados e discutir os resultados principais destes trabalhos de forma a contribuir no atendimento de pacientes com fibrose cística. **Metodologia**: a revisão foi realizada em artigos de revistas indexadas nas bases de dados: Medline, Lilacs, Scielo, Current Contents, Cochrane, descritos nos idioma português, inglês e espanhol, com ênfase em artigos publicados no período de 2000 a 2013. **Resultados**: Os fibrocísticos apresentam uma grande suscetibilidade à colonização e infecção. A antibioticoterapia, assim como a terapia de reposição enzimática, contribuiu para aumentar a sobrevida desses pacientes. Devido ao déficit energético, normalmente se recomenda um consumo maior da energia. O uso de suplementos energéticos pode ser recomendado, porém é importante assegurar que eles não estejam sendo utilizados como substitutos das refeições. O acompanhamento nutricional realizado com a periodicidade de três meses é essencial para detectar desvios nutricionais ou alterações de comportamento alimentar. **Conclusão**: práticas como atendimento multidisciplinar e intervenção clínico-nutricional devem ser incentivadas nos pólos de atendimento para que a assistência seja precoce e a mais efetiva possível.

Palavras-chave: fibrose cística; estado nutricional; terapêutica; doença pulmonar.

Abstract

Introduction: Cystic fibrosis (CF) or cystic fibrosis disease is considered the most common lethal hereditary in the white population and in Brazil. The estimated incidence is 1/9.500 births. The survival of CF patients has increased significantly. Currently survival is approximately 35 years in European and North American countries. **Objective:** To review the literature on the clinical and nutritional used treatment and discuss the main results of this work in order to contribute to the care of patients with cystic fibrosis. **Methodology:** The review was conducted in articles of journals indexed in databases: Medline, Lilacs, SciELO, Current Contents, Cochrane, described in Portuguese, English and Spanish, with emphasis on articles published in the period 2000-2013. **Results:** CF patients have a greater susceptibility to colonization and infection. Antibiotic therapy, as well as enzyme replacement therapy, contributed to increase the survival of these patients. Due to the energy deficit, usually recommends a higher intake of energia. The use of energy supplements can be recommended, but it is important to ensure that they are not being used as substitutes for meals. The nutritional follow up at intervals of three months is essential to detect nutritional problems or changes in eating behavior. **Conclusion:** practices such as multidisciplinary care and clinical nutritional intervention should be encouraged at the poles of care for that assistance is early and effective as possible.

Keywords: cystic fibrosis; nutritional status; therapy; lung disease.

2.1 INTRODUÇÃO

O relato proveniente do folclore da Europa antiga de que *"Bebês com sabor salgado certamente morrerão..."* é, provavelmente, o primeiro reconhecimento de Fibrose Cística (FC), uma doença que é caracterizada pelo transporte anormal de cloro e, antigamente, caracterizada pela morte na infância[1]. O histórico da FC pode ser visualizado na Tabela 1.

Tabela 1. Histórico da fibrose cística

1595, 1606 - Registro de autópsia que presumidamente morreu de FC com lesão pancreática. Relato que dedos de crianças ficavam salgados após passarem a mão na fronte[2].
1905 - Landsteiner[3] fez a primeira descrição anátomo-patológica da FC em recém-nascido falecido no quinto dia por íleo meconial relacionando-o com insuficiência pancreática exócrina.
1936 - Fanconi et al.[4] descreveram caso de criança com doença celíaca, alterações pancreáticas, intestinais e pulmonares (bronquiectasias).
1938 - Andersen[5] descreveu as características clínicas, anatomopatológicas e epidemiológicas da FC.
1944 - Farber[6] propôs a hipótese de que o muco espesso era responsável pelas lesões pulmonares e pancreáticas, criando o termo mucoviscidose.
1953 - Agnese et al.[7] observaram que pacientes com FC apresentavam perda excessiva de sal no suor . Marco no desenvolvimento do teste diagnóstico.
1958 - Shwachman e Kulczycki[8] elaboraram um escore para avaliação da gravidade da doença.
1959 - Gibson e Cooke[9] padronizaram a coleta do suor estimulada pela iontoforese com pilocarpina que é o padrão ouro para diagnóstico da FC.
1983 - Quinton et al.[2] descobriram o defeito do íon cloro nas glândulas sudorípadas.
1985 - O gene da FC foi localizado no cromossomo 7[10].
1990 - 2013 - Estudos focaram-se no diagnóstico precoce, tratamento adequado e caráter multidisciplinar.

A incidência da FC é variável de acordo com as etnias, variando de 1/2.000 a 1/5.000 caucasianos nascidos vivos na Europa, nos Estados Unidos e no Canadá. No Brasil, a incidência estimada é de 1/9.500 nascimentos, de acordo com os dados obtidos nos estados onde já houve implantação do programa de triagem neonatal (Paraná, Santa Catarina e Minas Gerais), possivelmente devido às variações geográficas decorrentes das diferentes imigrações que compõe a população brasileira[11].

Nas últimas décadas, a sobrevida dos pacientes portadores de FC vem aumentando significativamente. Nos anos 60, 70 e 80 vivia-se em média 10, 16 e 18 anos[12], respectivamente. Atualmente a sobrevida é de aproximadamente 35 anos em países europeus e norte-americanos[13].

Estudos brasileiros mostraram que a sobrevida média de pacientes com fibrose cística no período de 1979-1989 foi de 6,4 anos, subindo para 12,6 anos no período de 1970-1994[14, 15]. Em outra análise, desenvolvida na década de 1990-2000, foi observada

uma sobrevida de 18,4 anos de idade após o diagnóstico, estimativa que equivale àquela observada nos Estados Unidos nos anos 80[16].

Em Minas Gerais, no início da década de 90, a sobrevida dos fibrocísticos era de 12,6 anos[17].

A prevalência estimada para a região Sul é a mais próxima da população caucasiana centro-européia, decrescendo em direção à região Sudeste e Norte do país[18-21].

A FC é considerada a doença de caráter hereditário letal mais comum na população branca[22]. A mucoviscidose ou FC é uma doença de herança autossômica recessiva, que atinge as glândulas exócrinas, envolve múltiplos órgãos e evolui de forma crônica e progressiva[22]. Quando cada um dos pais tem um gene para FC, em cada gestação, o risco de nascer um filho com e sem a doença é de 25% e 75%, respectivamente, e a probabilidade de nascer um filho saudável, mas com um gene para FC, é de 50%[23].

O gene da FC localiza-se no braço longo do cromossomo 7, é formado por 250 quilobases de DNA, e tem a propriedade de codificar um RNAm de 6,5 quilobases, que transcreve uma proteína transmembrana, reguladora de transporte iônico, composta de 1480 aminoácidos, conhecida como CFTR (*Cystic Fibrosis Transmembrane Conductance Regulator).* A CFTR é essencial para o transporte de íons através da membrana celular, estando envolvida do fluxo de Cl, Na e água. Algumas centenas de mutações foram descritas no gene da FC, porém a mais frequente delas ocorre por uma deleção de três pares de bases, acarretando a perda de um aminoácido, a fenilalanina, na posição 508 (ΔF 508) da proteína CFTR, o que impede seu funcionamento adequado e espessamento das secreções[23].

A tríade clássica, doença pulmonar crônica, diarréia crônica esteatorréica e dificuldade de ganho pôndero-estatural, pode estar presente precocemente nos recém-nascidos[24].

Considerando a importância do diagnóstico da enfermidade e a intervenção precoce, este artigo tem como objetivo realizar uma revisão da literatura sobre o tratamento clínico-nutricional, atualmente utilizado e discutir os resultados principais destes trabalhos de forma a contribuir no atendimento de pacientes com fibrose cística.

2.2 MÉTODO

Trata-se de uma revisão da literatura realizada em artigos de revistas indexados nas bases de dados: *Medline, Lilacs, Scielo, Current Contents, Cochrane*, utilizando como unitermos: fibrose cística, estado nutricional, medicamentos, terapêutica, doença pulmonar, descritos nos idioma português, inglês e espanhol, com ênfase naqueles publicados no período de 2000 a 2013. Foram selecionados estudos observacionais e clínicos randomizados. Os critérios de inclusão para escolha dos artigos foram os artigos com pelo menos um dos descritores selecionados e que abordavam o tema fibrose cística. Os critérios de exclusão empregados foram artigos em outros idiomas e estudos que não tratavam especificamente do tema. Os artigos foram analisados e selecionados observando-se o ano e/ou a relevância do tema, o tipo e objetivo do estudo, a metodologia utilizada e a análise dos mesmos.

2.3 RESULTADOS

Diagnóstico de pacientes com fibrose cística

O diagnóstico da fibrose cística é atualmente feito de acordo com os critérios propostos no Consenso da *Cystic Fibrosis Foundation*[25]. Nos casos de apresentação atípica de FC, o diagnóstico costuma ser mais difícil, dependendo de exames diagnósticos mais complexos com pesquisa mais extensa de mutações, seqüenciamento completo do gene CFTR ou demonstração de transporte iônico anormal em epitélio nasal[24].

Quadro 1 - Diagnóstico da Fibrose Cística[25].

Manifestações clínicas (uma ou mais) como doença pulmonar obstrutiva/supurativa ou sinusial crônica, alterações gastrintestinais e nutricionais, síndrome da perda salina, anormalidades urogenitais resultando em azoospermia associadas à identificação de duas mutações para fibrose cística ou Cloro no suor ≥60mmol /L em duas dosagens. Também devem ser considerados: História familiar de FC ou teste de triagem neonatal pelo método da tripsina imunorreativa (IRT).

Em países desenvolvidos, a maioria dos pacientes tem o diagnóstico antes de dois anos de idade. No Brasil, a doença é sub-diagnosticada, e 40-50% dos casos são diagnosticados após três anos de idade[23]. Alguns Estados como Santa Catarina, Paraná e Minas Gerais, por meio de programas públicos do Ministério da Saúde, já realizam a busca precoce por meio do teste de triagem neonatal[26].

Desde o início da utilização dos testes de triagem há controvérsias quanto ao seu real impacto na evolução da doença, além do aspecto de custo-efetividade. Entretanto, os pacientes diagnosticados por meio de triagem neonatal, apresentam melhor evolução nutricional e do crescimento, além de melhores valores de função pulmonar aos 10 anos de idade[24, 27, 28].

Pode-se perceber que, nos últimos anos, houve um aumento da sobrevida dos pacientes fibrocísticos, devido às pesquisas e aos avanços científicos que possibilitaram um melhor conhecimento da doença, bem como à inclusão da dosagem da tripsina imunorreativa (IRT) na triagem neonatal em alguns estados brasileiros, permitindo o diagnóstico precoce da doença e a implantação de tratamento multidisciplinar visando à prevenção da desnutrição e da deterioração da função pulmonar[29].

Manifestações Clínicas em pacientes com fibrose cística

A distribuição multissêmica do defeito básico de ordem genética confere à enfermidade extensa variabilidade clinica de acordo com os órgãos ou tecidos glandulares exócrinos envolvidos. As áreas envolvidas referem-se à área respiratória que é considerada a mais crítica em severidade e letalidade, a área digestiva na qual se destacam o envolvimento do pâncreas exócrino, a má absorção com esteatorréia e creatorréia além do indicador clínico precoce, o íleo meconial. Também estão envolvidos a nutrição com um dispêndio calórico e hipercatabólico, a secreção anormal de eletrólitos no suor e a marca característica da enfermidade: a depleção eletrolítica, levando à desidratação aguda pelo calor [22, 24].

A doença pulmonar é a causa primária de morbidade e mortalidade na FC. É caracterizada por progressivos ciclos de infecções e inflamações que culminam com falência pulmonar. Ao nascimento, os pulmões dos pacientes que tem FC são anatomicamente e histologicamente normais. A lesão inicial é caracterizada pela dilatação e hipertrofia das glândulas mucosas, seguida de metaplasia escamosa do epitélio brônquico, presença de rolhas de muco nas vias aéreas periféricas, alterações

ciliares secundárias e infiltrados linfocitários na submucosa. A evolução é para bronquiolectasias e bronquiectasias[30, 31].

Os fibrocísticos apresentam uma grande suscetibilidade à colonização e infecção endobrônquica por bactérias específicas, sendo a infecção broncopulmonar crônica a maior causa do dano pulmonar progressivo na fibrose cística. Nos primeiros anos de vida, os pacientes têm seus tratos respiratórios habitualmente colonizados por *Staphylococcus aureus*. Em seguida, aparece a colonização pela *Pseudomonas aeruginosa,* uma característica marcante relacionada à progressão da doença pulmonar. Trabalhos recentes mostram que a prevalência de *P.aeruginosa* nos primeiros anos de vida é alta, mas geralmente identificam-se cepas não-mucóides. A *Pseudomonas aeruginosa* é a patologia mais comum, infectando aproximadamente 80% da população. Com o passar dos anos, a *Pseudomonas* muda seu fenótipo e passa a produzir grandes quantidades de uma substância denominada alginato, quando passa a ser denominada cepa mucóide[32-35].

O alginato facilita a aderência bacteriana nas vias aéreas e a formação de microcolônias, dificultando a opsonização, a fagocitose e a penetração de anticorpos e antibióticos. Esse fenótipo bacteriano associa-se a uma enorme dificuldade na erradicação dessa infecção, que se cronifica e gera uma intensa resposta inflamatória[32-35].

Com o avançar da idade, 70 a 90% dos pacientes são infectados por *P.aeruginosa*. Outros agentes como o *Haemophilus influenzae* e a *Burkholderia cepacia* também podem colonizar o trato respiratório. Está última relacionada a um pior prognóstico e quadro fulminantes com disseminação hematogênica e óbito, na chamada "síndrome da cepacia" [36, 37].

As manifestações gastrintestinais são na sua maioria, secundárias à insuficiência pancreática (IP). A obstrução dos canalículos pancreáticos por tampões mucosos impedem a liberação das enzimas para o duodeno, determinando má digestão de gorduras, proteínas e carboidratos. Há também diarreia de odor característico e perda de peso acentuada decorrente da má absorção [38-40].

A má absorção é predominantemente ocasionada pela disfunção pré-eptelial e decorre da rejeição de nutrientes não hidrolisados no lúmem pela insuficiência pancreática. Em 85% dos pacientes fibrocísticos, o pâncreas não produz enzimas suficientes para completa digestão dos alimentos ingeridos, e uma das primeiras manifestações é a má-absorção de nutrientes[41]. As proteínas requeridas para o

crescimento e reparo de tecidos do corpo não são totalmente utilizadas. A gordura, o nutriente mais energético não é absorvido; assim, o crescimento é atrasado e as deficiências de vitaminas lipossolúveis podem ocorrer[42].

A primeira manifestação da insuficiência pancreática na fibrose cística é o íleo meconial (obstrução do íleo terminal por mecônio espesso) que aparece em 15-20% dos bebês e a maioria dos diagnósticos de íleo meconial (90%) é relativa à fibrose cística[42].

A patôgenese tem sido relacionada à falha na secreção das enzimas pancreáticas e má–digestão e desidratação do conteúdo intestinal *in útero*, resultando em mecônio hiperviscoso e ressecado que leva à obstrução no nível do íleo distal. Síndrome da obstrução intestinal distal ou equivalente a íleo meconial ocorre em cerca de 20% dos pacientes, geralmente adolescentes e adultos[43].

Van der Doef et al.[44] verificaram a prevalência de 47% de constipação intestinal em uma coorte de 214 pacientes pediátricos com FC e associaram a ocorrência do diagnóstico com baixa absorção de gorduras totais e história de íleo meconial. Não houve associação com uso de fibras integrais e consumo de fluídos.

Prolapso retal ocorre em cerca de 20% dos pacientes, principalmente nos menores de dois anos. Os fatores contribuintes para o seu aparecimento são: fezes volumosas e viscosas que aderem à mucosa retal, perda da gordura peri-retal (que normalmente dá suporte ao reto), diminuição do tônus muscular pela desnutrição e aumento da pressão intra-abdominal pela tosse. Sua resolução é geralmente espontânea com o uso das enzimas pancreáticas e melhora do estado nutricional[45].

O fígado é afetado na FC de diferentes maneiras. A maioria dos pacientes que tem mucoviscidose desenvolve algum nível de doença do fígado que pode incluir esteatose hepática, ou doenças do trato biliar. Esteatose hepática é comum (20-60% dos pacientes). Colelitíase também é achada com freqüência e, 15% dos adultos têm cálculos biliares. As doenças do fígado são citadas como causas importantes de morte entre os fibrocísticos [34, 46].

A lesão hepática acarreta danos na síntese endógena de vitamina D e seus metabólitos, podendo resultar em doença óssea e alterações no metabolismo do cálcio, sendo que a absorção intestinal desse mineral se faz sob a influência da vitamina D. Os baixos níveis séricos de 25 (OH) vitamina D contribuem para liberação do paratormônio (PTH) com o objetivo de elevar a calcemia, porém altos níveis desse hormônio mobilizam cálcio e fósforo dos ossos, diminuindo ainda mais a massa óssea (CN1 39).

Vários estudos têm mostrado baixa densidade mineral óssea (DMO) em pacientes fibrocísticos [47-49].

Feijó et al.[49] encontraram pacientes com baixa DMO, inclusive na infância. No grupo de adultos, quase todos apresentavam comprometimento na densidade mineral óssea, estando 72% com osteopenia e 14% com osteosporose. Não foi observada correlação entre a condição óssea, o VEF 1 e a presença da mutação ΔF 508. Apesar disso, a patogênese dessa baixa DMO não é completamente compreendida. Uma variedade de potenciais fatores de risco pode contribuir para o desenvolvimento da osteoporose nesses pacientes, tais como má nutrição, insuficiência pancreática, má absorção de cálcio, inatividade física, terapia com corticóides, acidose respiratória crônica, níveis reduzidos de hormônios sexuais e diminuição dos níveis de insulina associada com diabetes[47].

Heron et al.[50] sugeriram que a perda da atividade da CFTR pode resultar em um aumento da reabsorção das células ósseas dos pacientes FC por meio da diminuição significativa da secreção de osteoprotegerina (OPG-proteina da superfamília de receptores TNF que atua como um inibidor solúvel na maturação e ativação dos osteoclastos) acompanhada pelo aumento da secreção de prostraglandina (PG) E2 em culturas de osteoclastos.

O mecanismo fisiológico da intolerância à glicose na FC é controverso. O tecido endócrino do pâncreas é preservado inicialmente, mas com o aumento da idade do paciente, células são perdidas e a glândula começa a ser completamente substituída por tecido fibroso. As alterações do canal de cloro levam à hiperviscosidade da secreção ductal pancreática, causando lesões obstrutivas, infiltração gordurosa, fibrose progressiva das ilhotas e redução da secreção de insulina, glucagon e polipetídeo pancreático[51, 52]. O acúmulo de substância amilóide dentro das células beta, presente nos pacientes com FC e diabetes e ausente naqueles com FC não diabéticos, contribui para a insulinopenia devido ao seu efeito citotóxico e limitador da secreção de insulina[52, 53].

È comum ocorrer atraso na puberdade, relacionado principalmente ao comprometimento nutricional do paciente e aos efeitos no organismo de uma doença crônica. No paciente com bom estado nutricional e com doença pulmonar controlada, a puberdade ocorre em época habitual. A esterilidade está presente em 98% dos pacientes do sexo masculino, decorrente de obstrução dos canais deferentes, levando a azoospermia obstrutiva. A fertilidade feminina está reduzida a 20 a 30% do normal[24].

Nas épocas de muito calor, exercícios intensos[54] ou quando o paciente apresenta vômitos ou diarréia[55], as excessivas perdas de sais no suor podem levar a depleção de sódio e cloro com desidratação hiponatrêmica, geralmente acompanhada de alcalose hipoclorêmica. Outro fator relacionado a quadros de hiponatremia em lactentes com FC é o aleitamento materno exclusivo. A OMS recomenda que ele seja exclusivo durante os seis primeiros meses de vida da criança, sendo também indicado para crianças fibrocísticas[56]. Porém, a concentração de sódio no leite humano pode ser inferior às necessidades diárias dessas crianças[57]. Assim, o Consenso Europeu de Fibrose Cística orienta a suplementação de sódio oral em todos os bebês amamentados ao seio materno, nos períodos de maiores perdas de sal, principalmente nas épocas mais quentes do ano[58].

Alterações nutricionais de pacientes com fibrose cística

Vários são os fatores que podem estar envolvidos na gênese e perpetuação da desnutrição nos FC. O aumento das necessidades de energia deve-se tanto ao aumento do gasto como ao das perdas. O aumento das perdas pode apresentar-se em nível digestivo (má-absorção por alterações pancreáticas, hepáticas e da própria mucosa intestinal), pulmonar (escarro), suor (sais e certas vitaminas) e urina (diabetes melito), levando à consequente perda de massa magra e depleção da função imunológica[59, 60].

Durante as fases de reagudização da patologia respiratória, o apetite costuma estar diminuído, levando a aportes significativamente menores que os habituais, e as necessidades aumentam em virtude do estresse metabólico provocado, principalmente, pelas infecções e pela insuficiência respiratória. A recomendação de ingestão diária de energia baseia-se na elevação do gasto energético apresentado por esses pacientes. Admite-se que os pacientes portadores de FC necessitam de, pelo menos 120-150% da energia estabelecida pelas *Recommended Dietary Alowances* (RDA's) de 1989[61].

Apesar dos avanços do tratamento clinico e nutricional, a Cystic Fibrosis Foundation, que compila os dados dos pacientes americanos com FC, relatou que 15,7% e 16,3% desses pacientes apresentavam valores abaixo do percentil 5 para peso e estatura, respectivamente[34]. Em 1993, o Registro Latino Americano de Fibrose Cística demonstrou que mais de 50% dos pacientes se encontravam abaixo do percentil 3 de peso e que 46,7% dos pacientes estavam abaixo do mesmo percentil na relação estatura para idade [60].

O gasto energético basal dos pacientes (GEB) com FC é elevado, entretanto existe muita controvérsia sobre as causas deste aumento. A doença pulmonar com infecções respiratórias de repetição (a inflamação crônica associada à liberação de citoquinas) e o aumento do trabalho respiratório contribuem com o aumento do GEB[62].

Para definição dos pacientes com desnutrição ou em risco nutricional os parâmetros utilizados são: peso, comprimento, perímetro cefálico, relação peso/estatura, indice de massa corporal (IMC), circunferência média do braço e pregas cutâneas. Estes parâmetros utilizados de acordo com gráficos de crescimento padronizados para idade e sexo são essenciais para adequado acompanhamento nutricional[62].

A fundação Americana de Fibrose Cística (Cystic Fibrosis Foundation-CFF) pelo seu comitê de Desenvolvimento de Nutrição publicou revisão sistemática sobre as recomendação e baseadas em evidências para o manejo nutricional dos pacientes com FC. Nelas comentam-se a dificuldade prática da utilização do percentual do peso(P) ideal em relação à estatura (E) e sugere-se a utilização do percentil do IMC para crianças maiores que dois anos de idade. Para menores de dois anos utiliza-se a relação %P/E e percentil P/E[63].

Alguns estudos mostraram que a utilização do percentil do IMC foi mais sensível que a porcentagem do peso ideal para idade, para as mudanças do volume expiratório forçado em um segundo[64, 65].

O acompanhamento nutricional realizado com a periodicidade de três meses é essencial para detectar desvios nutricionais ou alterações de comportamento alimentar[62]. O Recordatório de 24 horas, o Registro de três dias e Questionário de Frequência Alimentar são recomendados para avaliação da ingestão de calorias, qualidade e quantidade da dieta consumida, proporção de macronutrientes, horários, utilização de suplementos, enzimas e vitaminas[66].

Alguns Centros de Referência em FC, de acordo com protocolos de atendimento, preconizam o uso do Recordatório 24 horas como método de avaliação do consumo alimentar por apresentar de forma rápida, aspectos quantitativos da dieta[67].

Tabela 2. Estudos clínicos e nutricionais de crianças, adolescentes e adultos diagnosticados com fibrose cística.

Autor e Tipo de Estudo	Objetivo	Metodologia	Resultados
Steinkamp e Wiedemann, 2002. Estudo longitudinal[68].	Avaliar o EN e a FP.	Coorte de 3.298, acima de dois anos, agrupados pela presença ou ausência de desnutrição.	A prevalência de P/A anormal em crianças > de 6a até idade adulta aumentou de 19% para 38%. Associação* entre desnutrição e FEV1 ($p<0,05$).
Konstan et al., 2003. Estudo longitudinal[69].	Avaliar IN e a FP.	Coorte de 931 crianças, entre três e seis anos.	P/A, A/I e IMC são fracamente associados aos 3a, mas fortemente relacionados aos valores de FEV1 aos seis anos ($p<0,05$). A FP foi melhor naqueles com P/A > p10, dos três aos seis anos, e menor naqueles com < p10. Baixos IN e de crescimento aos três anos tendem a valores semelhantes aos 6 anos ($p<0,01$).
Adde et al., 2004. Estudo prospectivo transversal[24].	Avaliar EN, consumo alimentar e Escore de Shwachman.	74 pacientes, entre seis meses e 18 anos, em atendimento ambulatorial.	P/I, PCT e % gordura corpórea ↑ significativamente com o uso de enzimas pancreáticas e suplementos nutricionais ($p<0,05$). O consumo energético ↑ em relação à RDA ($p<0,05$). Associação*entre o EN e a gravidade da doença pulmonar avaliado pelo Escore de Shwachman ($p<0,05$).
Feijó e Silva Neto, 2006. Estudo transversal[49].	Avaliar a relação entre DMO, IMC e ΔF508.	25 pacientes, entre cinco e 14 anos e sete pacientes entre 18 e 28 anos, em atendimento ambulatorial.	Correlação positiva e significativa entre DMO e IMC ($p = 0,002$). Não foi verificada correlação entre DMO, ΔF508 e VEF1.
Morlin et al., 2006. Estudo transversal descritivo[70].	Avaliar EM e traçar plano de intervenção nutricional.	16 pacientes em acompanhamento ambulatorial, em todas as faixas etárias.	Diferença* entre o peso atual e ideal ($p = 0,04$). 43,7% dos pacientes apresentavam P/A ↓p10. A classificação de desnutrição pelos Consensos de Nutrição em FC detectou mais casos de desnutrição quando comparados a OMS.
Simon et al., 2009. Estudo transversal[60].	Determinar a relação entre consumo alimentar e EN.	85 pacientes, entre seis e 18 anos, em acompanhamento ambulatorial.	77% dos pacientes eutróficos (IMC > p 25) Média de ingestão de 124,5% da RDA. Associação* entre ingestão calórica e A/I ($p = 0,04$). O ↑ de 1% da ingestão calórica (RDA) ↓ em 2% a chance de ter déficit de estatura (OR = 0,98).

Pinto et al., 2009. Estudo prospectivo Transversal[71].	Avaliar EN e perfil clínico pelo Escore de Shwachman- ES.	21 pacientes, abaixo de 18 anos, em atendimento ambulatorial.	Maior comprometimento de EN em >10 anos para P/A, mas não houve diferença*. Depleção severa das reservas corpóreas pela AMB*, AGB. (p = 0,013). Escore Shwachman, 52,6 e 47,7, gravidade leve e moderada, respectivamente.
Chaves et al., 2009. Estudo descritivo transversal[72].	Avaliar EN e função pulmonar.	48 crianças e adolescentes, entre seis e 18 anos, em acompanhamento ambulatorial.	60% dos pacientes com baixa estatura (E/I<p5) tinham comprometimento moderado/grave da função pulmonar. Associação*entre IMC e VEF1 (p = 0,00001) e VEF1 e CMB (p = 0,0001).

EN: Estado Nutricional; FP: Função Pulmonar; IN: Índice Nutricional; P/A: Peso por Altura; A/I: Altura por Idade; IMC: Índice de Massa Corporal; PCT: Prega cutânea triciptal; *Estatisticamente significante; CVF: Capacidade Vital Forçada; a = anos; PO2: pressão parcial de oxigênio; FEV1: Volume Expiratório Forçado primeiro segundo; ↓: diminuição; DMO: Doença Mineral Óssea; RDA: Recommended Dietary Allowances; AMB: Área muscular do braço; AGB: Área Gordurosa do Braço.

Tratamento clínico e nutricional de pacientes com fibrose cística

O tratamento clínico deve ser realizado em centros especializados em FC, por isso está relacionado a um melhor prognóstico par o paciente. Apesar de não existir a cura definitiva para a FC, pois muitas das intervenções terapêuticas realizadas somente retardam a progressão da doença[24].

A boa fluidificação das secreções é muito importante, uma vez que são muito espessas. Além de uma hidratação adequada, recomenda-se o uso de nebulizações com solução fisiológica isoladamente ou com broncodilatadores, quando indicado (presença de sibilância ou resposta significativa ao broncodilatador na espirometria)[24].

Outras drogas mucolíticas são a N-acetilcisteína, cuja eficácia não está bem estabelecida na FC, e a DNase humana recombinante (rhDNase, dornase alfa-Pulmozyme). Esta última é uma enzima que digere o DNA extracelular derivado dos núcleos de neutrófilos degenerados, presentes em grandes quantidades no muco desses pacientes e um dos responsáveis por sua alta viscosidade[24].

A fisioterapia respiratória, após as inalações, é um ponto muito importante do tratamento, pois auxilia na eliminação das secreções respiratórias. É feita por meio de tapotagem, drenagem postural e por técnicas e aparelhos coadjuvantes, como as técnicas de expiração forçada, ciclo ativo da respiração, uso de máscaras com pressão expiratória positiva e uso do *flutter*. A tosse deve ser sempre estimulada, pois ela é o melhor

mecanismo para a eliminação das secreções. Atividade física regular deve ser incentivada, pois também é um estimulante da tosse [73].

A antibioticoterapia foi um dos fatores que melhoraram as taxas de sobrevida desses pacientes no decorrer das décadas. Os esquemas antibioticoterápicos usados variam muito nos diversos centros mundiais que cuidam de pacientes com FC. Alguns princípios devem ser seguidos como: seguir o diagnóstico microbiológico e evitar monoterapia para o tratamento da infecção por *P.aeruginosa*, para evitar o aparecimento da resistência[74].

Os antibióticos mais usados no combate ao estafilococo são as cefalosporinas, de primeira e segunda geração, amoxicilina-clavulanato, macrolídeos, sulfametoxazol-trimetropina, oxacilina, vancomicina, teicoplanina e linezolida. Essas três últimas devem ser reservadas para cepas de estafilococo resistentes à meticilina. Para infecção por *P. aeruginosa* o antimicrobiano de escolha para uso oral é a ciprofloxacina, com a qual já existe uma larga experiência em crianças com FC, mesmo as de pouca idade, tendo eficácia comparável aos antibióticos de uso parenteral para a maioria das exacerbações. Contudo, o uso repetido pode levar ao aparecimento de resistência que costuma ser transitória[24, 74].

Para o tratamento intravenoso da infecção por *P.aeruginosa* recomenda-se o uso da associação de um aminoglicosídeo (amicacina ou tobramicina) com uma cefalosporina de 3ª e 4ª gerações ou piperacilina/ticarcilina ou piperacilina-tazobactam ou carbapenêmico (imipenem, meropenem). Ceftriaxona e cefotaxima não devem ser utilizadas, mesmo se houver sensibilidade *in vitro*, pois não apresentam boa ação anti-*P. aeruginosa*. A associação mais freqüentemente usada no nosso meio é de amicacina com ceftazidima[24, 74].

Os antibióticos inalatórios são muito importantes no tratamento da infecção pulmonar, pois sua deposição local é alta, com baixa absorção e toxicidade sistêmica. Os mais usados são tobramicina, gentamicina, amicacina e colistin. São utilizados como terapia de supressão da infecção crônica por *P. aeruginosa* e no tratamento de erradicação da infecção inicial por *P. aeruginosa*[75].

Oxigênio deve ser usado se houver hipoxemia, utilizando-se os mesmos critérios de indicação dos doentes com doença pulmonar obstrutiva crônica[23].

Estudos com azitromicina têm mostrado que seu uso no paciente com FC e colonização crônica por *P. aeruginosa* pode levar a estabilização da doença pulmonar, diminuição das exacerbações e melhora nutricional. A supressão da secreção e síntese

de mediadores inflamatórios, alteração na função neutrofilica, inibição da síntese de alginato, protease e elastase pela *P.aeruginosa* e redução da sua aderência nas células epteliais são alguns dos prováveis mecanismos que fazem que os macrolídeos apresentem efeitos favoráveis nesses pacientes[24, 76].

A reposição de enzima pancreática deve ser feita junto a cada refeição. Atualmente as enzimas pancreáticas são administradas na forma de cápsulas contendo microesferas recobertas por resinas-resistentes, evitando com isso a sua inativação pela acidez gástrica. Assim, a enzima chega em forma ativa no duodeno e no jejuno, possibilitando um aumento na absorção de gordura para 85 a 90% do ingerido. Nos pacientes que necessitam de altas dosagens de enzima para o controle da esteatorréia devem-se associar inibidores da secreção gástrica de ácido, como a ranitidina ou o omeprazol, para aumentar o pH gástrico, otimizando então a ação da enzima[23, 24].

O uso do ácido ursodesoxicólico, em altas doses, parece exercer um efeito hepatoprotetor por ser um ácido biliar hidrofílico, repondo e aumentando o transporte dos ácidos biliares hidrofóbicos e tóxicos endógenos que se acumulam no fígado colestático, estimulando o fluxo biliar e inibindo a absorção intestinal dos ácidos biliares tóxicos. Também apresenta efeitos citoprotetor e imunomodulador no fígado. Apesar de ainda não haver evidências conclusivas de que o ácido ursodesoxicólico altere a evolução para a fibrose progressiva é recomendado o seu uso nos pacientes com a sequência colestase-fibrose-cirrose[38].

O segmento laboratorial da doença hepática e de suas complicações deve ser realizado mais frequentemente nesses pacientes[77, 24].

A importância de manter um bom estado nutricional se baseia na relação direta desta com a função pulmonar e com o aumento do tempo de sobrevivência desses pacientes. Uma vez que se trata de doença multisistêmica crônica e evolutiva, é a expressão clínica de cada paciente que deve determinar os requerimentos energéticos, individualizando o tratamento segundo a faixa etária e a fase evolutiva da patologia[68].

Devido ao déficit energético que ocorre nestes pacientes, normalmente se recomenda um consumo maior da energia estabelecida para indivíduos saudáveis da mesma idade e sexo, embora seja comum não alcançar valores calóricos elevados em fibrocísticos inapetentes[62, 67].

O aleitamento materno não está contra-indicado, mas requer controle cuidadoso da esteatorréia e administração de enzimas digestivas. O uso de hidrolisado, até os dois

anos de idade, tem-se generalizado, baseando-se no fato de diminuir a necessidade de enzimas a serem ingeridas[78].

O uso de suplementos energéticos pode ser recomendado, porém é importante assegurar que eles não estejam sendo utilizados como substitutos das refeições. Existem vários tipos de suplementos nutricionais disponíveis e o uso permite um melhor estado nutricional, acesso a dietas especializadas e melhores indicadores de saúde da saúde pulmonar[79].

A escolha do suplemento é frequentemente determinada pela necessidade energética, 1 a 2 Kcal/ml . Podem ser oferecidos antes ou após as refeições, ou ainda antes de dormir para manter normal o apetite das refeições[62, 78].

Quando a via oral não atingir o peso desejado, a suplementação via enteral poderá ser administrada via nasogástrica ou gastrostomia, preferencialmente durante à noite[78, 80].

No passado, dietas hipogordurosas eram preconizadas para se tentar diminuir a esteatorréia, atualmente dietas hipercalóricas ricas em gorduras são preconizadas, no entanto, seu uso deve ser incentivado com cuidado para evitar o aparecimento de complicações[78, 80].

Rhodes et al.[81] (2010) realizaram um estudo com 334 pacientes pacreato-suficientes (PS) e insuficientes (PI) e encontraram nos PS , quando comparados aos PI, níveis maiores de colesterol ($p<0,01$) e maiores concentrações de triglicerídeos o que sugere a necessidade de maiores estudos e cuidados na prescrição destas dietas.

Quadro 2- Características da dieta prescrita a pacientes com fibrose cística[61, 66, 80].

-Recomendação energética: 120 a 150% (RDA) 110 a 200% (DITEN)
-Proteínas: 15% do total das calorias;
-Gorduras: 35 a 40% do total das calorias;
-Adequar o aporte de enzimas pancreáticas (500 a 2000 unidades de lípase/kg/refeição);
-Adicionar sal às refeições: < 1 ano - 500 mg; 1-7 anos - 1g; >7 anos - 2 a 4 g;
-Nutrientes com alta densidade energética duas a três vezes por dia;
-Suplementar vitaminas A, D, E, K, Cálcio, Ferro e Zinco;
-Fornecer ácidos graxos poliinsaturados das séries ômega 3 e ômega 6 (usar óleos vegetais como canola, soja , peixes de água fria, TCM com ácidos graxos essenciais 1-2 ml/Kg/dia);
-Suplementar com nutrição enteral à noite, se necessário, visando atingir 40-50% das necessidades.

RDA- Recommended Dietary Allowances; DITEN- Diretrizes Brasileiras para Terapia Nutricional Enteral; TCM- Triglicerídeo de Cadeia Média.

2.4 CONCLUSÃO

Nos últimos anos os avanços no tratamento farmacológico e dietético - com dietas hipercalóricas, hiperproteicas e hiperlipídicas, assim como o acompanhamento clínico dos pacientes, aumentaram a sobrevida e proporcionaram uma maior qualidade de vida durante a infância, adolescência e idade adulta.

O entendimento da doença, a suplementação nutricional, o uso de enzimas, o tratamento com fármacos, entre eles a antibioticoterapia, propiciaram o aparecimento de indivíduos menos comprometidos em suas funções pulmonares e digestórias.

Devido a complexidade da enfermidade e as inúmeras alterações que podem advir, inclusive com a idade do fibrocístico, a definição de protocolos de atendimento podem contribuir para que sejam estabelecidas rotinas de atendimento que sigam diretrizes internacionais e nacionais e, dessa forma, aproximar a terapêutica desenvolvida no território nacional com outras de outros países.

Práticas como atendimento multidisciplinar, triagem neonatal e estudos na área clínico-nutricional devem ser incentivados nos pólos de atendimento para que a assistência seja precoce e a mais efetiva possível.

2.5 REFERÊNCIAS BIBLIOGRÁFICAS

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ARTIGO 2 –ARTIGO DE REVISÃO

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3 ARTIGO DE REVISÃO

MULTIDISCIPLINARY CARE IN CYSTIC FIBROSIS: A CLINICAL-NUTRITIONAL REVIEW

Abstract

The multidisciplinary care, at different referral centers of cystic fibrosis, is aimed at monitoring and treating cystic fibrosis patients. Mortality attributed to this hereditary disease is high, since it affects the exocrine glands, involving multiple organs, and evolves in a chronic, progressive way. However, systemized care and the improved, shared understanding of gastroenterologists, nutritionists and pulmonologists, contribute to prolonged survival and abated morbimortality. The aim of this study is to describe the main aspects of clinical and nutritional intervention in cystic fibrosis patients so that monitoring by a multidisciplinary team is optimized and performed as early as possible. The review was carried out on articles indexed in the Medline, Lilacs, SciELO, Current Contents and Cochrane databases, finding 189 articles in Portuguese, English and Spanish, with emphasis on articles published between 2000 and 2011. Due to the scientific relevant contribution, some publications before 2000 were included totalized 77 related to the multidisciplinary care. The reviewed studies suggest that multidisciplinary care is essential for knowledge integration in order to impose permanent update of scientific information, thereby contributing to the development of intervention strategies that enhance survival and motivate the development of skills to cope with the complex treatment regimen that is necessary for cystic fibrosis treatment and prevention of related complications.

Keywords: cystic fibrosis; lung disease; nutritional status; neonatal screening; spirometry.

Resumen

La atención multidisciplinaria, en diferentes centros de referencia de la fibrosis quística, tiene por objeto el seguimiento y el tratamiento de pacientes con fibrosis quística. La mortalidad atribuida a esta enfermedad hereditaria es alta, ya que afecta las glándulas exocrinas, afecta múltiples órganos, y evoluciona de manera crónica y progresiva. Sin embargo, la atención sistematizada y la mejor comprensión compartida de los gastroenterólogos, nutricionistas y neumólogos contribuen a la prolongación de la supervivencia y disminuye la morbi-mortalidad. El objetivo de este estudio es describir los principales aspectos de la intervención clínica y nutricional en pacientes con fibrosis quística, para que la supervisión de un equipo multidisciplinario se optimice y realiza lo más pronto posible. La revisión se llevó a cabo en artículos indexados en el Medline, Lilacs, SciELO, Current Contents y bases de datos Cochrane, la búsqueda de 189 artículos en Portugués, Inglés y Español, com énfasis en los artículos publicados entre 2000 y 2011. Debido a la destacada contribución científica, algunas publicaciones antes de 2000 se incluyeron totalizado 77 relacionados con la atención multidisciplinaria. Los estudios revisados sugieren que la atención multidisciplinaria es esencial para la integración del conocimiento con el fin de imponer actualización permanente de información científica, contribuyendo así al desarrollo de estrategias de intervención que mejoren la supervivencia y motivar el desarrollo de habilidades para hacer frente a la pauta de tratamiento complejo que es necesario para tratamiento de la fibrosis quística y la prevención de las complicaciones relacionadas.

Palabras clave: fibrosis quística; enfermedad pulmonar; estado nutricional; detección neonatal; espirometría.

3.1 INTRODUCTION

Cystic Fibrosis (CF) is a disease that reduces life span and has high morbidity[1]. Despite therapeutic advances and increased survival, patients with CF often experience decreased lung function, malnutrition and pancreatic insufficiency among other complications[2]. New treatments offer hope, but also present challenges for patients, practitioners and researchers[3].

The study by Farrel[4] combined a variety of methods to determine the prevalence of cystic fibrosis in the European Union. The results of literature reviews, surveys, and registry analyses revealed a mean prevalence of 0.737/10,000 in the 27 European Union countries, which is similar to the value of 0.797 in the United States, and only one outlier, namely the Republic of Ireland at 2.98.

In Spain, some regions have a prevalence of 1 in every 5:750 live births[5].

Combined multidisciplinary care at CF Centers and aggressive treatment of pulmonary symptoms with careful attention to nutritional well-being have substantially improved life expectancy in the past 10 years[6].

This paper aims to describe the main aspects related to the clinical and nutritional management of cystic fibrosis patients so that individual coaching is optimized and carried out at early stages. The adoption of such management guidelines at reference centers is necessary in order to maintain standard care service in centers equipped with multidisciplinary teams.

3.2 MATERIALS AND METHODS

The review was conducted on journal articles indexed in the Medline, Lilacs, SciELO, Current Contents and Cochrane databases, finding 189 articles when using cystic fibrosis, lung disease, nutritional status, neonatal screening and spirometry as key words, described in Portuguese, English and Spanish, with emphasis on articles published from 2000 to 2011. Due to the scientific relevant contribution, some publications before 2000 were included totalized 77 related to the multidisciplinary care.

3.3 RESULTS AND DISCUSSION

Genetics

CF is an autosomal recessive disorder that affects the exocrine glands, involving multiple organs, and evolves in a chronic and progressive way[7]. When each parent has one CF gene, the risk in each pregnancy of the child being born with or without the disease is 25% and 75% respectively, and the probability of being born healthy, but with one CF gene, is 50%[8].

The CF gene is located on the long arm of chromosome 7, consists of 250 kilobase DNA fragments, and has the ability to encode a 6.5 kb mRNA, which transcribes a transmembrane protein, an ion transport regulator, consisting of 1480 amino acids, known as CFTR (Cystic Fibrosis Transmembrane Conductance Regulator). The CFTR is essential for the transport of ions through the cell membrane and is involved in the flow of chlorine, sodium and water. More than 1600 mutations in the CFTR gene, however the most common of these occurs through a deletion of three base pairs, resulting in the loss of an amino acid (phenylalanine) at position F508 del of the CFTR protein which impedes proper functioning and thickening of secretions[8].

Disease manifestations are due to changes in the CFTR function, thus resulting in mild and more severe chronic lung disease manifestations, chronic diarrhea and steatorrhea, difficulty in gaining weight and height[9].

Cystic fibrosis diagnosis

According to the Cystic Fibrosis Foundation, in order to diagnose cystic fibrosis[10] one or more clinical manifestations must be considered such as obstructive/suppurative lung disease or chronic sinusits, gastrointestinal and nutritional changes, salt loss syndrome, urogenital abnormalities resulting in azoospermya associated with identification of two mutations for cystic fibrosis or sweat chloride ≥ 60mmol/L in two dosages. Also the family history of CF, demonstration of abnormal ion transport in nasal epithelium or neonatal screening test by the trypsin method[9, 10] should be considered. The clinical evaluation of not classic or doubtful FC cases may be performed through rectal biopsy which is well tolerated by young infants e not require general anaesthesia or sedation[11-14].

Population screening programs for newborns were imposed because the need for early treatment and improved of clinical. The screening is done simultaneously with the other constants in newborn screening, by immunoreactive trypsin blood tested. Cases screened as positive, do not give a definite diagnosis, because there is substantial proportion of false-positive. Confirmation is performe by genetic analysis of DNA from suspected patient[8].

In CF patients the assessment of exocrine pancreatic function is a mandatory procedure for diagnosis. The measure of faecal elatase -1(EL-1) has shown promise in early treatment of children after neonatal screening; it is an indirect test, accurate and reproducible pancreatic function whose values are reliable in a small sample of faeces[15].

Since the early use of screening tests, there is controversy as to the real impact on the progression of the disease, beyond the cost-effective aspect. However, those diagnosed through neonatal screening had a better evolution of nutrition and growth, and better lung function values at 10 years of age[9, 16].

In recent years there has been increased survival of CF patients due to research and scientific advances that have enabled a better understanding of the disease also the inclusion of serum immunoreactive trypsin (IRT) in neonatal screening[17].

Clinical Manifestations

The diseases of genetic origin are characterized by exocrine gland dysfunction, including pancreas, sweat glands and mucous glands of the respiratory tract, gastrointestinal and reproductive systems. The involvement of the respiratory system is considered the most critical in severity and lethality. Usually patients present a combination of diarrhea, recurrent respiratory infections and weight and height defficiency. There are less common manifestations, of which, the most important is meconium ileus[6, 9].

CFTR dysfunction impairs hydroelectric epithelial transport causes alterations to viscoelastics mucus proteins and provides greater susceptibility to respiratory infections such as pneumonia, bronchitis, bronchiectasis and rhinosinusitis[11].

CF patients have great susceptibility to colonization and endobronchial infection by specific bacteria, the chronic bronchopulmonary infection being the major cause of progressive lung damage in cystic fibrosis. In the first years of life, the respiratory tract of patients is usually colonized with Staphylococcus aureus. Then comes colonization

by *Pseudomonas aeruginosa*, wich is usually related to the progression of lung disease. Recent studies have shown that the prevalence of *P. aeruginosa* in the first years of life is high, but generally nonmucoid strains are detected. *Pseudomonas aeruginosa* is the most common pathogene, infecting approximately 80% of the population; however, variations may occur between percentage fibrocystics. Over the years, *Pseudomonas* changes its phenotype has changed and started producing large quantities of a substance (polysaccharide polymer) called alginate, when it becomes known as mucoid strain. This morphology is pathognomonic of cystic fibrosis[12].

Alginate facilitates bacterial, adherence to airways and the formation of microcolonies, hindering opsonization, phagocytosis and the penetration of antibodies and antibiotics. This bacterial phenotype is associated to a major difficulty in eradicating the infection, which becomes chronic and generates an intense inflammatory response. With advancing age, 70-90% of patients are infected by *P. aeruginosa*. Other agents such as *Haemophilus influenzae* and *Burkholderia cepacia* can also colonize the respiratory tracts. The latter is related to a more serious prognosis and hematogenous dissemination in addition to death called "cepacia syndrome"[18].

The presence of active CFTR in intestinal epithelium predicts that the gastrointestinal tract will be a site of disease. The gastrointestinal manifestations are most often the first changes in CF**,** may also occur in intrauterine life and mostly secondary to pancreatic insufficiency or gastric motility disorders. Obstruction of pancreatic canaliculi by mucus plugs impedes the release of enzymes into the duodenum, determining poor digestion of fats, protein and carbohydrates[19]. Bulky stools, greasy and pale are resulting from poor digestion and protein calorie malnutrition marked by loss of nutrients, and other factors inherent in the cystic fibrosis[20].

Malabsorption is predominantly caused by epithelial dysfunction, resulting from rejection of nutrients not hydrolyzed in the lumen due to pancreatic insufficiency. In 85% of CF patients, the pancreas does not produce sufficient enzymes for complete digestion of ingested food and one of the first signs is the malabsorption of nutrients[21]. The proteins required for growth and body tissue replacement are not fully used. Fat, the most energetic nutrient, is not absorved growth is delayed and liposoluble vitamin deficiencies may appear[22].

Patients who have pancreatic insufficiency have worse prognosis than who are pancreatic sufficient, but whether this is because of nutritional deficits or because the CFTR deficit is more severe is uncertain[23, 24].

Gastroesophageal reflux (GER) is common in CF and several factors likely contribute including large meals and medications that reduce lower esophageal sphincter. GER symptoms are present in a majority of patients and may worsen the respiratory condition[25]. The contribution of GER disease to the progression of pulmonary disease in CF is uncertain, but many physicians are vigorous in their treatment in part because of the possibility that there is some exacerbation associated with it[23].

The first manifestation of pancreatic failure in cystic fibrosis is meconium ileus -obstruction of the terminal ileum by thick meconium - which appears in 15-20% of infants and most diagnoses of meconium ileus (90%) are cystic fibrosis related. The pathogenesis has been linked to impaired secretion of pancreatic enzymes and poor digestion and dehydration of intestinal contents in the uterus, resulting in dried hiper viscose meconium which leads to obstruction at the distal ileum level. The distal intestinal obstruction syndrome or meconium ileus equivalent occurs in about 20% of patients, usually adolescents and adults[26].

Van der Doef et al.[27] determined the prevalence, risk factors and treatment of constipation in patients with CF in a cohort of 214 patients and have associated the occurrence of this diagnosis with low absorption of total fat and a history of meconium ileus. There was no association with the use of integrated fiber and fluid intakes.

Rectal prolapse occurs in about 20% of patients, especially those under two years of age. Contributing factors for this occurrence are bulky viscous stools which adhere to rectal mucosa, loss of peri-rectal fat, decreased muscle tone due to malnutrition added to increased intra-abdominal pressure by coughing. Resolution is usually spontaneous with the use of pancreatic enzymes and the improvement of the nutritional status[2].

CF affects the liver in different ways. Due to change in the CFTR protein, occurs a decrease insecretory function the bile duct epithelium making thicker secretions, this would lead to obstruction of bile ducts. This obstruction would lead to gradual changes in the liver may even get to cirrhosis[17, 23].

According Nash et al.[30] liver disease detected and closely monitored in adults appeared to have a milder course than childhood CF.

Liver lesion results in damage to the endogenous synthesis of vitamin D and its metabolism, and may bring about bone disease and changes in calcium metabolism, being that, intestinal absorption of this mineral is made under the influence of vitamin D. The low serum levels of 25 (OH) vitamin D contribute to the release of parathyroid

hormone (PTH) with the goal of raising calcium levels, but high levels of this hormone mobilize calcium and phosphorus from the bones, further decreasing bone mass Several studies have shown low bone mineral density (BMD) in patients with CF[24, 31].

Feijó et al.[31] found patients with low BMD, even in childhood. In the adult group, almost all had involvement in bone mineral density; 72% had osteopenia and 14% had osteoporosis osteoporosis. No correlation was observed between bone status, FEV 1 and the presence of F508 del mutation. Actually, the pathogenesis of such low BMD is not completely understood. A variety of potential risk factors may contribute to the development of osteoporosis in these patients, such as malnutrition, pancreatic insufficiency, calcium malabsorption, physical inactivity, corticosteroid therapy, chronic respiratory acidosis, reduced levels of sex hormones and decreased levels of insulin associated to diabetes[24].

A recent analysis has suggested that loss of CFTR activity may result in the increased resorption of bone cells in CF patients by means of a significant decrease of osteoprotegerin secretion (OPG-protein of TNF receptors superfamily that acts as a soluble inhibitor in the maturation and activation of osteoclasts) accompanied by increased prostaglandin secretion (PG) E2 in cultured osteoclasts[32].

Cystic fibrosis-related diabetes mellitus (CFRD) is an increasingly common complication of cystic fibrosis and did not match any of the types 1 and 2 classic disease. A minority developed diabetes mellitus requiring drug treatment, but changes in subclinical increase with age. The prevalence of diabetes increases with age, reaching up 40% of the cases in patients older than 30 years and provide adverse effects on clinical status, nutrition and lung function[33, 34].

Ripa et al.[35] demonstrated the presence of glucose intolerance and impairment insulin secretion in a significant percentage of children with CF. The reduction in insulin secretion appears to be associated with impairment of growth possibly via reduction of the levels of the growth-promoting insulin - like growth factor (IGF) axis.

The physiological mechanism of glucose intolerance in CF is controversial. Initially the endocrine tissue of the pancreas is preserved, but with increasing patient age, cells are lost and the gland begins to be completely replaced by fibrous tissue. Changes of chloride channel lead to hyperviscosity of pancreatic duct secretion, causing obstructive lesions, fatty infiltration, progressive fibrosis of the islets and reduced secretion of insulin, glucagon and pancreatic polypeptide. The accumulation of amyloid substance inside beta cells, present in patients with CF and diabetes, but absent in

nondiabetic CF patients, contributes to insulin deficiency due to respective cytotoxic and limiting effect of insulin secretion[36].

Delayed puberty is a common fact mainly related to nutritional impairment of the patient and the effects that chronic illnesses have on the body. In patients with good nutritional status and controlled pulmonary disease, puberty occurs at the customary time. Sterility is present in 98% of male patients, due to obstruction of vas deferens, leading to obstructive azoospermia. Female fertility is reduced by 20-30%[9].

Nutritional Manifestations

CF patients have high caloric requirements due to an increased resting energy expenditure (REE) bacterial infection and malabsorption[38]. REE is higher in patients with more severe phenotype[33, 39]. In rest, patients with moderate pulmonary disease may experience a slight increase basal energy metabolism and during exercise, total energy expenditure increases dramatically. In patients with severe disease, this spending also increased in the basal resting, due to lack of respiratory reserve. Possibly, patients with moderate pulmonary disease adapt to increased resting energy expenditure, reducing the level of physical activity[40].

Growth deficiency and malnutrition occur primarily owing to the difficulty these patients have in achieving energy needs and energy losses caused by the disease, which are mainly due to chronic lung inflammation and infections, malabsorption caused by pancreatic insufficiency, decreased bile flow and lung inflammation. The hepatic manifestation is much less prevalent and reaches approximately one third of patients. The gene CFTR is expressed exclusively in the apical membrane of colangiocytes and the epithelium of the gall bladder and not in hepatocytes leading to cholestasis and periportal fibrosis[38].

Malnutrition may be aggravated by the presence of anorexia, resulting from gastroesophageal reflux and/or cough, respiratory infections and chronic psychosocial stress. The role of dietary treatment is to improve or maintain adequate nutritional status of the patient and break the vicious malnutrition-infection cycle[33].

It is recognized that CF patients require at least 120-150% of the energy established by the Recommended Dietary Alowances (RDA's)[41] published in 1989 for the same age and sex. Lung function and nutritional status are closely correlated, and the severe weight loss can lead to a decrease in lean body mass, with consequences on

respiratory muscles. The protein-energy malnutrition is recognized as the worst prognostic factor of the disease[42].

As a definition for patients with malnutrition or nutritional risk, the parameters used areweight, length, head circumference, body mass index, mid-arm circumference and skinfold thickness. These parameters used in accordance with standardized growth charts for age and gender, are essential for proper nutritional monitoring[42].

The American Cystic Fibrosis Foundation (CFF) through the CFF Development Committee on Nutrition has published a systematic review of evidence-based recommendations for the nutritional management of patients with CF. It highlights the difficulties of using the weight percentage in relation to ideal height and suggests the use of BMI percentile for children older than two years of age. For children under two, it is used the % weight for height percentile and weight for height[10, 42 ,43]. Milla[1] showed that utilization of the BMI percentile was more accurate than the percentage of ideal weight for age, for the changes in forced expiratory volume in one second.

The nutritional follow up, at least at three months intervals, is essential to identify nutritional problems or altered eating habits. The use of three-day food records is recommended for caloric intake assessment, macronutrient proportion, timing, and use of supplements, enzymes and vitamins[42, 43].

In a cohort of 3298 patients 2 years old or older with cystic fibrosis, grouped by presence or absence of malnutrition, Steinkamp & Wiedemann found a statistically significant association between malnutrition, forced vital capacity (FVC), partial pressure of oxygen and of forced expiratory volume in one second (FEV1) ($p < 0.05$). This was also found between *Pseudomonas aeruginosa* and decreased lung function[44].

Chronic bacterial infection of the respiratory tract by microorganisms as *Pseudomonas aeruginosa*, members of the *Burkholderia cepacia* complex or *Staphylococcus aureus*, cause destruction and loss of lung function and is closely related to nutritional status. A major cause of nutritional depletion is the increase in energy expenditure due to inflammation and lung infection[8, 45].

In a longitudinal study aiming to evaluate the relationship between nutritional status and lung function, a strong association was found between FEV1, FVC and weight-height,height-age and body mass index ($p < 0.05$). Observed lung function was better in those with weight-height > 10th percentile, from 3 to 6 years, and lower for those with <10th percentile[46].

A survey conducted on outpatient care assessed the nutritional status, food consumption and values obtained by the Shwachman-Kulczycki score[47] in CF patients, observation noted that the weight-age, triceps skinfold thickness and body fat percentage increased significantly with the use of pancreatic enzymes and nutritional supplements ($p<0.05$). Hamill et al.[48] conducted a nutritional assessment which involved taking measurements of weight, height by length, arm circumference and skinfold (triceps, biceps, subscapular and suprailiac).

These measurements were compared to growth charts Healths National Center for Healths Statistics and converted into scores based on age and gender[49]. In this analysis, energy consumption increased in relation to RDA ($p<0.05$) and there was statistically significant association between nutritional status and severity of pulmonary disease assessed by Shwachman-Kulczycki score ($p<0.05$)[49].

This score consists of four criteria: general activity, physical examination, nutritional and radiological chest, scored on a scale of 5 to 25 points (best performance, highest score). The maximum score is 100 points and represents a patient with an excellent clinical[47].

To assess nutritional status and establish an intervention plan, 16 patients, with an average of 8.15 years, were monitored in a cross-sectional study and observation attested a statistically significant difference between current and ideal weight ($p = 0.04$)[50]. In those age groups studied, 43.7% of patients had weight-height below the 10th percentile. The study showed that CF Nutrition Consensus[51, 52] detected more cases of malnutrition in CF than the World Health Organization recommendation[50-53].

The CF Nutrition Consensus carry out the assessment of nutritional status % by weight for age, body mass index and percentile weight for height allowing the identification of patients with normal weight at risk for nutritional failure and need for invasive support. The recommendations of the World Health Organization using percentiles of weight for height, weight for age, height for age and body mass index identifying the eutrophic and nutritional risk[51- 53].

Satisfactory results were found in a 2009 study that assessed the nutritional status and food intake. In a sample of 85 patients, between 6 and 18 years, 77% were eutrophic (BMI>p25) and average intake was at 124.5% of RDA. In the univariate logistic regression analyses was found a significant association between the independent variable calorie intake and the Z score for weight/age. The multivariate analyses, based

on the hospitalizations, demonstrated that a 1% increase in the calorie intake decreases the chance of having short stature by 2% (OR: 0.98; 95% CI: 0,96-1.00)[38].

In a study by Pinto et al.[54] CF patients above the age of 10 had greater nutritional status impairment. Malnutrition was also found in 66.7% of the sample and severe depletion of body reserves in the arm muscle area and upper arm fat area (p = 0.013)[54].

Chaves et al.[45] was found in CF patients (n = 48) statistically significant association between body mass index and triceps skinfold (p = 0,001 e p = 0,0300 respectively) with the degree of pulmonary involvement, while the arm muscle circumference showed only a trend (p = 0.06) for this same association. Linear regression revealed a moderate relationship between body mass index and FEV1(r = 0,46; p = 0,00001) and between FEV1 and arm muscle circumference (r = 0.46, p = 0.0001). 60% of children and adolescents were stunted (<p5) and had moderate to severe impairment of lung function.

Treatment of cystic fibrosis

Clinical treatment should be performed in specialized CF centers, given that this represents better patient prognosis. Although there is no cure for CF, many therapeutic interventions do retard progression of the disease[9]. The use of the multidisciplinary approach model to treat the disease is based on the observation that the creation of comprehensive care centers for CF is related to the progressively better prognosis to patients[55].

Treatment for CF patients includes antibiotic therapy, mucolytic agents, bronchodilators, anti-inflammatory agents, pancreatic enzyme replacement and ursodeoxycholic acid, nutritional support, oxygen supplementation and physiotherapy[56].

Antibiotic therapy

Antibiotic therapy is one of the factors that have contributed to survival rates. The antibiotic regimens used vary widely, but some principles should be followed such as: performing microbiological diagnosis and avoiding monotherapy for treatment of *P. aeruginosa* infection, in order to avoid resistance. Antibiotics commonly used to combat staph are the cephalosporins of first and second generation such as amoxicillin-clavulanate, macrolides, trimethoprim-sulfamethoxazole, oxacillin, vancomycin,

teicoplanin and linezolid. The last three should be reserved for strains of staphylococci resistant to methicillin. For infection by *P.aeruginosa*, the antibiotic of choice for oral use is ciprofloxacin; with which there is already considerable experience in CF children with comparable efficacy to the parenteral use of antibiotics. Repeated use can cause resistance that is usually transitional[9-57].

For intravenous treatment of *P. aeruginosa* infection, it is recommended to use a combination of an aminoglycoside (amikacin or tobramycin) with a cephalosporin, 3th and 4th generations or piperacillin/ticarcillin or piperacillin-tazobactam or carbapenems (imipenem, meropenem). Cefotaxime and ceftriaxone should not be used; even if there is in vitro sensitivity, since it does not show good anti-*P. aeruginosa* action. The association most frequently used in our midst is amikacin with ceftazidime[9-57].

Inhaled antibiotics are very important in the treatment of pulmonary infection because the local deposition is high; with low absorption and systemic toxicity. Tobramycin, gentamicin, and amikacin are used most as suppressive therapy of chronic infection by *P. aeruginosa* and treatment of initial infection by *P. aeruginoasa*[57].

Studies with azithromycin have shown that use in patients with CF and chronic colonization by *P. aeruginosa* can lead to stabilized lung disease, reduced exacerbations and nutritional improvement. The suppression of secretion and synthesis of inflammatory mediators, alteration in neutrophil function, inhibition of alginate synthesis, protease and elastase by *P. aeruginosa* and reduction of their grip in the epithelium cells, are some of the possible mechanisms which cause macrolides to have a beneficial effect on these patients[9].

Mucolytics and bronchodilators

Good fluidity of secretions is very important, since they are very thick. Besides adequate hydration, the use of a humidifier/nebulizer is recommended with simple saline or with bronchodilators, when indicated (presence of wheezing or significant spirometric response to bronchodilators)[58].

Nebulization of the hypertonic saline solution increases ciliary transport, improves the rheological properties of the sputum, and improves the hydration of the surface of the airways[8]. Elkins et al.[58] demonstrated a significant improvement in lung function and no worsening of the bacterial infection or the inflammation. Therefore, in

CF patients, nebulization of hypertonic saline solution, preceded by bronchodilator inhalation, is a safe, affordable treatment, providing therapeutic benefits.

Recombinant human deoxyribonuclease (rhDNase, dornase alfa, Pulmozyme) has been shown to improve lung function, reduce sputum viscosity and the number of pulmonary exacerbations in patients with cystic fibrosis[59].

RhDNase is a purified solution for use inhaled, which reduces the viscosity of the mucus derived from the nucleus of degenerated neutrophils. Several studies show alfadornase that is safe, effective and well tolerated in patients with mild lung disease, moderate or grave[60]. Studies reporT short-and long-term maximum improvement in FEV1 of about 5% -13%, depending on the severity of disease[61]. Early initiation of treatment is related the rate of improvement in function pulmonar[62].

Inhaled bronchodilators have been used as part of the standard treatment in CF and the agents most frequently employed are the short-acting agonists. The bronchodilators can improve the respiratory function, because these patients often have bronchial hyperactivity[8, 63].

Anti-inflammatory agents

Some of the most important pathobiology in cystic fibrosis occurs not as a direct result of impaired chloride transport, but the downstream consequences of defective CFTR function, particularly the lung infection and inflammation that ultimately takes the lives of most patients. Interrupting the vicious cycle of infection and inflammation is effective in slowing the course of the disease[64].

The pathophysiological process in CF has been the target of numerous studies. Despite such efforts, a drug that is efficient and safe for this purpose has not yet been identified[65]. Although oral corticosteroids at a dose of 1-2 mg/kg on alternate days seem to retard the progression of the pulmonary disease, the benefits are offset by the significant adverse effects, especially growth impairment. There is as yet little evidence for the use of systemic corticosteroids to treat CF exacerbations. However, systemic corticosteroids have been used as a therapeutic resource in patients with severe exacerbations, especially in the presence of bronchial hyperreactivity[66].

Inhaled corticosteroids and high doses of ibuprofen have also been studied in CF with the objective of reducing the inflammatory process and decreasing lung injury. However the current evidence is insufficient to establish whether there is benefit in its use[67].

Other anti-inflammatory drugs have been much less widely studied in CF like pentoxifylline, tyloxapol, gelsolin, surfactant, and hypertonic saline in varying concentrations. None of these substances should also be routinely used in the treatment of pulmonary manifestations in cystic fibrosis[8].

Pancreatic enzyme replacement and ursodeoxycholic acid

Pancreatic enzyme replacement should be undertaken along with meals. Currently pancreatic enzymes are administered in the form of capsules containing microspheres coated with resin-resistant, thus avoiding inactivation by gastric acidity. The enzyme comes in active form in the duodenum and jejunum, allowing an increase in the absorption of fat to 85-90% of ingested substances. In patients requiring high doses of enzyme for control of steatorrhea, it is necessary to associate this with gastric acid secretion inhibitors, such as ranitidine or omeprazole to increase the intestinal pH and enhance the action of the enzyme[8, 9].

The use of ursodeoxycholic acid in high doses seems to exert a hepatoprotective effect by being a hydrophilic bile acid, increasing the transport of hydrophilic bile acids that accumulate in the cholestatic liver stimulating bile flow. Although there is no conclusive evidence regarding the use of ursodeoxycholic acid, this is recommended for patients with cholestasis-fibrosis-cirrhosis sequence. Laboratory monitoring of liver disease and its complications should be performed more often in these patients[9, 68].

Use of oxygen

People with cystic fibrosis (CF) suffer from breathing problems. Giving additional oxygen has long been a standard of care for people with chronic lung diseases. It is common for doctors to prescribe this treatment for people with CF when there is not enough oxygen in their blood[69]. Oxygen should be used if there is hypoxia, using the same criteria of indication for patients with chronic obstructive pulmonary disease[8].

In the short term, treatment has shown some improvement in blood oxygen levels in people with CF during sleep and exercise. However, caution needs to be

exercised in those with advanced lung disease where this may require further monitoring[69].

Recent Department of Health changes to the provision of home oxygen have emphasized the importance of cost and the need for evidence of efficacy through proper assessment. The decision to start and to continue home oxygen therapy should be carefully assessed and reassessed at regular intervals[70].

Physiotherapy

The Respiratory Therapy (FR) aims to promote improvement in the patient's respiratory mechanics, reducing your caloric expenditure, and removes the sticky mucus and exudate caused by lung infections and is the main non-pharmacological treatment[71].

The maneuvers of airway clearance help in the removal of secretion reducing the bronchial obstruction and its consequences, such as atelectasis and hyperinflation. The main resources used in cystic fibrosis are: postural drainage, clapping, percussion, and manual and mechanics vibration, forced expiration technique, positive expiratory pressure mask, active cycle of breathing techniques, flutter, shaker, acapella and autogenic drainage[1, 71].

Chest physiotherapy (CP) is seen as a cornerstone of Cystic Fibrosis treatment. However, previous studies have suggested that adherence to CP is low. Myers & Horn investigated CP adherence and associated factors. Only 29.5 per cent reported undertaking daily CP.

Predictors of adherence included problems with fitting CP into lifestyle, a perception that CP does not help, physical consequences of CP, doing exercises instead and doing CP as and when necessary[72, 73].

Nutritional Support

The importance of maintaining good nutritional status is based on a direct relationship between lung function and patient survival. Since cystic fibrosis is a chronic and multisystemic disease in constant evolution, the clinical expression of each patient should determine the energy requirements, individualizing treatment according to age and developmental stage of pathology[42].

Due to the energy deficiency that occurs in these patients, a greater daily

calorie intake is usually recommended, although it is common not to reach high caloric values in inappetent CF[42].

Breastfeeding is not contraindicated in CF patients, but requires the careful control of steatorrhea and administration of digestive enzymes. The use of hydrolyzed milk up to two years of age is widespread, based on the need to reduce ingested enzymes[74].

The use of energy supplements may be recommended, but it is important to ensure that they are not being used to substitute meals. There are several nutritional supplements available whose prolonged use allows an effective nutritional recovery, demonstrated by significant increase in weight, growth rate and stabilization of lung disease. The choice of supplement is often determined by the energy requirement and 1-2 kcal/ml is recommended. This may be offered before or after meals or at bedtime to maintain normal appetite[42, 74].

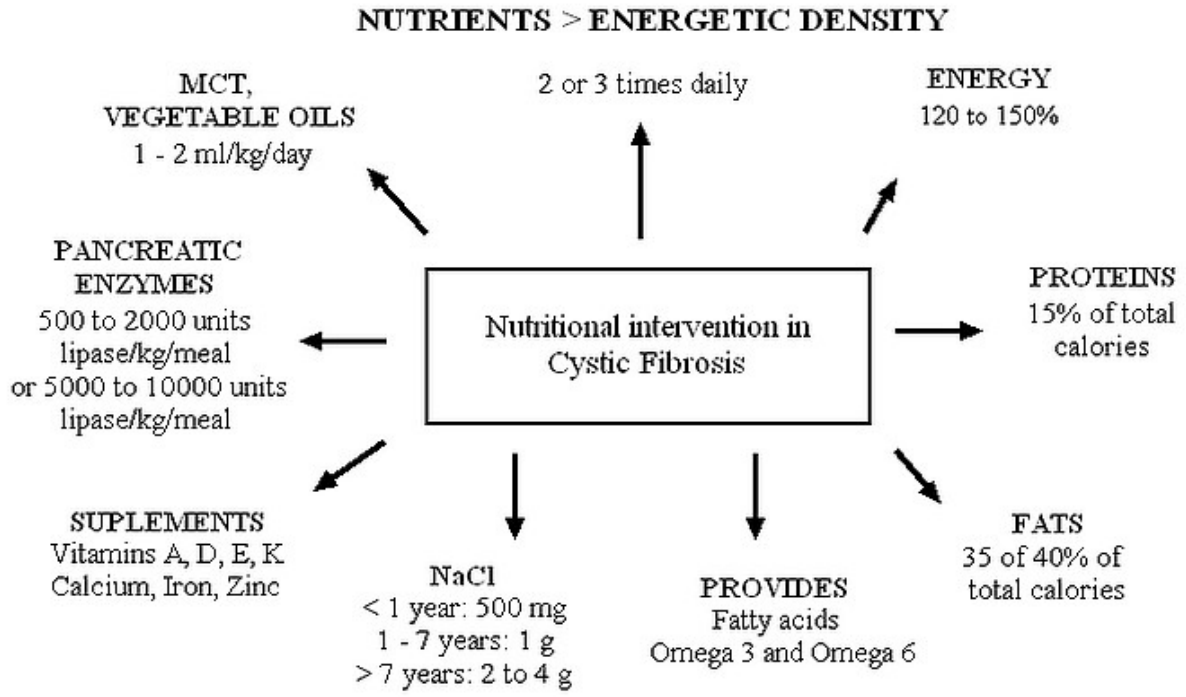
When oral food intake is not enough to reach desired weight, supplementation may be administered enterally via nasogastric or gastrostomy, preferably during the night[74-75].

In the past, low-fat diets were recommended in an attempt to reduce steatorrhea, but nowadays high-fat hypercaloric diets are being recommended. However, care should be encouraged in order to avoid complications. Rhodes et al. conducted a study involving 334 patients pacreato-sufficient (PS) and insufficient (PI) and found in PS, when compared to the PI, higher levels of cholesterol ($p<0.01$) and higher triglyceride concentrations, suggesting the need for further study and care in prescribing these diets[76].

Attainment of a normal growth pattern in childhood and maintenance of adequate nutritional status in adulthood represent major goals of multidisciplinary cystic fibrosis centers. International guidelines on energy intake requirements, pancreatic enzyme-replacement therapy and fat-soluble vitamin supplementation are of almost importance in daily practice.[2]

The Figure 1 summarizes the most up-to-date information on nutritional management.

Figure 1 – Nutritional intervention in Cystic Fibrosis.



DRI's - Dietary reference Intakes (77) (2005), DITEN - Brazilian Guidelines for Nutritional Enteral Therapy (75) (2009): MCT - Medium-Chain Triglycerides

3.4 **FINAL REMARK**

The literature shows the need for multidisciplinary care for CF to be comprehensive because the disease is multi-systemic. The multidisciplinary, neonatal screening and clinical studies dies in the clinical and nutritional area should be encouraged in all centers so that support is initiated early and effectively.

The studies reviewed suggest that multidisciplinary care is essential for the integration of knowledge so as to impose the permanent update of scientific information, thereby contributing to the development of intervention strategies that enhance survival and motivate the development of skills to cope with a complex therapeutic regimen that is necessary for the treatment of CF and the prevention of its complications.

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ARTIGO 3 – ARTIGO REVISÃO

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4 ARTIGO REVISÃO

PATHOPHYSIOLOGY OF CYSTIC FIBROSIS AND DRUGS USED IN ASSOCIATED DIGESTIVE TRACT DISEASES

Abstract

Cystic fibrosis (CF) causes chronic infections in the respiratory tract and alters the digestive tract. This paper reviews the most important aspects of drug treatment and changes in the digestive tract of patients with CF. This is a review of the literature, emphasizing the discoveries made within the last 15 years by analyzing scientific papers published in journals indexed in the Scientific Electronic Library Online, Sciences Information, United States National Library of Medicine and Medical Literature Analysis and Retrieval System Online databases, both in English and Portuguese, using the key words: cystic fibrosis, medication, therapeutic, absorption, digestion. Randomized, observational, experimental, and epidemiological clinical studies were selected, among others, with statistical significance of 5%. This review evaluates the changes found in the digestive tract of CF patients including pancreatic insufficiency, constipation and liver diseases. Changes in nutritional status are also described. Clinical treatment, nutritional supplementation and drug management were classified in this review as essential to the quality of life of CF patients, and became available through public policies for monitoring and treating CF. The information gathered on CF and a multiprofessional approach to the disease is essential in the treatment of these patients.

Key words: Cystic fibrosis; medication; therapeutic; absorption; digestion

Core tip: Cystic fibrosis (CF) has been studied in Brazil and in many other countries. Digestive manifestations may significantly compromise the nutritional status of CF patients, leading to numerous symptoms. Supplementation with enzymes, vitamins and nutrients is usually necessary. When infections are present, antibiotics are necessary, and these infections are often multisystemic, involving the digestive tract. The pharmaceutical assistance included in public policies, especially those which are financed, and the constant incentive to study the digestive manifestations in CF patients are essential, as without them, there would be infinite clinical changes which would compromise patient survival.

4.1 INTRODUCTION

Cystic fibrosis (CF) is a chronic progressive disease, it exists in every ethnic group and it is equally common in both sexes. The *CF* gene has been isolated, cloned and sequenced, enabling the study of biochemical mechanisms responsible for the physiopathogenesis of the disease. It also enables easier

treatment of the patient's complications, such as the thick and viscous fluids which obstruct the lungs, the pancreas and the biliary duct[1,2].

The prevalence of CF varies according to ethnicity, from 1/1800 to 1/5000 in Caucasians born alive in Europe, in the United States and in Canada, 1/14000 in Afro-Americans, and 1/40000 in Finland. It is considered a rare disease among Asians and Africans. In Brazil, local studies show variable statistical data which suggest an approximate incidence of 1/7000. The average lifetime of CF patients has increased in the last few years, which is the result of early diagnosis and specialized treatment in the early stages of the disease[1,3,4].

The treatment of CF aims to clear the lungs using aerosols and respiratory physiotherapy, and to maintain nutritional status with nutrient supplementation and pancreatic enzymes. Recent medical advances have improved survival, but with increased costs, especially when the disease has progressed and when hospitalization is required. When infections are present, antibiotics are necessary, usually due to clinical complications which are often multisystemic, and involve the digestive tract[5,6]. Due to many involved systems and the variety and chronicity of the disease, a multitask approach is essential to help the patients and their families to comprehend the disease and undergo medical treatment[7].

The current therapy for CF includes the maintenance of nutritional status, clearance of the pulmonary tract, utilization of antibiotics and other medication, treatment and monitoring of gastric, pancreatic and hepatobiliary changes, in addition to dietary supplementation with hypercaloric and hyperproteic foods, and the utilization of enzymes, minerals and vitamins[1, 8,9].

When chronic CF is diagnosed, with many clinical manifestations, the continuous use of medication (antibiotics, bronchodilators, mucolytics) and related procedures (respiratory physiotherapy, oxygen therapy, lung transplantation, digestive enzyme replacement and nutritional support) are required[8,10]. Due to the chronicity and the need for precautions in CF, the development of a Reference Center and the establishment of an organization that involves family members is crucial, together with an increase in cooperation between groups of CF patients and other organizations[4,11,12].

CF requires the continuous use of medication which increases the average cost of treatment, and is too expensive for families. For that reason, CF patients and their families have the right to receive government help under the Unique Health System.

The clinical record of the Health Ministry guarantees access to alpha dornase for pulmonary complications and pancreatic enzymes in patients with pancreatic insufficiency[3]. There are many deeds in every unit of the federation, including the Distrito Federal, to promote early diagnosis and even provide special formulas such as the alimentary supplements provided by Ordinance number 94/1809, published at the Distrito Federal in 2009[13].

In Brazil, the dedication to diagnosing CF during infancy is significant, with the use of programs for newborn screening or sweat testing. It is known that early treatment, including drug treatment, contributes to the prognosis and survival of CF patients[14-17].

The objective of this study was to review the most important aspects of drug treatment and changes in the digestive tract of patients with CF. We also aimed to assess the pharmaceutical monitoring offered to CF patients undergoing treatment by public agents from the public health care system.

4.2 MATERIALS AND METHODS

This review focused on CF literature over the last 15 years, and included scientific papers indexed in the databases of Scientific Electronic Library Online, Sciences Information, United States National Library of Medicine and Medical Literature Analysis and Retrieval System Online, using the key words: cystic fibrosis, medication, therapeutic, absorption, digestion. Studies in English and Portuguese were selected.

The survey focused on the major advances in the understanding of CF during this period, both in understanding the disease and its treatment.

Articles that included at least one of the mentioned key words were selected. Controlled clinical studies were included, as well as observational epidemiological studies and meta-analyses, among others. Papers which did not include information on the diagnosis of CF or adherence to treatment were excluded as were experimental animal studies and gene therapy studies and those published in languages other than English and Portuguese.

4.3 RESULTS AND DISCUSSION

Physiopathology of the disease: overall symptoms

The manifestation of CF is very changeable and may appear in the neonatal period or later in life. Some patients are completely asymptomatic for several years. The most common clinical signs of CF include a chronic cough, chronic diarrhea and malnutrition; however, the disease can appear in other ways, and can affect multiple systems and organs[18].

Mutation of the *CF* gene causes absence or dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which works as a chloride canal in the apical membranes of epithelial cells. The CFTR also affects the production of mucus, secretory granules and intracellular organelles. This defect affects cells in many organs, not all organs have similar clinical responses, and different organs may be affected. Involvement of the respiratory tract is associated with a higher death rate and leads to death in 90% of patients[18-20].

The most common and important symptom which affects the digestive tract is exocrine pancreatic insufficiency, characterized by chronic diarrhea with undigested food present. A decrease in the secretion of sodium bicarbonate reduces the efficacy of pancreatic enzymes and the precipitation of bile salts, which results in a more acidic pH in the duodenum, contributing to malabsorption[18].

The obstruction of pancreatic canaliculi by mucous plugs prevents the release of enzymes into the duodenum, which causes poor digestion of fat, proteins and carbohydrates. Malabsorption is caused by pre-epithelial dysfunction, which occurs after the rejection of non-hydrolysable nutrients in the lumen. Therefore, malnutrition occurs due to inadequate food digestion and increased energy needs (dietary recommendations) that are rarely achieved by CF patients due to anorexia and recurrent respiratory disease among other diseases[18,21-23].

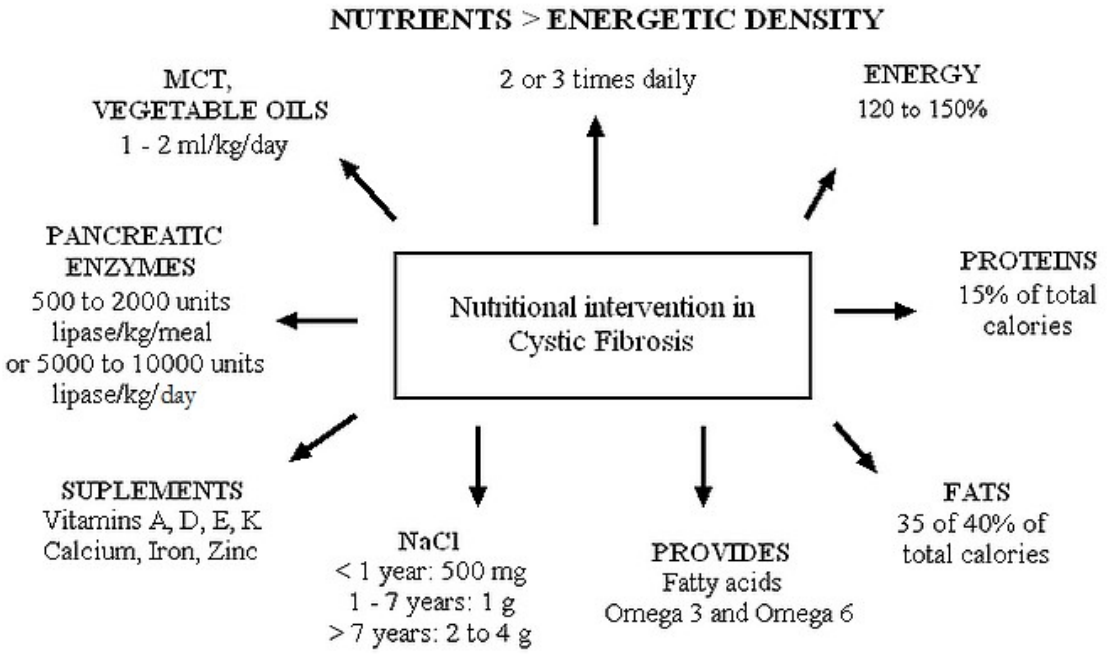
The endocrine pancreas also undergoes changes and the prevalence of CF related to glucose intolerance has increased proportionally with the rate of survival. The main cause of diabetes is damage caused to the pancreas, leading to a decrease in insulin secretion. Diabetes in CF patients results from microvascular and macrovascular complications associated with accelerated lung deterioration, consequently increasing the death rate. Since nutrition is critical in CF patients, blood glucose should be monitored and the insulin dose should be adapted, with a focus on adequate intake of nutrients[24].

Symptomatic vitamin A and vitamin E deficiency has been reported in patients with CF presenting with deficit nutrient consumption and absorption[25,26].

Many newly diagnosed infants have low levels of one or more fat-soluble vitamins[27,28] and due to the prevalence of fat-soluble vitamin deficiency, all infants with CF should receive standard, age-appropriate non–fat-soluble vitamins and vitamins A, D, E, and K as recommended in the CF Foundation Consensus Report on Nutrition for Pediatrics[29].

Most patients who are vitamin deficient can be treated adequately with the doses of fat-soluble vitamins recommended in the CF Foundation Consensus Report on Nutrition for Pediatric Patients[30] . Figure 1 shows relevant information on the nutritional care of CF patients [7].

Figure 1- Macronutrients and micronutrients essential for the recovery and maintenance of nutritional status in cystic fibrosis patients

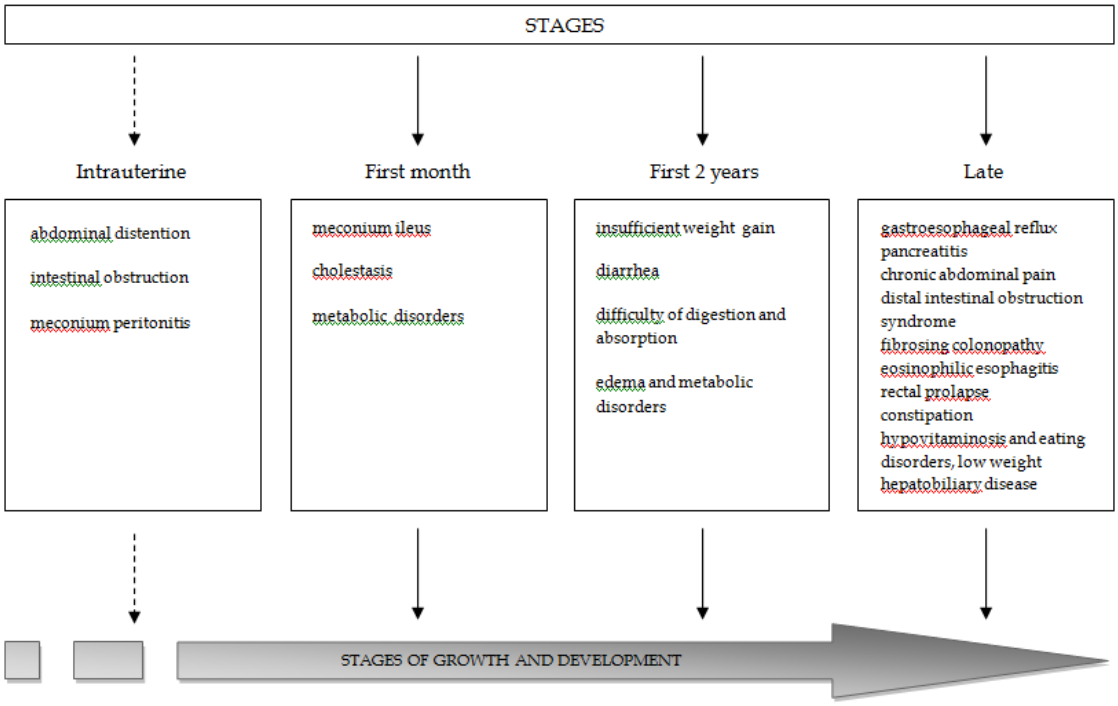


MCT: Medium Chain triglycerides

Among other events related to CF, meconium ileus, obstruction of the terminal ileum by thick meconium, is the first signal of pancreatic insufficiency, which affects 15% of babies. Therefore, treating patients with meconium ileus is very important until proved otherwise[31].

Early diagnosis and the treatment of complications of the respiratory and gastrointestinal tract in CF can lead to an improvement in the survival rate of CF patients. Those who live beyond the fourth decade have a higher risk of developing additional diseases associated with chronic manifestations; hence, patients with a higher risk of chronic diseases should be monitored closely to improve the chances of early diagnosis[32]. Figure 2 summarizes the majority of abnormalities observed in the digestive tract of patients diagnosed with CF from intrauterine life to adulthood.

Figure 2- Sumary of major abnormalities observed in the digestive tract patients diagnosed with cystic fibrosis from intrauterine life to adulthood.



Gastrointestinal disease

In CF patients gastrointestinal symptoms, such as nausea, vomiting, malnutrition and indigestion are frequent. In addition, gastroesophageal reflux disease, esophageal adenocarcinoma, distal intestinal syndrome and cholelithiasis are often seen in CF patients[33-35].

There is increasing evidence to suggest that chronic inflammation is present in the gastrointestinal tract of CF patients. Some CF patients continue to have many severe gastrointestinal symptoms despite conventional CF treatment[36].

A recent publication indicated the presence of eosinophilic esophagitis (EoE) in cf patients aged from 4, 12 and 15 years. Patients with CF may have clinically persistent emesis, food aversion and failure to thrive. It is possible that EoE has been underappreciated in CF due to symptom overlap with other common gastrointestinal disorders, including gastroesophageal reflux disease, infections, medication side effects or others conditions[37].

Because the symptoms in EoE are non-specific and are also common in CF, when a patient with CF presents with food avoidance, regurgitation, heartburn or dysphagia, EoE should be considered, particularly if symptoms do not respond to empiric treatment and if endoscopic evaluation is contemplated[38-40].

Secretory cells of CF patients show modification in their absorptive-digestive function in the gastrointestinal tract and the entire digestive process is altered, which results in malabsorption of nutrients, malnutrition and several gastrointestinal tract-related symptoms[34,41].

Abdominal pain is a common complaint in CF patients, and distal bowel obstruction syndrome and fibrosing colonopathy are characteristics of gastrointestinal complications in CF patients. The main causes of epigastric pain in patients with CF are gastroesophageal reflux disease, biliary tract disease, pancreatitis and gastritis[42, 43].

Among the frequently observed gastrointestinal manifestations, gastroparesis has been diagnosed by a variety of methods and has been described by CF patients. Gastroparesis is a frequent complication of lung or heart-lung transplantation. It is predominantly found in children and individuals with severe deterioration of the pulmonary tract[43, 44].

After meconium ileus, the main area affected by distal bowel obstruction syndrome (DIOS) is the right colon. DIOS is more common in patients with pancreatic insufficiency. Several factors can trigger the syndrome, such as dehydration, the use of medicines which interfere with intestinal motility and pancreatic enzyme replacement. The most common signs and symptoms of DIOS are decreased defecation and colic pain in the right lower quadrant. During clinical examination, a reduction in intestinal peristalsis can be observed, with the possibility of cessation at some point. In some cases, a mass in the lower right quadrant can be palpated, which is related to distention of the cecum and right colon[45].

Intestinal obstruction syndrome is similar to meconium ileus; however, one of the differences between these conditions is patient age. Intestinal obstruction syndrome is characterized by the impaction of fecal residues in the terminal ileum and one of the precipitant factors for obstruction is dehydration. This obstruction can be total or partial, and may cause symptoms such as abdominal distention, constipation, anorexia, vomiting, and early satiety, which result in weight loss[45].

Fibrosing colonopathy is another characteristic of CF, and includes a change in the colon submucosa, inflammation, and progressive fibrosis associated with managing the high doses of pancreatic enzymes. The clinical symptoms are pain and abdominal distention after ingesting food, anorexia, difficulty in gaining weight and digestive bleeding[34, 46].

Pancreatic disease

The pancreas is one of the main organs affected by dysfunction of the CFTR. The exocrine pancreas is responsible for producing enzymes for food digestion in the intestinal lumen and exocrine pancreatic insufficiency is a well-known complication of CF and leads to fat loss in feces. Loss of function of the pancreas is associated with every genotype of CFTR mutation, leading to pancreatic insufficiency[47-49].

Pancreatic exocrine insufficiency (PEI) is considered the main cause of intestinal malabsorption in CF, affecting 85% to 90% of patients[50], and if inadequately treated high stool energy losses will occur, which is an important determinant of energy imbalance and malnutrition[51].

Intestinal malabsorption is usually of early onset: signs and symptoms of maldigestion are often present at birth, and in the majority of patients, during the first years of life. At the time of diagnosis, at least 50% of infants identified by neonatal screening have PEI, and most of those carrying severe CFTR mutations on both alleles develop PEI during the first years of life[52-55].

PEI is clinically characterized by weight loss or difficulty in gaining weight, diarrhea with a greasy appearance and malabsorption of fat-soluble vitamins A, D, E and K. Thus, the supplementation of these vitamins is routinely recommended, followed by blood examinations to manage the dose and the correct nutrients according to the patient's needs[27, 56-58].

Vitamin D is of great interest in CF due to its role in bone mineralization and its deficiency has been hypothesized to play a role in the development of depression. Hypovitaminosis is almost universal in patients with CF. Insufficient levels are widely reported and is associated with increasing age and obesity. Vitamin D screening and supplementation should be considered in all children with chronic illness, particularly those who are overweight[59-62]. Table 1 shows treatments with fat-soluble vitamin supplementation in CF patients[1].

Table 1- Fat-soluble vitamins used for supplementation in cystic fibrosis patients.

Vitamins	Dosage	Dosage
A	400-10000 UI (≅ 2240 µg)	Daily
D	400-1800 UI (≅ 18 µg)	Daily
E	50 mg (1 yr) 100 mg (1- 10 yr) 180 mg (adolescents and adults)	Daily
K	0.3-0.5 mg	Daily

Hepatobiliary disease

The primary hepatic changes in CF involve a genetic defect in the CFTR protein, leading to the production of a thick biliary secretion, followed by biliary fibrosis[34]. Cirrhosis, ascites, portal hypertension, esophageal varices and bleeding are complications of hepatobiliary disease associated with CF, and frequently affect teenagers and adults[33].

This dysfunction is predicted to result in defective (sluggish) bile flow, and is associated with a cholangiocyte-induced inflammatory response with activation and proliferation of hepatic stellate cells, which results in cholangitis and fibrosis in focal portal tracts[63-66].

Approximately 5%-10% of CF patients develop multilobular cirrhosis during their first decade of life. Subsequently, most tend to develop signs of hypertension with complications, especially variceal bleeding. Annual examinations are recommended to detect hepatic disease, and when presymptomatic signs are present

therapy with ursodeoxycholic acid is recommended, which can prevent disease progression[67,68].

Cystic fibrosis-related liver disease (CFLD) is defined if at least 2 of the following conditions are present on at least 2 consecutive examinations spanning a 1-year period: (1) Ultrasound confirmed hepatomegaly; (2) elevated serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase; (3) ultrasound abnormalities other than hepatomegaly (*i.e.*, increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). An ultrasonographic pattern of simple liver steatosis does not represent a diagnostic criterion. In the case of distinct ultrasonographic signs of liver cirrhosis (*i.e.* coarse nodularity, presence of portal hypertension and rarefication of peripheral portal veins) and clinical signs (*e.g.* esophageal varices, splenomegaly) of liver cirrhosis, CFLD patients are classified as cirrhotics[63, 69].

Liver disease can only be taken into consideration if the physical examination is abnormal and abnormal hepatic function persists, and the latter has to be proved using ultrasound. If there are any doubts, a liver biopsy is suggested. All patients with liver disease require to be monitored annually to evaluate the progress of hypertension, portal cirrhosis or liver failure. Prophylactic measures for liver disease are nutrition monitoring, bleeding prevention and variceal decompression. In liver transplantation, deterioration of the organ has to be taken into consideration, especially in children with hepatic dysfunction or advanced hypertension[68].

Treatment

Treatment with pancreatic enzymes in patients with pancreatic insufficiency is associated with an increase in the coefficient of fat absorption, a decrease in bowel movement frequency, an improvement in the consistency of feces and weight gain. One of the aims of pancreatic enzyme replacement therapy is to abolish unpleasant gastrointestinal symptoms[45].

The response to treatment is individually evaluated, and doses are adjusted according to nutritional status. The use of antacids is recommended in patients taking enzymes to increase bioavailability, although, there is insufficient evidence to indicate whether there is an improvement in quality of life or survival[1,70].

In young children whose fat intake is known to vary with age, particular attention needs to be paid to fat malabsorption during pancreatic enzyme supplementation. More importantly, young children often have difficulty swallowing the available enzyme formulations, which may lead to suboptimal compliance and treatment effects[71].

The initial dose of pancreatic enzymes can be calculated based on the weight of the patient taking into consideration the dietary fat intake. 500 to 1000 U of lipase/kg is administered per main meal, the dosage can be increased according to clinical signs, and the maximum daily dose should not exceed 2500 U/kg per meal or 10000 U/kg per day of lipase[3]. Figure 1 summarizes pancreatic enzyme dosage[7].

The guidelines recommend that if dose increases are required, they should be increased with careful monitoring of body weight and stool fat content. When controlled clinical trials are designed to assess the safety and efficacy of pancreatic enzyme replacement therapy, the dose in terms of lipase units is usually limited to a level within the recommended range. However, in everyday clinical practice it is possible that maldigestion is not adequately controlled by the recommended doses in a proportion of CF patients: these patients may, therefore, require higher lipase doses[72-74].

The United Kingdom Cystic Fibrosis database indicates that lipase dose often exceeds 10000 units/kg per day for extended periods in clinical practice, both with standard-dose and high-dose pancreatic enzyme preparations. These high-dose regimens appear to have good safety and tolerability profiles, and fibrosing colonopathy has not been reported in recent years. However, it is essential that the safety and efficacy of higher doses of pancreatic enzyme replacement therapy are fully explored, particularly in the long-term, clinical practice setting[74,75].

There are several options for the treatment of EoE, including pharmaceutical agents and dietary elimination. Consensus recommendations advocate first-line treatment with oral corticosteroids (*e.g.* fluticasone, budesonide) or dietary therapy depending on patient preference and illness severity[38].

Dietary therapy can be very effective in children if culprit food allergens are identified, and recent data show this to be effective including the elimination of offending agents (targeted elimination diet), or an allergen-free diet consisting only of an elemental formula (elemental diet)[76-78].

The correction of steatorrhea is essential in CF. In the past, diets low in fat were recommended to try to reduce steatorrhea. Currently, restrictive diets have been replaced by hypercaloric diets rich in fat, which is a source of energy, are more economical and their intake should be encouraged[79]. The dose and timing should be followed very strictly, and patients should adhere to treatment. For infants, apple juice or small quantities of milk are consumed, and meals should be carried out in block in order to benefit from the bioavailability of the entire quantity of administered enzyme[49]

Medium chain triglyceride fats should be included in the standard dietary regimen used in the management of any child with CF and failure to thrive. Their use is fully justified due to clinical improvement and alleviation of steatorrhoea[80].

In clinical practice, probiotics have been frequently prescribed for patients suffering from diarrhea to protect the body against pathogens[81].

A probiotic is a "live microbial food ingredient that, when ingested in sufficient quantities, exerts health benefits on the consumer". Probiotics exert their benefits through several mechanisms; they prevent colonization, cellular adhesion and invasion by pathogenic organisms. The strongest evidence for their clinical effectiveness has been in their use for the prevention of symptoms of lactose intolerance, treatment of diarrhea, and attenuation of antibiotic-associated gastrointestinal side effects[81].

Probiotics reduce the rate of pulmonary exacerbations in patients and may have preventive potential for pulmonary deterioration in CF patients[82-84].

To ensure a continuous effect, probiotics and prebiotics need to be ingested daily. Favorable changes in the composition of intestinal microbiota were observed at doses of 100 g of food product containing 109 colony forming units (cfu) of probiotic microorganisms and doses of 5 to 20 g inulin and/or oligofructose, usually during the administration period of 15 d. Thus, to be of physiological importance to the consumer, probiotics must reach populations greater than 106 to 107 cfu/g or mL bioproduct[85].

The goal of nutritional therapy is to maintain the ideal weight, reduce malabsorption and digestion and control the intake of vitamins and minerals[1]. CF patients require diets with a high energetic rate (120% to 150% of the regular daily need for weight, height and age), hypercaloric, high-fat and high protein, divided into 5-6 meals a day and supplemented with vegetable oils such as medium chain triglycerides. In cases where dietary treatment does not result in weight

gain, the diet can be offered in small volumes, several times a day or administered in the evening of through a nasogastric tube or gastrostomy. Enteral tube feeding has been evaluated in pediatric and mixed child and adult populations with CF, demonstrating positive outcomes post-insertion. The diet may be administered through an infusion pump or gravitational and it is recommended that the night diet reaches 40%-50% of the daily energy requirements so that there will be recovery or maintenance of the nutritional state[7,86,87].

CF may include intestinal inflammation and CF patients have altered fatty acid metabolism characterized by an imbalance in the arachidonic/docosahexaenoic acid ratio in favor of the former, which can contribute to an increase in inflammation. Recent studies indicate that changes in fatty acid metabolism are responsible for abnormalities, and dietary supplementation with fish oils high in the omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid may have an anti-inflammatory effect[88-91].

Various anti-inflammatory therapies, including dietary omega-3 polyunsaturated fatty acids supplementation, have been investigated in CF patients. The composition of dietary omega-3 and omega-6 influenced the inflammatory markers in CF and dietetic integration seems to improve clinical condition and the inflammatory pulmonary and intestinal state in patients suffering from CF[92,93].

With a partial bowel obstruction, intestinal desimpactation is stimulated by hypertonic solutions, such as N-acetylcysteine, polyethylene glycol or hypertonic contrast, orally or by using probes. In cases of total obstruction the desimpactation is performed through enemas, while keeping the patient hydrated.

After the desimpactation, pancreatic enzyme treatment should be included in the preventive treatment in obstructive conditions, administering lactulose, mineral oil, polyethylene glycol or N-acetylcysteine to the patient. Prokinetic drugs may also be helpful[34].

It is recommended that, in the case of fibrosing colonopathy, there is a reduction in the enzyme dose associated with nutritional support with either semi-elemental or elemental formulas according to the evaluation by the nutritionist for nutritional enteral therapy, and if necessary, associated with parenteral nutrition in the most severe cases. In the case of digestive bleeding, a surgical procedure is prescribed[34,46].

The treatment of liver diseases focuses mainly on preventing disease progression which follows the sequence of cholestasis, fibrosis and cirrhosis. The maintenance of nutritional status is a part of this treatment, and aims to achieve and maintain the ideal weight of the patient, reduce malabsorption and maldigestion and control the intake of vitamins and minerals. However, nutritional treatment consists of enzyme replacement therapy, hypercaloric, high fat and micronutrient supplementation diets[1].

Supplementation with taurine has also been suggested to improve the solubilization of lipid micelles by bile acids. Taurine is a conditionally essential amino acid that possibly improves the micellar phase of fat digestion. Patients with CF and severe steatorrhea, despite appropriate enzyme therapy, showed a significant improvement in the absorption of triglycerides, total fatty acids, and linoleic acid while receiving taurine supplements. Taurine supplementation could be a useful adjunct in the management of patients with CF with ongoing fat malabsorption and essential fatty acid deficiency[94,95].

If CF patients also have taurine deficiency, this will result in malabsorption of bile acid and will require treatment with ursodeoxycholic acid (UDCA). The use of UDCA can increase the need for taurine administration for conjugation of bile acid[33].

UDCA is the drug currently used in CF patients and aims to slow the progression of liver disease. UDCA is a hydrophilic drug and is not significantly concentrated in bile. It has a hepatoprotective effect with rare collateral effects reported[33] and is frequently used in CF. UDCA inhibits the hepatic synthesis of cholesterol and promotes the synthesis of bile acids, thereby restoring the necessary balance between cholesterol and bile salts. The suggested dose is 14-18 mg/kg per day, 2 to 3 times a day up to 30 mg/kg per day[3,96].

Although it is one of the therapeutic options currently used for early changes in the liver, the use of UDCA as a preventive method requires further investigation as there are insufficient data on its long-term use, although adverse effects are rarely reported[97].

Liver transplantation may be necessary in patients with progressive liver failure and/or evidence of major portal hypertension in the absence of significant pulmonary involvement[98,99].

Careful monitoring and treatment should be offered to patients with CF associated liver disease (CFALD) and portal hypertension as they may require

supplemental feeding by gastrostomy. However, this could lead to the development of stomal varices, which is an unwanted complication. A recent study evaluated the risk of gastrostomy in a series of seven children with CFALD and portal hypertension. The research concluded that gastrostomy placement for poor nutrition in children with CFALD and portal hypertension is safe and contributes to improved nutritional and pulmonary outcome[100].

CF is a multisystem disease and therefore requires different input from different professional reference centers for the treatment and monitoring of CF, supported by public health policies.

4.4 CONCLUSION

CF has been extensively studied in Brazil and many other countries. Digestive manifestations significantly compromise the nutritional status of the patient and lead to numerous symptoms, organ deterioration, the need for transplantation and resections which can worsen the multisystem disease.

Reference Centers with up-to-date medical teams to monitor and treat CF patients and initiatives such as the Brazilian Cystic Fibrosis Research Group can contribute to the dissemination and standardization of information, in addition to improving the quality of treatment.

The scientific literature contains an important variety of drugs, including many that are available without charges through programs from the Unique Health System, Brazil.

The pharmaceutical assistance and the constant incentive to study digestive manifestations in CF patients are essential, as without them, there would be infinite clinical changes that would compromise patient survival.

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ARTIGO 4 – ARTIGO REVISÃO

Versão em inglês:

Pathophysiology of Cystic Fibrosis and drugs commonly used in respiratory manifestations: what should we know? Haack A, Aragon GG, Novaes MRG. Em avaliação. Investigación Clínica.

5 ARTIGO REVISÃO

PATHOPHYSIOLOGY OF CYSTIC FIBROSIS AND DRUGS COMMONLY USED IN RESPIRATORY MANIFESTATIONS: WHAT SHOULD WE KNOW?

Abstract

Introduction: Cystic fibrosis is a disease characterized by chronic airway infections and changes in the digestive tract. It is an autosomal recessive disease caused by mutation in Cystic Fibrosis transmembrane conductance regulator. The disease can be diagnosed in children through programs such as newborn screening and thus it can establish early treatment. **Objective:** To identify the pathophysiology of respiratory disease caused by cystic fibrosis, correlating the treatment with the main administered drugs. **Methods:** This is a review of the literature with emphasis on the last 12 years, using scientific articles published in journals indexed in databases SciELO, Lilacs, PubMed and MedLine, in Portuguese and English, through descriptors: cystic fibrosis, medications, therapy, antibiotics and microbiology. We selected randomized clinical trials, observational, experimental, epidemiological, among others, with statistical significance of 5%. **Results and Discussion**: The dissemination more broadly the disease and its treatment is related to places where there are Reference Centers and several difficulties are found in the treatment and monitoring. Thus, the study of the pathophysiology of the disease and drugs commonly used in respiratory manifestations aims to demonstrate current drugs, which has shown a proven and significant improvement in the clinical picture of patients, quality of life and longer survival. **Conclusion**: Cystic Fibrosis is a disease that affects a variety of organs and there are a variety of drugs available for treatment, monitoring and improvement in survival of cystic fibrosis patients, especially when are offered access to public health policies to these patients, such as early diagnosis and assistance for the acquisition of specialized medicines available for users of specialized programs and high complexity of the Unified Health System.

Keywords: Cystic fibrosis, medications, therapy, antibiotics and microbiology.

5.1 INTRODUCTION

Cystic Fibrosis (CF) is an autosomal recessive, progressive and chronic disease, prevalent in the Caucasian population and may be present in all ethnic groups and affect both sexes equally. It is an autosomal recessive disease caused by mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) located on chromosome 7,

which induces the body to produce thick and sticky secretions that clog the lungs, pancreas and bile duct. The CF gene was identified, cloned and sequenced in order to know the biochemical mechanisms responsible for the pathophysiology of the disease facilitating the treatment and its complications[1, 2].

The prevalence of CF varies according to the ethnicity, from 1/1900 to 1/5 thousand live-born Caucasians in Europe, in the United States and in Canada, 1/14 thousand black Americans, and 1/39 thousand in Finland, being considered rare in Asians and Africans. In Brazil, regional studies show statistical variables that suggest an incidence of about 1:7.000 in the country, but the incidence is still ignored. The average life of CF patients has increased in recent years reaching the third decade, as a result of early diagnosis and specialized treatment instituted in the early stages of the disease[1, 3].

There are implementations of records about the disease around the world, promoting the collection and storage of patient data, which are accompanied in Service Centers for Cystic Fibrosis. In Brazil, in the Midwest region the number of patients by region of origin (birth) is 18 (1.5%)[4].

CF patients have thick, viscous and mucus secretions, blocking ducts of exocrine glands, which contribute to the appearance of: chronic obstructive pulmonary disease, high levels of electrolytes in sweat[1].

CF treatment aims to keep the lungs clean, through aerosols and respiratory therapy and maintain good nutritional status, with supplementation of nutrients and pancreatic enzymes. When there are infections in effect, antibiotics are needed, often requiring the patient hospitalization[5].

The disease is also characterized by dysfunction of the exocrine glands. Secretory products of mucous glands in the lungs and gastrointestinal tract have physical changes and the clinical complications associated with these changes include the development of suppurative chronic bronchitis with destruction of lung parenchyma, pancreatic insufficiency, diabetes mellitus, liver disease and impaired of male and female reproductive system[6].

Due to the various systems involved and the variability and chronicity of the disease, a multidisciplinary approach is essential to help patients and their families understand the disease and adhere to treatment[7].

The current therapy of CF includes the maintenance of nutritional status, removal of secretions from the airways, antibiotics, and supplementation of the diet and the use of minerals and vitamins[1, 8, 9].

When the disease is diagnosed, and has chronic character with various clinical manifestations, requires continuous medication use (antibiotics, bronchodilators, mucolytics) associated with procedures (respiratory physiotherapy, oxygen therapy, lung transplantation) replacement of digestive enzymes and nutritional support.

The lung disease in cystic fibrosis is characterized by colonization of bacteria in the respiratory tract, which can lead to irreversible damage that appears most often in this order: *Staphylococcus aureus, Haemophilus influenzae, Non-mucoid Pseudomonas aeruginosa, Mucoid Pseudomonas aeruginosa, Pseudomonas cepacia* and members of *Burkholderia cepacia* complex[1, 8, 10].

The World Health Organization recommends the following actions in CF care services in developing countries: neonatal screening to identify newborns affected; laboratories implementations to identify mutations of the CF; development of diagnostic treatment center with a multidisciplinary team; establishment of a national organization involving family, and increased collaboration among groups and other organizations[11, 12, 4].

CF requires continuous use of medications, as well as multidisciplinary care, which makes the average cost of treatment very expensive for families. Therefore, CF patients and their families are guaranteed the right to receive government assistance through the Unified Health System (UHS), according to the clinical protocol of the Ministry of Health that provides DNase for pulmonary manifestations and pancreatic enzymes to pancreatic insufficiency[3].

There are many actions in all the federation units, including the Federal District, in favor of early diagnosis and even the supply of special formulas as dietary supplements provided by Ordinance nº 94/1909, published in the Federal District in 2009[13].

In Brazil, the efforts that CF be diagnosed early in childhood are major, by neonatal screening programs or by the sweat test. In this sense, it was published the Law nº 4.180, 06/08/2008 and Decree nº 28.375, 08/08/2008 so that actions could be standardized and followed in the national territory[14, 15].

The aim of this study was to perform, in literature, a literature review on the pathophysiology of cystic fibrosis and drugs commonly used in respiratory manifestations, which are essential knowledge during the management of CF, as well as, to show the pharmaceutical care offered to this clientele in treatment and monitoring by public health care.

5.2 METHODS

This is a review of the literature with emphasis on the last 12 years, understood on the topic "Cystic Fibrosis", using scientific articles published in journals iindexed in databases Virtual Scientific Electronic Library Online (SciELO), Sciences Information (LIlacs), United States National Library of Medicine (PubMed) and Medical Literature Analysus and Retrieval System Online (MedLine), using the key words: cystic fibrosis, medications, therapy, antibiotics and microbiology, present in the descriptors in health sciences (MeSH), in English and Portuguese. We selected articles containing at least one of the selected descriptors, that reported on the Cystic Fibrosis; included randomized clinical trials, epidemiological studies, observational studies, meta-analyzes among others. We excluded articles that did not specifically address the issue, published in other languages that were not in English or Portuguese.

5.3 RESULTS AND DISCUSSION

General clinical manifestations

CF is presented in a very variable way and can already manifest in the neonatal period or later in life. Some patients are completely asymptomatic for several years. The most common manifestations are: chronic cough, chronic diarrhea and malnutrition; however, it can manifest itself in many other ways, because it is a disease that affects multiple systems or organs[16].

The mutations in the CF gene result in the absence or dysfunction of the CFTR protein, which functions as a chloride channel on the apical membranes of epithelial cells. The CFTR also performs functions on the mucus, secretory granules and intracellular organelles. The defect affects cells of various organs, and not all express similar clinical responses, and may affect different organs. The involvement of the respiratory tract is associated with higher morbidity and causes death in 90% of patients[8, 16, 17].

Respiratory Manifestations

The involvement of the airways, which is progressive and of variable intensity, occurs in more than 95% of patients and the intensity of lung involvement that determines the ultimate prognosis, the pulmonary involvement is the most critical aspect of CF. The best way to diagnose and manage respiratory problems are on chest radiographs. Initially, it may be normal, but very early, will show signs of complete obstruction of the bronchi, as collapses or atelectasis. The radiography of the sinuses shows changes compatibles with the diagnosis of sinusitis in 90% of patients[16].

The lung disease in CF is characterized by colonization and chronic respiratory infection by bacteria and, consequently, worse prognosis[1, 18]. The colonization by *Pseudomonas* is very difficult to eradicate, even with the use of antibiotics. Recurrent infections by *Pseudomonas* are found only in the respiratory tract, not in other organs[19].

Respiratory viruses play an important role in the exacerbation of upper airways, thus, it must be taken a clinical decision on the use of antivirals and administration of antibiotics [20].

The obstructive process is an early pathophysiological event, and chronic infection of the respiratory tract contributes to the worsening of lung function and eventual death of these patients[1].

Upper airways

With the increased survival of CF patients, it has been observed patients with nasal obstructions by nasal polyps and sinusitis, which are subclinical manifestations. Cystic fibrosis patients present symptoms such as nasal obstruction and purulent secretion, which may lead to chronic rhinosinusitis and nasossinusial polyposis, and may well worsen the lung background when the nasossinusal region is serving as bacterial reservoir[21].

The nose and paranasal sinuses have the function of warming, humidifying and filtering the air. The paranasal sinuses need factors for its perfect physiology as, quality of nasal secretions, ciliary function and patency of drainage ostia. The *"Globet cells"* present in the mucosa of the paranasal sinuses are cells that produce a thick mucus layer. When stimulated by irritants substances appears the inflammation and favorable conditions for bacterial growth[21, 22].

In the respiratory epithelium, the mucus viscosity increase, by the greater absorption of sodium, entails a greater influx of water into cells, and ciliary beat

becomes ineffective in the *clearance* of viscous substances, predisposing the ostium obstruction, so the increase of bacteria[22].

The rhinosinusitis is acquired when the mucociliary transport is interrupted, since foreign bodies penetrate in the paranasal sinuses and the interruption of mucociliary clearance occurs, which serves to drain the paranasal sinuses which function as a barrier to infection. While mucociliary clearance is not affected by the disease, it can not carry that viscous secretion[21].

The factors responsible for colonization of bacteria in paranasal sinuses are: the decrease in sinus drainage, the impaired of mucociliary clearance and viscosity of secretions from the paranasal sinuses[23].

The microbiology of sinusitis in cystic fibrosis is characteristic of each patient. The bacteria most commonly found in the paranasal sinuses are:

- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Haemophilus influenzae*
- *Burkholderia cepacia*

The patient may be colonized by *Pseudomonas aeruginosa* (PA) in the first years of life, *Staphylococcus aureus* is most common in infants and *Haemophilus influenzae* is more common after the two years of life [21].

It is essential in Cystic Fibrosis maintaining the upper airway in good conditions, to prevent infectious. The diagnosis of chronic rhinosinusitis should be strict and should be done by the association of symptoms, and by tomography of the paranasal sinuses[24].

Lower airways

It is known that cystic fibrosis leads to chronic impaired in respiratory tract through infections in the lungs. These infections contribute to morbidity and are aggravated by the intense inflammatory response, and as a consequence, we have the suppurative lung disease, bronchiectasis and respiratory failure characterized by extensive dysfunction of the exocrine glands[25].

After the discovery of mutations in the CFTR gene, it was determined the defect in the transport of Cl and Na ions in epithelial tissues. The membrane of epithelial cells

has a mechanism that allows agents to affect the permeability of the cells. In normal cells, the chloride channel when stimulated by calcium ionophore or cAMP, opens giving exit to chloride. In cystic fibrosis patients, the chloride channel is unresponsive preventing the output of chloride and only channels stimulated by calcium inophore open. Thus, the lower output of Cl from the cell, makes it has sodium reabsorption, to keep the balance Cl/Na inside the cell. Thus, we have as defect, less chloride secretion and higher sodium and water absorption, by changing the physicochemical properties of mucus, making it thicker and blocking the ducts[1].

The formation of bronchiectasis and lung injury is given from the inflammation present in the normal lungs, with progression leading to respiratory failure and infectious process increases the obstruction. Chronic infection in the respiratory tract is the event that contributes to the worsening of lung function leading to death of these patients[1].

Treatment of upper and lower airways

Treatment should be done individually, taking into account the affected organs. Early treatment slows the progression of pulmonary lesions, improves prognosis and increases survival[19].

Specific components of a standard treatment regimen include pulmonary antibiotic therapy for exacerbations and chronic suppressive therapy, airways clearance and exercises, therapy with mucolytic agents, bronchodilators, anti-inflammatory and nutritional support[26].

Aerosol drug treatments are universally used for the treatment of respiratory disease. Inhalation may increase the topical effectiveness, being quick its onset of action, and reduces toxicity systemic exposure of many drugs. There are a wide variety of inhaled drugs, but it is necessary to understand the variables of function of the aerosol, as distribution of particles size, hygroscopic properties, viscosity and surface tension of the drug to improve the therapeutic regimens for patients with CF. The variables that must be analyzed to prescribe inhaled medications for CF patients include the inspired flow rate, respiratory frequency, tidal volume, upper airway anatomy and obstruction of the upper airways. These factors vary widely among patients, because they are different in relation to age and disease severity[27].

The nebulizers suitable to CF patients are for the jet, because they are easier to operate, they do not require a special breathing standard, however, require a source system or source of air, cleaning and disinfection. The aerosol systems have been innovated and formulations have been developed to increase the efficiency of drug delivery, and may alleviate the burden of the treatment and improve the adhesion and results in CF patients[27].

In the treatment of CF, systemic antibiotic therapy is most used from the determination of germs more frequent, lasting at least three weeks, but can reach up to six weeks. The most commonly used antibiotics are ciprofloxacin, oxacillin, amikacin, tobramycin and the third generation cephalosporin, for cases of resistance, meropenem, vancomycin and teicoplanin are administered[21].

In the region nasossinusial, different pathologies are found, as chronic sinusitis and nasossinusial polyposis. Only symptomatic patients should be treated. Medical treatment for chronic sinusitis consists of antibiotic therapy, and for polyposis, corticosteroid nasal sprays. Surgical treatment is chosen in more severe cases, since there is a high recurrence[21].

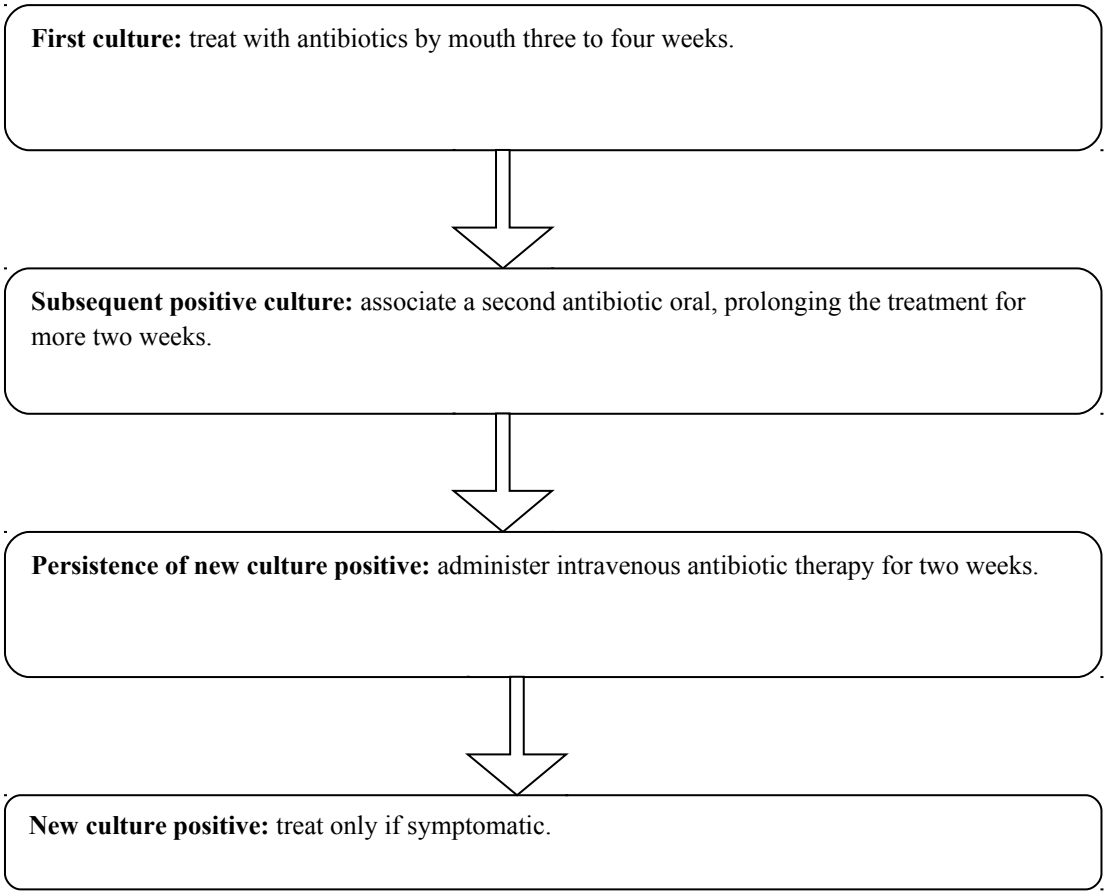
Staphylococcus aureus

Generally, *S. aureus* is the first bacterium grown in respiratory secretions in CF patients; many centers recommend the early eradication of this bacterium even in the absence of symptoms, although there is the possibility of recurrence[28].

In cystic fibrosis patients, the bacterium *S. aureus* adheres more on hair, nasal, squamous and oral epithelial cells[29.] The presence of *S. aureus* in lower respiratory tract is representative of an infectious process, however exacerbations associated with pathogens are aggressive and the use of long term antibiotic therapy is recommended[30].

Even with antibiotic therapy, cultures will always be performed in order to diagnosis, independent of symptoms, following the diagram of Figure 1.

Figure 1- Schemes of treatment for eradication of *Sthaphylococcus aureus*[31]



Pseudomonas aeruginosas

The infection by *P. aeruginosa* adheres more easily the epithelial cells of the CF patients airways by comparing to healthy individuals. Once established the *P. aeruginosa* in the airway, it is difficult to be eradicated by antibiotics which can only reduce the number of colonies of this bacterium. The antibiotics may be administered orally, intravenously or by inhalation. Its administration is directed according to the definitions of colonization and infection[16].

Acute pulmonary colonization is given by the presence of *P. aeruginosa* in the bronchial tree without presenting symptoms such as inflammation, fever, antibody responses specific for at least six months, based on at least three positive cultures. The acute pulmonary infection also can be diagnosed on the basis of antibodies positive responses in examinations for patients who do not expectorate[19].

The aggressive innate inflammatory response by recruiting neutrophils is controversial in the literature, and there are contradictory experimental evidences - particularly involving tissue culture. Consensually, it is admitted the increased oxidative

stress and acidification of the extracellular medium. The contribution of stress to the recruitment of neutrophils, in a process that self-amplifies as these cells and its effector molecules accumulate, was indirectly assessed by administering adequate oral doses (over 1.8 g/day) of N-acetylcysteine. In preliminary work, the reduction observed was significant - around 49% ($p = 0.005$) in the number of neutrophils in sputum[32, 33].

Currently, several inhaled antibiotics are administered to treat cystic fibrosis in a chronic pulmonary infection by *Pseudomonas aeruginosa* (*PA*) such as tobramycin, colistimethate sodium, and aztreonam, and all clinically substantiated by studies and with the significant efficacy for the treatment of *Pseudomonas aeruginosa* and pulmonary infection[34].

In the treatment of PA with mild exacerbations, ciprofloxacin is used for two weeks, and may continue for three weeks if necessary while maintaining antibiotic used as inhaled amikacin or colimycin[31].

For moderate to severe exacerbations, the patient is hospitalized involving the use of amikacin and ceftazidime or intravenous gentamicin, according to the antibiogram for two weeks. The colimycin or tobramycin should be used after the tenth day of hospitalization. In chronic colonization by *P. aeruginosa*, the scheme will depend on the severity and evolution, as an individual assessment[31].

Haemophilus Influenzae

H. Influenzae is found early in CF patients in respiratory tract, being the most frequently isolated agent early in life. The incidence of this pathogen has been decreasing among adolescents and adults. Vaccination has no effect in preventing in cystic fibrosis patients, because the vaccine strain is serotype B[29].

H. Influenzae is more frequent in cases of exacerbations, being rare data related to the pathogenic potential of this microorganism, nevertheless, the colonization of the lower respiratory tract must be considered, for it is done the therapy, the microorganism is isolated occasionally, but has a limited role in the pathogenesis of lung injury[35].

The administration of macrolides is used, such as azithromycin for these infections, but prolonged use is being associated with resistance[31].

Burkholderia Cepacia complex

Burkholderia Cepacia complex is a group of seventeen species of bacteria that may cause lung infection in cystic fibrosis patients. Infections can be varied, including *Cepacia* syndrome which is classified as a rapidly progressive, necrotizing pneumonia. Aggressive treatments are administered with a combination of intravenous antibiotics, oral corticosteroids and cyclosporin[36].

When there is identification of *Burkholderia Cepacia* there is a major concern in the medical staff, because in most cases, it is related to the severity of disease and rapid deterioration of pulmonary function[8]. The clinical syndrome characterized by high fever, progressive respiratory failure, leukocytosis and erythrocyte sedimentation rate[16].

Once in the *Burkholderia Cepacia* was identified in Cystic Fibrosis some techniques have been implemented in diagnosis routine, aiming to complement infection control measures that should be accurate. Genotyping techniques were applied as part of an infection surveillance program for species and *Burkholderia cepacia* positive status, thus seeking to map the evolution of the outbreak. A contributing factor to the end of the epidemic is the segregation of infected patients, being of great importance currently[37].

Burkholderia Cepacia complex is resistant to many antibiotics, making it difficult to eradicate in the respiratory tract of CF patients, even with appropriate antimicrobial therapy[16]. The species of the genus *Burkholderia,* are versatile and can use other energy sources, and thus can provide a variety of environments for their proliferation. Bacteria are reported as case of infection in the respiratory tract and are taken as the cause of worsening in pulmonary function in cystic fibrosis patients[17]. To be intrinsically resistant to aminoglycoside and multiresistants, difficulties occur in eradicating the bacteria *Burkholderia* and therapy is aimed at decreasing the bacterial load during exacerbations[29].

Cepacia syndrome is characterized by its antibiotic resistance and transmissibility through social contact among patients and one should observe its isolation indicating clinical worsening and pulmonary function[4]. In the treatment of bacterial eradication *Burkholderia cepacia*, carbapenems are administered, ceftazidime, quinolones and trimethoprim sulfamethoxazole, with the antibiogram assisting since studies have proven antibiotic resistance[31].

It is indicated for *Burkholderia cepacia,* always treating the patient following the antibiogram and preventing situations that maintain contact with other CF patients[31]. Tables 1 and 2 summarize the treatments used in the outpatient and inpatient CF.

Table 1- Antibiotics used in the ambulatory treatment of cystic fibrosis patients[31].

Pathogens	Antimicrobial	Dose
Staphylococcus aureus (sensitive)	Amoxicillin+clavulanate	500 mg, 8/8 h
	Cephalexin	500 mg, 6/6 h
	Clarithromycin	490 mg, 12/12 h
	Azithromycin	500 mg (initial dose), followed by 250 mg, 24/24h
	Erythromycin	500 mg, 6/6 h
	Clindamycin	120 mg to 180 mg/day of 6/6 h
Staphylococcus aureus (Methicillin - resistant) Clinically stable	Linezolid	600 mg, 12/12 h, by 21 dias
Haemophilus influenzae	Amoxicillin	500 mg, 8/8 h
	Amoxicillin+clavulanate	500 mg, 8/8 h
	Cefixime	400 mg, 12/12 h
	Cefaclor	750 mg,12/12 h
Pseudomonas aeruginosa	Ciprofloxacin Associated with one of the following::	750 mg, 12/12 h
	inhaled tobramycin	300 mg, 12/12 h
	inhaled colimicina	150 mg, 12/12 h
	inhaled amikacin	239 mg, 12/12 h
Burkholderia Cepacia	trimethoprim + sulfamethoxazole	800 mg + 160 mg 12/12h
	doxycycline	200 mg initial dose followed by 100 mg, 12/12 h
	minocycline	200 mg, initial dose followed by 100 mg, 12/12 h

mg = miligram; h = hours
Source: Brasil, 2008

Table 2- Antibiotics used in hospital treatment (intravenous) of cystic fibrosis patients[31].

Pathogen	Antimicrobial	Dose
Staphylococcus aureus (sensitive)	Oxacillin	1,0 g, 6/6 h
	Cefazolin	1,0 g, 8/8 h
	Vancomycin	1,0 g, 12/12 h

Staphylococcus aureus (Methicillin - resistant)	Teicoplamin	12 mg/kg of 24/24h (severe cases: the first 03 doses should be of 12/12 h)
Pseudomonas aeruginosa	b-lactams (1st choice)	
	Ceftazidime	2 g, 8/8 h
	Ticarcillin	3 g, 6/6 h
	Piperacillin	3 g, 6/6 h
	Imipenem	500 mg, 6/6 h
	Meropenem	2 g, 8/8 h
	Aztreonam	2 g, 8/8 h
	Associated with an aminoglycoside:	
	Tobramycin	3 mg/kg, 8/8 h
	Amikacin	5-7,5 mg/kg, 8/8 h
Burkholderia cepacia	Meropenem	2 g, 8/8 h
	Associated with:	
	Minocycline	100 mg, IV or O 12/12h
	Amikacin	5-7,5 mg/kg , 8/8 h
	Ceftazidime	2 g, 8/8 h
	chloramphenicol	15-20 mg/kg, 6/6 h
	trimethoprim + sulfamethoxazole	4-5 mg/Kg (trimethropim) 12/12h

g = grams; h = hours; mg = miligram; IV= intravenous; O = oral
Source: Brasil, 2008

General aspects of antibiotic therapy

Treatment of *Pseudomonas aeroginosa* in patients with CF determines a positive effect on the clinical condition, pulmonary function, inflammatory parameters, quality of life and nutritional status of patients. The health condition of the lungs is the best indicator of survival, and treatment with antibiotics has led to improved lung function. The degree of improvement of the lungs is correlated with the degree of reduction of *Pseudomonas aeroginosas* in sputum samples[38].

There is a bacterial diversity in the airways of CF patients, clinically important, and, therefore, there is a relative impact of antibiotics used predominantly to achieve *PA*[39].

Treatment with antibiotics has been used as a pillar of the therapy in conjunction with other treatment modalities, resulting in a significantly higher survival rate, however, the use of antibiotics in many cases led to an increase in specific pathogen resistance to various classes of antibiotics, and there is a need for new strategies of antibiotics, as new therapies, new goals and other experimental therapies[40].

The quinolone treatment is often used in situations of mild to moderate exacerbation and two antibiotics are used in combination, such as a B-lactam antibiotic and an aminoglycoside, in patients who are more likely to be infected with multiresistants. Associated antibiotics differ in the distribution and elimination of the drug and in CF patients are required higher doses and shorter dosing intervals[38].

The major impact on morbidity and mortality in cystic fibrosis is associated with respiratory infections including opportunistic bacteria. Aminoglycosides, especially tobramycin have been used with great success to combat infections. Fogging allows the direct action of the drug to sites of infection in the airways, while avoiding systemic exposure. The inhaled tobramycin reduces the bacterial load, improves pulmonary function and reduces the number of hospitalizations and has been administered in patients with early infection, eradicating the bacterium. This antibiotic has been introduced to minimize the appearance of *Psedomonas aeruginosa* resistant to aminoglycosides[41].

The daily administration of a dose of aminoglycoside is widely used, but this administration is limited by slow infusion, and requires the infusion three times a day in combination with B-lactam. It may be administered twice a day, if more convenient. Studies have shown that two daily doses of tobramycin and ceftazidime are safe and effective and are more convenient than commonly used schemes[42].

Use of Anti-Inflammatory Agents

The efficacy of anti-inflammatory therapy, long-term, was confirmed in separate reports, on the reduction of lung function decline. CF patients are prone to episodes of acute pulmonary exacerbation, characterized by worsening of symptoms of respiratory tract infection accompanied by decline in acute lung function[26].

The most prescribed anti-inflammatory drugs so far are: oral corticosteroids with significant side effects, long-term, inhaled corticosteroids, with a difficulty in absorption

through the viscous secretions of the surface of the lung and ibuprofen, potentially effective.

Featuring an excellent safety profile, macrolide antibiotics such as azithromycin, act as a long-term inflammatory, being the most promising of the class[43].

In patients treated with ibuprofen, clinical and functional improvements were observed, however, favorable results were not observed in pediatric patients treated even with high doses, it has been observed the drug metabolism individually for each patient, according to the patient plasma levels, associated with the dosage and considering its side effects[25].

The study of inhaled corticosteroids in CF has been a potential way to reduce the systemic inflammation. It has already been observed that therapeutics doses of ibuprofen (19 to 29 mg) delayed the progression of pulmonary tuberculosis in patients slightly affected. However, long-term trials are needed before this therapy can be recommended[44].

Corticosteroids are potent anti-inflammatory drugs; however, one should be careful in prescribing the time of treatment, because its side effects are undesirable, when used for prolonged periods. Inhaled corticosteroids are administered in case of asthma associated with the main pathology[25].

In the cases of wheezing, inhaled corticosteroids with oral budesonide spray is administered, 190 mcg/jet, from one to four jets per day[31].

In oral corticosteroid is used prednisone for one to two mg/kg per day, as routine, the indication for allergic bronchopulmonary *aspergillosis*, bronchospasm difficult to control and terminal states[31]

Bronchodilators

Bronchodilators have been used in the treatment of patients with CF. Its use is of great importance when the patient shows background of bronchial hyperactivity, which occurs in most cases, therefore, bronchodilators become a standard component for therapy. The most commonly prescribed agents are beta-adrenergic agonists are of short duration. They are often used to provide symptomatic relief, and before the physiotherapy, to facilitate airways clearance[44], open the airways and promote more intensive deposition of the other inhaled drugs, and in prevention of bronchospasm[45].

One should evaluate declines in lung function after the use in order to identify the reversibility of airway obstruction overlapping the possibility of paradoxical bronchoconstriction after inhalation[25].

The use of bronchodilators should be examined particularly as it varies from patient to patient therapeutic response and adverse effects. These drugs are well tolerated, which most often bring beneficial effects[31].

Formoterol and salmoterol are representatives of this class of drugs, with a long half-life of 12 hours, making it more practical use. They may be administered interchangeably with short-acting bronchodilators, thus causing a synergistic effect, resulting in an improvement in bronchodilator effect. The indacaterol belongs to the class of bronchodilators lasting 24 hours, however, its use is not recommended for patients with Chronic Obstructive Pulmonary Disease[44].

The table 3 shows the bronchodilators usually administered in the treatment of Cystic Fibrosis.

Table 3 - Bronchodilators usually administered to CF patients cystic fibrosis patients.

Bronchodilators		
Beta-adrenergic agonists		Anticholinergic
Long Term	Short Term	
Salmeterol 50 mcg 12/12h	Salbutamol spray 100 mcg	Bromide ipratóprio Spray
Formoterol 12 mcg 12/12h		

mcg = micrograms; h = hours; Source: Brasil, 2000

Mucolytics

The abnormal viscosity of sputum in CF is caused by extracellular DNA released by neutrophils. The inhalation administration of recombinant human DNase or alfadornase decreases sputum viscosity in CF through a mechanism of degradation of extracellular DNA into small fragments[46].

The recombinant human DNase is an enzyme which breaks down the DNA structure and, to be inhaled, reduces the viscosity of secretion. The DNase may be administered in patients with varying degrees of commitment; its effectiveness is proven in improvement in lung function and a significant decrease in the frequency of respiratory exacerbations. The cost of treatment is high and the answer varies from fibrocystic to fibrocystic, therefore, the functional clinical response should be monitored keeping the drug, or suspending the dosage. The drug has a single daily dose of 2.5 mg

and it is recommended a minimum interval of one hour after antibiotic because it can denature the enzyme[25].

The DNase has shown good efficacy in decreasing the inflammatory response of neutrophils in cystic fibrosis patients, thus suggesting a potential benefit of early administration on illness. In studies of early intervention of DNase in cystic fibrosis patients with lung disease, we observed significant improvements in lung function and decreased risk of exacerbation. The early onset with DNase has the potential to alter the course of CF, decreasing the rate of decline of lung function, suggesting an important role in the treatment of CF, which can help to preserve the lung function and patient survival[47].

Studies show that alfadornase is safe and well tolerated in patients with mild, moderate or severe lung disease. In patients with more severe disease it may require longer therapy Inflammations in the airways are found in patients with mild lung disease, suggesting the need for an early treatment with DNase, thus causing a reduction in the number of hospitalizations due to infection, especially in patients with more than five years old. The management system with a smaller droplet size tends to provide a significant improvement compared with the larger droplet, if a higher dose[48].

In the CF treatment, one should consider the possibility of instilling alfadornase directly to the lower airways through the fiberoptic caused by obstruction or mucoid impaction of the airways[3].

The continuation of treatment should be stimulated without duration set for the improvement in lung function, and the monitoring of therapeutic responses should be performed with spirometry and chest radiograph[3].

Osmotic agents (Hypertonic Saline Solution)

The nebulized hypertonic saline solution is water with a concentration of 3% or more of salt, inhaled with a fine mist through a mouthpiece or mask. It was observed that 10 ml of saline solution with 3% to 7% concentration, twice a day, helps the mucus become clearer without showing adverse effects. The treatment after 47 weeks with hypertonic saline solution 7%, twice a day, reduces episodes of infections, thus being linked to an improvement in lung function[49].

There is an improvement in lung function and pulmonary exacerbations in CF patients with the administration of the solution and the early treatment can potentially reduce the decline in lung function in children and adults with CF[50].

The inhalation through nebulizer improves the physical properties of mucus and stimulates cough in individuals with cystic fibrosis, aids in realising sputum and accelerates the mucociliary clearance, being recommended the administration twice a day, with a long term outcome[51].

Given the complexity of CF treatment, the Ministry of Health (MOH) established a clinical protocol for patients diagnosed with cystic fibrosis. All the patients are attended in public services and assisted by MOH with the access to the pancreatic enzymes and DNase for treatment. Antibiotics and other drugs are not still provided in the Protocol, leaving to the Secretaries of Health Municipalities or States the management and care of patients' needs. It is recommended that the prescription is performed by doctors linked to the Reference Center of Cystic Fibrosis, so that the patients are periodically evaluated regarding the effectiveness of treatment[3].

Modulating therapies

Since discovery of the CFTR gene in 1989, research has focused on targeting the underlying genetic defect to identify a disease-modifying treatment for CF. Investigated management strategies have included gene therapy and the development of small molecules that target CFTR mutations, known as CFTR modulators. CFTR modulators are typically identified by high-throughput screening assays, followed by preclinical validation using cell culture systems. Recently, one such modulator, the CFTR potentiator ivacaftor, was approved as an oral therapy for CF patients with the G551D-CFTR mutation. The clinical development of ivacaftor not only represents a breakthrough in CF care but also serves as a noteworthy example of personalised medicine[52].

Ivacaftor (VX-770), a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator , has been shown to improve lung function, pulmonary exacerbation rate, respiratory symptoms, and weight gain in patients 6 years and older who have a G551D mutation[53].VX-770 (150 mg) should be taken orally every 12 hours (300 mg total daily dose) with fat-containing food[53, 54].

The G551D CFTR mutation is the third most common CF disease-causing mutation, in which the CFTR protein localizes to the epithelial cell membrane but has defective gating. With restoration of adequate CFTR function through pharmacotherapy, it is possible that the clinical course of patients with CF could be markedly improved, including longevity, quality of life and treatment burden[55].

5.4 CONCLUSION

The scientific literature shows that Cystic Fibrosis is a disease that affects a variety of organs and there are a variety of drugs available. Besides the knowledge of the pathophysiology and treatment available, we should know that monitoring is also essential in improving the survival of CF patients, especially when offered access to public health policies to these patients, such as early diagnosis and assistance for the acquisition of specialized medicines available for users of the Unified Health System.

Although several studies have demonstrated the efficacy of drugs commonly used in Cystic Fibrosis, investments are needed in the area of clinical research and pharmaceutical industries, as well as ongoing involvement of public institutions, associations and community in general so that there is knowledge about the use of new drugs and the health conditions that provide a rising life expectancy in this population be maintained.

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ARTIGO 5 – ARTIGO REVISÃO

Versão publicada em português:

Exercício físico e fibrose cística: uma revisão bibliográfica. Haack A, Novaes MRG. Comunicação em Ciências da Saúde 2013; 24(2) [no prelo]

6 ARTIGO REVISÃO

EXERCÍCIO FISICO E FIBROSE CÍSTICA: UMA REVISÃO BIBLIOGRÁFICA

PHYSICAL EXERCISE AND CYSTIC FIBROSIS: A LITERATURE REVIEW

Resumo

Introdução: A Fibrose Cística reduz o tempo de vida e possui alta morbimortalidade. A atividade física regular tem sido recomendada como recurso adjunto à limpeza brônquica e fortalecimento dos músculos respiratórios. **Objetivo:** Realizar uma revisão sobre o exercício físico em fibrocísticos. **Metodologia:** Foram selecionados artigos em inglês, realizados com crianças, adolescentes, adultos e idosos, entre cinco e 62 anos, de ambos os sexos, atletas ou não, acompanhados ou não por educadores físicos. Foram selecionadas 23 referências, sendo, dez ensaios clínicos abertos, nove ensaios clínicos controlados, duas coortes, um estudo transversal e um estudo de caso. **Resultados e Discussão:** Os estudos mostram a melhora do condicionamento e da força da musculatura ventilatória, além da resposta positiva ao tratamento com o exercício físico. Identificou-se a melhora da qualidade de vida, no entanto, os dados a respeito do aumento da sobrevida permanecem sem maiores esclarecimentos. Embora os exercícios físicos sejam recomendados, os mecanismos celulares responsáveis por estas melhorias são pouco claros. **Conclusão:** O exercício físico colabora positivamente na função do pulmonar e são necessárias pesquisas e equipes multidisciplinares, estudos de intervenção e metanálises. Estudos com características homogêneas, com uma amostra maior, podem oferecer maior segurança aos acadêmicos ou para aqueles interessados no tema.

Palavras-chave: fibrose cística; exercício físico; exercício.

Abstract

Introduction: Cystic Fibrosis is a disease that decreases the lifetime and has a high mortality. New treatments offer hope but also present challenges for patients, practitioners and researchers. **Objective:** To conduct a review literature on exercise in CF patients, selecting articles published in scientific literature in English and discussing the main results of this work in order to contribute with new knowledge about Cystic Fibrosis. **Method:** selected articles in English, performed with children, adolescents, adults and the elderly, between five and 62 years, of both sexes, athletes or not, whether or not accompanied by physical educators. We selected 23 references, ten open clinical trials, nine controlled clinical trials, two cohorts, one cross-sectional study and one case study. **Results and Discussion:** Studies show improved conditioning and strength of respiratory muscles, besides the positive response to treatment with exercise. Identified the improvement of quality of life, however, the data regarding the increased survival remain without further clarification. Although the exercises are recommended, the cellular mechanisms responsible for these improvements are unclear. **Conclusion:** Exercise contributes positively in lung function and researches are needed to address the issue and urge you to review involving multidisciplinary, longitudinal studies and meta-analyzes. Studies with homogeneous characteristics, with a larger number of respondents, noting the age interval are also important to allow the results to provide greater security for academics or for those interested.

Key words: cystic fibrosis; physical exercise; exercise.

6.1 INTRODUÇÃO

A Fibrose Cística (FC) é uma doença que reduz o tempo de vida e possui alta morbidade[1]. Apesar dos avanços no tratamento e o aumento da sobrevida, pacientes com FC frequentemente experimentam diminuição da função pulmonar, desnutrição e insuficiência pancreática entre outras complicações. Novos tratamentos oferecem esperança, mas também apresentam desafios para pacientes, profissionais especializados e pesquisadores[2]. A FC é uma doença de herança autossômica recessiva, que atinge as glândulas exócrinas, envolve múltiplos órgãos e evolui de forma crônica e progressiva. Quando cada um dos pais tem um gene para FC, em cada gestação o risco de nascer um filho com e sem a doença é de 25% e 75%, respectivamente, e a probabilidade de nascer um filho saudável, mas com um gene para FC é de 50%[3].

A muscoviscidose, outra denominação da FC, é predominante na população caucasiana mundial, com incidência de 1:3.000 nascidos vivos e pode estar presente em todos os grupos étnicos[4]. No Brasil, a incidência da FC varia de acordo com a região. No estado do Rio Grande do Sul, parece aproximar-se da população caucasiana centro-europeia (1:2.000 a 1:5.000 nascidos vivos), enquanto que nos estados de Minas Gerais, Paraná, e Santa Catarina, reduz-se para cerca de 1/9.000 a 1:9. 500 nascidos vivos[5,6] .

A atividade física regular tem sido recomendada como recurso adjunto à fisioterapia respiratória na doença pulmonar obstrutiva crônica, favorecendo a limpeza brônquica, o desempenho cardiovascular e a endurance dos músculos respiratórios. A análise de estudos envolvendo a adição de exercício físico entre os fibrocísticos identificou aumento significativo no padrão espirométrico do Volume de Expiração Forçada no primeiro segundo (VEF_1)[7]. A aptidão física contribui para a sobrevida e para a qualidade de vida por essa razão, recomenda-se que todos os acometidos pela enfermidade sejam encorajados a praticar exercícios várias vezes por semana[8, 9, 10, 11].

Considerando a importância da enfermidade, tratamento e acompanhamento, este artigo tem como objetivo realizar uma revisão sistemática na literatura sobre o exercício físico, com enfoque na doença pulmonar dos fibrocísticos, publicados na literatura científica e discutir os resultados principais destes trabalhos de forma a contribuir para a qualidade de vida destes pacientes com fibrose cística.

6.2 METODOLOGIA

Foram pesquisados artigos que analisaram a prática de exercício físico com ênfase na doença pulmonar obstrutiva crônica em fibrocísticos.

Critérios de inclusão e exclusão de estudos

Foram incluídos estudos observacionais e do tipo ensaio clínico (aleatorizados ou não, controlados ou não) e que apresentassem resultados referentes ao tema estudado. Estudos de revisão foram incluídos somente na discussão para melhor elucidar os aspectos contraditórios e não participaram do resultado da pesquisa bibliográfica e nem da estratégia de busca nas bases de dados. Os demais critérios de inclusão foram: terem sido realizados em crianças, adolescentes, adultos e idosos, de ambos os sexos e publicados no idioma inglês, acompanhados ou não por educadores físicos, fibrocísticos atletas ou não. Não foram usados filtros referentes a anos de publicações. Foram excluídos os estudos que abordavam somente aspectos ligados à fisioterapia respiratória, exercícios de mobilidade torácica e experimentais com animais. Também não foram incluídos estudos onde os pacientes foram submetidos a transplante pulmonar ou retirada de um dos pulmões, pois estes não teriam os comprometimentos e deteriorações pulmonares observadas normalmente nos acometidos pela FC prejudicando a análise da revisão.

Estratégia de busca

A pesquisa dos artigos foi realizada na base de dados PubMed, Medline e Proquest , utilizando-se a intersecção de termos na busca bibliográfica mediante seleção de palavras-chave do *MeSH® Medical Subject Headings*. São elas: "cystic fibrosis" [MeSH Terms] AND ("exercise" [MeSH Terms] OR "exercise" [All Fields] OR ("physical" [All Fields] AND "exercise" [All Fields]) OR "physical exercise" [All Fields]. Realizou-se uma primeira avaliação, tendo por base os títulos e os resumos dos artigos e rejeitaram-se aqueles que não preencheram os critérios de inclusão ou apresentaram algum dos critérios de exclusão. Os artigos foram baixados mediante a disponibilidade das bibliotecas virtuais e aqueles que não estavam disponíveis para download foram solicitados junto ao Serviço Cooperativo de Acesso a Documentos

(SCAD) - Biblioteca Virtual em Saúde. Foram encontradas 359 referências com os descritores selecionados. Depois de uma verificação de referências duplicadas e a exclusão daquelas que não estavam relacionadas ao tema e todos os critérios de inclusão aplicados, restaram 23 referências submetidos a uma revisão completa do texto.

Características gerais do estudo

Todos os artigos selecionados abordavam a FC nos dois gêneros, somente um dos estudos selecionados foi realizado com apenas um dos gêneros, pois se tratava de um caso clínico com uma criança do sexo feminino. O estudo foi incluído devido a qualidade e quantidade das informações descritas. A revisão bibliográfica foi composta por crianças, adolescentes, adultos e idosos com diagnóstico confirmado de FC para os casos, e indivíduos saudáveis para aqueles estudos que utilizavam controles. As características gerais dos 23 estudos incluídos foram organizadas em relação ao tipo de estudo e são apresentados nas Tabela 1 e Tabela 2. Os estudos foram realizados entre os anos de 1971 a 2012. A faixa etária foi ampla, entre cinco e 62 anos de idade. Dez (10) estudos tratavam de ensaios clínicos abertos[12, 7, 13, 14, 15, 16, 17, 18, 19, 20], nove (9) ensaios clínicos controlados[21, 22, 23, 24, 25, 26, 27, 28, 29], dois (2) coortes[30, 31], um (1) estudo transversal[32] e um (1) estudo de caso[33]. Dentre todos os artigos, cinco deles apresentavam avaliação da capacidade de fisioterapia respiratória associado ao exercício, previstos entre os critérios de inclusão. Aspectos positivos sobre a utilização do exercício na Fibrose Cística, doença pulmonar e maior ventilação, entre os acometidos, foram elencados na maioria dos artigos pesquisados, outras referências não foram conclusivas e/ou foram cautelosas quanto à utilização do exercício principalmente pela necessidade de informação e responsabilidade na prescrição do exercício, com educador físico capacitado, como por exemplo, para o controle da excessiva produção de dióxido de carbono, além da saturação de oxigênio considerada um risco.

6.3 RESULTADOS E DISCUSSÃO

A Tabela 1 mostra estudos de intervenções na FC associada ao exercício físico. Três (3) desses estudos necessitam maiores investigações, segundo os autores, e, portanto, não foram conclusivos.

Tabela 1. Ensaios clínicos abertos e ensaios clínicos controlados incluídos na revisão da literatura de pacientes com fibrose cística praticantes de exercício físico.

Autor e Tipo de estudo		Amostra (n), idade (anos)	Efeitos dos exercícios aplicados nos fibrocísticos
(Schmidt et al., 2011)	Aberto[12]	42, 14-50a	Demonstrou efeito positivo em fibrocísticos em usar capacidade de transportar e usar oxigênio (VO2 max) em um programa de exercícios adaptados individualmente e sem supervisão aeróbica. O exercício físico regular é um fator muito importante na manutenção da boa saúde.
(Brown et al., 2011)	Controlado[22]	21, 18-40a	Observou-se que a sede não foi diferencialmente afetada pelo suor elevado durante o exercício. A sede foi semelhante para fibrocísticos apesar da atenuada hiperosmolalidade. Fibrocísticos usaram menos líquido em comparação com controles. Estudo necessita maiores investigações. Não conclusivo.
(Elbasan et al., 2012)	Aberto[7]	16, 5-13a	O treinamento aeróbio ajuda a melhorar o desempenho aeróbio, a mobilidade torácica e o condicionamento físico em crianças com fibrose cística.
(Zach et al.,1982)	Aberto[13]	12, ---	O exercício físico regular pode substituir a rotina de inalação de fisioterapia em algumas crianças com fibrose cística. Observou-se melhora da função das vias aéreas com treinamento muscular ventilatório.
(Schrage et al., 2007)	Controlado[23]	19, 21-38a	A resposta de hiperemia no exercício moderado é semelhante entre indivíduos saudáveis e pacientes com FC. A vasoconstrição relativa em resposta à ativação simpática também foi semelhante entre os grupos.
(Salh et al.,1989)	Aberto[14]	22, 16-32a	Exercícios desempenham papéis importantes na expectoração de pacientes com fibrose cística, mas não devem ser considerados como um substituto para fisioterapia.
(Ruf et al., 2012)	Aberto[15]	41, 12-42a	Embora possam ser utilizados questionários de medição de atividade física em fibrocísticos, estes não podem ser usados no

			aconselhamento e avaliação individual. Estudo necessita maiores investigações. Não conclusivo.
(Moorcroft et al., 2004) Controlado[24]		48, ---	Benefícios para a função pulmonar foram observados no estudo e os resultados sugerem que programas de exercícios devem ser incentivados como componentes importantes dos cuidados na FC.
(Kruhlak et al.,1986)	Aberto[16]	9, 18-28a	Os resultados sugerem que pacientes FC com obstrução das vias aéreas melhoram com períodos de exercícios e ventilação, principalmente nas obstruções moderadas ou graves.
(Blomquist et al.,1986)	Aberto[17]	14, 13-23a	O estudo mostra que a atividade física diária melhora a troca gasosa pulmonar e que o tratamento autocombinado com atividade física é tão eficiente quanto à fisioterapia convencional.
(Mcloughlin et al., 1997) Controlado[25]		20, ----	A análise evidenciou a necessidade de cautela na prescrição do exercício por causa da produção de lactato e excreção deficiente de dióxido de carbono durante o exercício na FC.
(Godfrey et al., 1971)	Aberto[18]	41, 5-21a	O exercício foi limitado pela mecânica pulmonar. Observou-se um aumento na ventilação total durante o esforço.
(Bradley et al., 1999)	Aberto[19]	20, ---	Este estudo mostrou que o teste "Shuttle" modificado apresenta validade para medir a capacidade de exercício físico em adultos com fibrose cística.
(Alsuwaidan et al., 1994) Controlado[26]		14, ---	O exercício na FC reduz os valores anormalmente elevados do potencial nasal negativo em pacientes com fibrose cística. Estudo necessita maiores investigações. Não conclusivo.
(Schmitz et al., 2006)	Aberto[20]	84, 16-62a	No grupo estudado a qualidade de vida, a saúde geral, a respiração e a condição física foram melhor alcançados em programas de reabilitação com acompanhamento.
(Upton et al., 1988)	Controlado[27]	89, 5-16a	Observou-se que crianças com FC, a partir dos 5 anos de idade, podem realizar testes de curta distância para avaliar a tolerância ao exercício e ajudar a avaliar a resposta ao tratamento.
(Meer et al., 1995)	Controlado[28]	27, 12-17a	Pacientes com FC apresentam desempenho

		reduzido do trabalho oxidativo do músculo esquelético. Isso pode estar relacionado com alterações fisiopatológicas secundárias no músculo esquelético na FC.
(Brown et al., 2011) Controlado[22]	18, 18-40a	Fibrocísticos apresentam sinais fisiológicos voltados para preservação do equilíbrio de sal sobre a restauração do volume ao realizar exercício físico.
(Paranjape et al., 2012) (Controlado)[29]	70, 6-16a	Os participantes melhoraram a capacidade de exercício e apresentaram aumentos significativos na função pulmonar e nas atividades habituais.

FC = Fibrose Cística; a = anos; ---- artigo sem informação.

Foram identificados estudos de acompanhamento, além de um estudo transversal com a análise entre as variáveis: tolerância ao exercício, estado clínico e estudo de imagens radiográficas. Estes estudos estão elencados na Tabela 2.

Assim como na tabela acima, foram verificados estudos onde não foi descrita a faixa etária avaliada, o que pode prejudicar a análise, pois os eventos relacionados à deterioração pulmonar estão também relacionados ao tempo de exposição ao agravo à saúde [34, 35].

Tabela 2. Estudos longitudinais e transversais incluídos na pesquisa da literatura de pacientes com fibrose cística praticantes de exercício físico.

Autor e Tipo de Estudo	Amostra (n), Idade (anos)	Efeito do exercício físico aplicado nos fibrocísticos
(Moorcroft et al.,1997) Coorte[24]	62, ----	Os resultados dos testes de exercício máximo estão correlacionados com a sobrevivência, mas eles não são melhores

		do que o Volume de Expiração Forçada no primeiro segundo como indicadores de prognóstico.
(Javadpour et al., 2005) Coorte[31]	58, 11-13a	Observou-se a incapacidade do fibrocístico de se defender do dióxido de carbono produzido durante o exercício e foi associado com um declínio mais rápido da função pulmonar.
(Massery M, 2005) Caso Clínico[33]	1, 9a	Em quatro meses de acompanhamento foi notado que houve melhora clínica da musculatura esquelética após o uso do exercício e fisioterapia.
(Coates et al.,1981) Transversal[32]	18, 5-16a	Concluiu-se que a radiografia é um bom indicador da gravidade global da doença pulmonar e que se correlaciona bem com a tolerância ao exercício e com o estado clínico da FC.

a = anos; ---- artigo sem informação.

Os ensaios clínicos foram realizados com amostras reduzidas dadas as características de prevalência da doença o que pode prejudicar a análise deste trabalho. Amostras com número elevado de participantes são preferíveis, pois trabalhos com populações maiores oferecem maior segurança nos resultados das intervenções clínicas, no entanto, devido à frequência desta afecção, os pesquisadores não têm acesso às informações ou apresentam dificuldades na coleta dos dados. A variação das faixas etárias também prejudica a homogeneização das discussões e análises na revisão, no entanto, observou-se respostas positivas ao uso do exercício físico como coadjuvante ao tratamento, preferencialmente associado à fisioterapia e vinculado a avaliação médica por meio de testes laboratoriais, de imagens e de esforço físico[14, 17].

São mais comuns estudos relacionados a crianças e adolescentes, embora o estudo de Schmitz et al. tenha avaliado idosos[20], o que é incomum já que a expectativa de vida está em torno de 40 anos[36].

Um dos artigos sugere a substituição da fisioterapia em algumas crianças com fibrose cística pelo exercício[13] o que vai de encontro com os estudos recentes[7]. A substituição total da fisioterapia pelo exercício físico deve ser vista com cautela visto que a maioria dos trabalhos enfatiza a necessidade de se aliar uma prática a outra[25, 28].

Embora a doença pulmonar da FC leve à deterioração progressiva da capacidade de se realizar exercícios, o desenvolvimento de programas de exercícios com rotina

podem beneficiar estas populações, como retratou Paranjabe et al.[29] no seu estudo controlado, onde foi observado o aumento na capacidade do exercício ao longo de um período de dois meses e um melhora significativa da função pulmonar.

Portadores de FC poderiam ser facilmente desencorajados a praticar exercícios como mostrou Godfrey et al.[19] onde o exercício foi limitado pela mecânica pulmonar. A observação de um esforço anormal e a falta de ar poderiam ser utilizados como sintomas que indicariam a inadequação da atividade física para estes pacientes, no entanto, na década de 80 já haviam relatos de melhora da função das vias aéreas com treinamento muscular ventilatório[13].

Portanto, há diferentes pesquisas relacionadas ao exercício, dúvidas e cuidados no seu manejo, mas percebe-se o papel crescente da atividade física, de forma positiva e fundamental no tratamento e prevenção de complicações, assim como a necessidade de maiores investigações devido à falta de conclusões.

Os estudos ainda mostram alguns resultados conflitantes como observado em recentes pesquisas em 2012, a respeito do comportamento da força muscular respiratória nos fibrocísticos. A maioria dos estudos parece indicar que as alterações mecânicas ventilatórias que ocorrem na fibrose cística podem levar a alterações nos níveis de força respiratória, porém os resultados sobre o perfil de força nestes pacientes são ainda contraditórios[36].

Embora os exercícios físicos sejam recomendados como parte da fisioterapia dos fibrocísticos, pois atrasam o desenvolvimento pulmonar da doença, os mecanismos celulares responsáveis por estas melhorias são pouco claros de acordo com Cholewa et al.[38]. Estes pesquisadores hipotetizaram que as perturbações mecânicas e metabólicas que ocorrem com o exercício pode ser benéficas na prevenção da patogênese do pulmão fibrocístico melhorando a hidratação das vias aéreas, a depuração mucociliar, aumentando a frequência de batimento ciliar das vias aéreas por mecanismos Ca^{+2} dependentes e reduzindo os marcadores de inflamação[38].

O exercício físico está presente no tratamento e acompanhamento da FC conforme descrito na Tabela 2. À medida que foram adotadas práticas de exercícios físicos regulares observou-se uma tolerância ao exercício[32] e, testes puderam ser realizados para se avaliar a tolerância e, posteriormente, na avaliação da resposta ao tratamento[27].

Embora estudos transversais retratem análises realizadas somente em um momento, sem acompanhamento, para as avaliações clínicas de imagens, como o estudo

de Coates[32] foi possível observar uma associação entre a radiografia, a doença pulmonar e a tolerância ao exercício.

A qualidade de vida e a sobrevida são abordadas frequentemente pelas equipes multidisciplinares, sendo o clínico, o educador físico e os fisioterapeutas indispensáveis durante o tratamento. A evolução no caso clínico identificado nesta revisão mostra de maneira científica e descritiva os aspectos positivos do exercício em uma criança de nove anos, durante quatro meses de acompanhamento[33]. Os ensaios clínicos identificados nesta revisão também evidenciaram estes aspectos e contextualizaram os diferentes pontos a serem abordados de maneira sistêmica durante o tratamento e acompanhamento[7].

Está bem estabelecida nos Centros de Referência em FC a importância da abordagem multiprofissional destes pacientes, mas outro aspecto deve ser ressaltado ao se estabelecer os cuidados; a capacitação dos profissionais que manejam a FC. Javadpour[31] acompanhou adolescentes entre 11-13 anos e identificou a incapacidade dos fibrocísticos de se defenderem do dióxido de carbono produzido durante o exercício e a sua relação com o declínio da função pulmonar. Dessa forma, a aplicação do exercício nesta população com diagnóstico de FC deve ser avaliada e manejada constantemente e corretamente, necessariamente com a presença de profissionais habilitados para que o exercício possa contribuir de maneira positiva, sem levar a possíveis danos pulmonares.

Os estudos documentam a melhora do condicionamento, o aumento da força da musculatura ventilatória e a melhora da resposta ao tratamento do fibrocístico com o exercício físico, além da qualidade de vida, no entanto, os dados a respeito do aumento da sobrevida permanecem sem maiores esclarecimentos. Esse tipo de informação exige grandes estudos com longos períodos de acompanhamento, os quais ainda não estão disponíveis e nem foram observados nesta revisão.

O exercício físico deve ser um hábito a ser seguido rigorosamente pelo portador da FC, principalmente entre os adolescentes e crianças com hábitos eventualmente sedentários, típicos desta faixa etária.

O treinamento físico não deve ser visto por pacientes e familiares com uma grande barreira a partir da própria limitação funcional imposta pela doença, pois como observado o modelo de programa de treinamento físico é similar ao que normalmente se é praticado, no entanto, máxima atenção deve ser dada a prescrição do exercício físico, principalmente nas exacerbações da doença e respeitados o número de horas disponíveis para a prática.

6.4 CONCLUSÃO

A revisão sistemática mostrou que exercício físico colabora positivamente na função do pulmonar dos fibrocísticos, desde que realizada com o manejo adequado, assim como os conhecimentos a respeito da Fibrose Cística tem aumentado nos últimos anos alcançando décadas posteriores à fase adulta. Esses avanços estão ligados ao tratamento especializado instituído nas fases iniciais da doença não somente clínico, mas também buscando outras áreas do conhecimento como a utilização do exercício físico para um melhor condicionamento, para a melhora da função pulmonar, a *performance* de atletas fibrocísticos em situações de distúrbios hidroeletrolíticos , além de estudos comparativos com imagens entre outros.

Nota-se a cautela nas publicações principalmente por se tratar de uma doença multissistêmica onde a inobservância de cuidados e a falta de conhecimento especializado da doença pode rapidamente causar prejuízos como a deterioração da função pulmonar, quadros de desidratação ou prejuízos metabólicos pela presença de dióxido de carbono não expelido.

São necessárias pesquisas que abordem o tema e estimulo a revisões que envolvam equipes multidisciplinares, estudos de intervenção e metanálises. Estudos com características homogêneas, com um número maior de pesquisados, observando-se o intervalo de idade também são importantes para que os resultados possam oferecer maior segurança aos acadêmicos ou para aqueles interessados no tema.

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ARTIGO 6 – ARTIGO ORIGINAL

Versão publicada em inglês:

Cystic fibrosis patients assisted by a program nutrition therapy: assessment of the use of supplements in patients colonized and non colonized by P. aeruginosa.

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7 ARTIGO ORIGINAL

CYSTIC FIBROSIS PATIENTS ASSISTED BY A PROGRAM NUTRITION THERAPY: ASSESSMENT OF THE USE OF SUPPLEMENTS IN PATIENTS COLONIZED AND NON COLONIZED BY *P. AERUGINOSA*

PACIENTES CON FIBROSIS QUÍSTICA ATENDIDOS POR UN PROGRAMA DE LA TERAPIA NUTRITIONAL: EVALUACIÓN DEL USO DE SUPLEMENTO DE LOS PACIENTES COLONIZADOS Y NO COLONIZADOS CON *P. AERUGINOSA*

Resumem

Objetivo: Evaluar el uso de suplementos dietéticos utilizados en el consumo de alimentos, el perfil nutricional y clínico, la bioquímica de los pacientes colonizados y no colonizados con *Pseudomonas aeruginosa* participantes de un programa nutricional enteral domiciliario. **Material y métodos:** Estudio observacional, analítico, realizado con 47 pacientes, 2-19 años. La insuficiencia nutricional fue clasificada "con déficit nutricional", y aquellos con estado nutricional adecuado y en riesgo como "sin déficit nutricional", según el Consenso Internacional Americano. La espirometría fue realizada con punto de corte de 80%. La Terapia de Reemplazo de Enzima Pancreática y la suplementación nutricional fueron registradas. **Resultados:** En la asociación entre el uso de suplementos nutricionales y los pacientes con fibrosis quística "Sin déficit nutricional", se encontró que la proporción de pacientes que toman suplementos fue estadísticamente menor que entre los no usuarios, según el Consenso Americano ($p = 0.0098$). La variable de estado nutricional se asoció significativamente con los tipos de suplementos dietéticos y con la frecuencia de suplementación ($p = 0.0445$ y $p = 0.0266$, respectivamente). No se encontró correlación entre las variables: estado nutricional y colonización por *Pseudomonas aeruginosa* en el consenso ($p = 0.2355$) **Conclusión:** Programas de atención domiciliaria que prestan asistencia nutricional, clínica y seguimiento nutricional de pacientes crónicos, como los pacientes con fibrosis quística deben fomentarse en los países de América Latina a fin de que la enfermedad pueda ser tratada con eficacia, con reducción de la morbilidad y cuadros de exacerbación de la enfermedad.

Palabras clave: fibrosis quística; suplementos dietéticos; estado nutricional; espirometria; *Pseudomonas aeruginosa.*

Abstract

Objective: To assess the use of dietary supplements used in food consumption, the clinical nutritional status and biochemistry of patients colonized and not colonized with *Pseudomonas aeruginosa* participants of a Program of Home Nutritional Therapy. **Material and Methods:** Observational analytic study, carried out with 47 patients, 2-19 years. The nutritional failure was referred to as "With Nutritional Deficit" and those in adequate nutritional status and in risk were considered "Without Nutritional Deficit", according to the International Consensus. Spirometry was performed with the cutoff point of 80%. The Pancreatic Enzyme Replacement Therapy and nutritional supplementation were recorded. **Results:** In the association between the use of nutritional supplements and Cystic Fibrosis patients "Without Nutritional Deficit" found that the proportion of patients taking supplements was statistically lower than among non users, when considering the American Consensus ($p = 0.0098$) The variable nutritional status was significantly associated with the types of dietary supplements and frequency of supplementation ($p = 0.0445$ and $p = 0.0266$, respectively). There was no correlation between the variables: nutritional status and colonization by *Pseudomonas aeruginosa* on Consensus ($p = 0.2355$). **Discussion:** Home care programs which provide nutritional and clinical support, and nutritional follow-up of chronic patients such as cystic fibrosis patients should be encouraged in Latin American countries so that the disease might be treated effectively, with reduction of morbidity and frames of disease exacerbation.

Keywords: cystic fibrosis; dietary supplements; nutritional status; spirometry; *Pseudomonas aeruginosa.*

7.1 INTRODUCTION

Cystic Fibrosis (CF) is an autosomal recessive disease, considered the most prevalent in white Caucasians (1). The product of the CF gene is the protein *cystic fibrosis transmembrane conductance regulator* (CFTR) present on the apical surface of the epithelial cells. In the absence or deficiency of this protein, there is no adequate rehydration fluid lumen leading to more viscous secretions that predispose to colonization and subsequent chronic infection by opportunistic agents such as non-mucoid and mucoid strains of *Pseudomonas aeruginosa*, an important characteristic related to pulmonary disease progression (2, 3).

Diseases related to nutrition are common and associated with poor clinical outcomes with delayed recovery from illness and reduced quality of life. The inadequate nutritional status, airway colonization with *Pseudomonas aeruginosa*, pancreatic insufficiency and frequent pulmonary exacerbations are associated with fast deterioration of pulmonary function (4). Spirometry performed in attendance of CF patients is considered the most widely used functional parameter in the CF and Forced Expiratory Volume in one second (FEV1) and its rate of decline is identified as the most reliable parameters in prediction of survival (5).

A variety of laboratory data could be useful in the nutritional evaluation of patients with CF, and biochemical indicators may enhance the nutritional and clinical evaluation. Albumin and hemoglobin, when reduced, present physiological stress as an important protein catabolism, in addition to the reduction of substrate. The alteration in blood glucoses due to CF, although late at times, is directly related to food intake and infirmity that may affect both exocrine and endocrine pancreas, the latter being responsible for insulin production (6).

Pancreatic exocrine insufficiency (PEI) is generally well controlled with modern Pancreatic Enzyme Replacement Therapy (PERT). Maldigestion due to PEI is a characteristic feature of CF and the majority of patients, therefore, requires PERT for weight gain and nutritional status during the critical period of intense growth in young children and adolescents with diagnosed CF (1, 6).

The scoring system was used to evaluate objectively the severity and the clinical status of the patient with Cystic Fibrosis. The Shwachman-Kulczycki (SK) score is divided into four categories according to degree of impairment: general activity (attendance to school or home confinement), physical examination (cough manifestation

and frequency, digital clubbing), nutrition (nutritional status evaluation in percentis), and radiological findings (manifestation of emphysema, atelectasia and bronchiectasis). The SK score comes with functional decline and is correlated with spirometric data (7).

The SK score is a useful tool for monitoring the severity of cystic fibrosis, adequately reflecting the functional impairment and chest radiography and tomography changes, especially in patients with greater impairment of lung function (7).

The cost and managing patients with medium or high risk disease related to malnutrition is high, particularly in patients with chronic diseases. Public health policies related to nutrition and quality of life offered by the Government of the Federal District (GFD) allow access without financial costs (free access) of the patient with cystic fibrosis to the home nutritional therapy service and dietetics supplements. The GFD believes that it is necessary to improve the clinical-nutrition and prevalent epidemiological characteristics in patients with cystic fibrosis (8, 9).

Nutritional supplementation may contribute to increasing muscular and adipose tissue reservations and also the total caloric intake of patients, once adequate nutrition is essential to the survival, stability and improvement of pulmonary function of patients.

There are many types of nutritional supplements available. High-energy dense preparations and polymeric diets should be used wherever necessary, however, at the present time, there is a lack of evidence to support the use of dietary supplements (1, 6).

Scientific investigations performed in reference centers like this in Brazil can show and prove the need to ensure the actions and provide financial resources for the assistance program for cystic fibrosis patients in the community, and to expand the understanding of the economic benefits of appropriate use of oral nutritional supplements.

This study aims to assess the use of dietary supplements used in food consumption, the clinical nutritional status and biochemistry of patients colonized and not colonized with *Pseudomonas aeruginosa* participants of a Program of Home Nutritional Therapy.

7.2 MATERIAL AND METHODS

Observational analytic study, carried out with 47 patients, 2-19 years (9.6 mean ± 4.2), from August 2009 to July 2011, all participants of the Program of Home Enteral Nutrition (PHEN) performed in a Cystic Fibrosis Reference Center of the Federal

District, Brazil. Although the Reference Center has 66 registered patients, 14 CF patients were excluded because they were adults who were not accompanied by the same team or in breastfeeding. There were two deaths (one child and a teenager) and 3 refused to participate. In the sample, no patient had been undergone lung transplantation.

The diagnosis of CF was made according to the Guidelines of the Cystic Fibrosis Foundation (10). The research protocol was based on the patient chart formulated by the service staff of the Reference Center and included clinical and nutritional data. Adolescents aged from 10 to 19 years were taken into account, and the remaining samples were considered children, according to the World Health Organization classification (11). The weight (W) and height (H) were measured as children and teenagers wearing only light clothing and no shoes. It was used a platform-type anthropometric scale, brand *Filizola*® Brazil, with a maximum capacity of 150 Kg. The height was measured with a stadiometer, brand *Sanny* ®, with the child or adolescent wearing no shoes, standing upright with their heels against the wall with no baseboard, staring straight ahead. Measurements of weight and height were used to determine the Body Mass Index (BMI) percentile (12) and W/H% for the definition of acceptable nutritional status (>25th percentile or W/H% above 90%), with risk (10th - 25th percentiles or W/H% 85-89) and nutritional failure (<10th percentile or W/H% <85) according to the recommendations proposed by the American Consensus on CF (13, 14). The anthropometric assessment was conducted by a nutritionist at the Center of Reference.

To summarize the statistical analysis of the nutritional status, patients with nutritional failure were referred to as “With Nutritional Deficit” and those in adequate nutritional status and at risk, were considered “Without Nutritional Deficit”.

According to the protocol of the Reference Center, biological sample was collected from expectorated sputum and material from oropharynx (swab) during the attendance, for research of colonization by mucoid and non mucoid *Pseudomonas aeruginosa (15).*

The most common methods used to identify the existing pathogen in the respiratory tract are sputum tests, oral-pharynx swab post respiratory physiotherapy/coughing and bronchoalveolar lavage (BAL). The BAL is considered the gold standard procedure, since it improves the chance of presenting colonization of

respiratory tract but, being an invasive procedure; it is not a part of infection diagnosis routine at the Reference Center, mainly due to small children medical care (15).

The SK score was performed by the pediatric pulmonologist and nutritionist during the monitoring routine. It was scored according to the degree of impairment of general activity, physical examination, nutrition and radiological findings. The four scores were totaled and the obtained score was classified for the study into> 70 or ≤ 70, following the pattern Shwachman & Kulczycki of excellent (86-100), good (71-85), medium (56-70) bad (41-55), and severe (≤ 40) (16).

As nutritional status is one of SK score components, the statistic correlation was not performed with other variables such as total caloric value and nutritional status. However, the result of the four conditions demanded by the score was summed up considering patients ranging from excellent to critical profile of the disease.

In their assessment of spirometry and clinical associations, 37 cystic fibrosis patients were taken into consideration due to the peculiar characteristics of the pulmonary function test, such as the need for patient cooperation (age) and the use of standardized technique (17).

Spirometry was performed in children older than 6 years due the difficulty of conducting the examination in young children and the cutoff predicted point was 80% for height and sex as the lower limit of normality for the parameter of forced expiratory volume in one second (FEV1) (17). The technique of examination followed the recommendation of the American Thoracic Society (ATS) (18) and was held in portable equipment of standardized volume, model *Spida* ®. The technician responsible for the spirometry was able to evaluate correctly the curves and maneuvers of pulmonary function test.

It was conducted by a 24-hour dietary recall (24HDR) by a nutritionist in order to register the amount of food consumption and the Total Caloric Value (TCV) of the diet. The 24HDR was analyzed by Avanutri 4.0 software. For the recommendations of energy intake, they were based on guidelines from 120 to 150% of the established energy for healthy individuals of similar age and sex according to the *Recommended Dietary Allowances/DRIs* (19).

The dietetic supplements used by CF patients were classified in present or absent, during food consumption, and regarding the dietary types of supplements in normocaloric polymeric formula (1.0 Kcal/ml) and hypercaloric ones (1.25 Kcal/ml and 1.5 Kcal/ml) or whether they use or not supplements. The definition of formulas was

followed with special industrialized purposes and specially formulated for people in specific metabolic conditions offered by home nutritional therapy service (6, 9). The frequency in which the supplements consumed were also registered as twice a day, 3 times a day, 4 times a day or no supplements.

The Pancreatic Enzyme Replacement Therapy (PERT) were recorded and classified as present and absent. There was no difference in the use of supplements provided orally or via gastrostomy.

Biochemical tests were performed after 12 hours fasting and included blood glucose (mg/dl), albumin (mg/dl) and hemoglobin (g/dl) dosages.

Data were analyzed using the statistical program SAS 9.2 for Windows. Student t test was used for variables with Gaussian distribution. For those which did not present a Gaussian distribution, the Mann-Whitney test was used. The chi-square or Fisher's exact test was used for the analysis of qualitative variables. In the evaluation, it was used a significance level of 5%.

To ensure the reliability of the results in some associations and statistical analysis, 37 cystic fibrosis patients' samples were taken into consideration, not 47, because not all patients could go through spirometry, and values related to the use of nutritional supplements enzymes and vitamins were absent.

The study was approved by the Ethics Research Committee of Health Secretary of the Federal District, Brazil (Protocol 186/2009). All patients were invited to participate and signed a Free Informed Term of Consent.

7.3 RESULTS

In this study, 59.5% of the patients were male, the average age of CF patients and the ages of diagnosis were 9.61 years and 23.33 months, respectively. The analyses of the evidence of pulmonary function FEV1, SK score, and biochemical tests of glucose, albumin and hemoglobin were within normal limits. However, the Caloric Value of Diet did not reach the average percentage of achievement of the *Recommended Dietary Allowances/DRIs* among CF patients, being below the recommended 120 to 150% (20). The Table 1 shows description of sex, age, dietary intake and clinical profile of cystic fibrosis patients.

Table 1 - Description of sex, age, dietary intake and clinical profile of cystic fibrosis patients on home enteral therapy in Brazil. Period: 2009-2011.

Variable	n = 47
Sex (male/female)	28/19
Age (months), mean ± sd	9.61 ± 4.2
Age diagnostic (months), mean ± sd	23.33 ± 33.81
TCV (Kcal), mean ±dp	1959.30 ± 501.45
Shwachman Score, mean ± sd	77.61 ± 15.37
Glucose (mg/dl), mean ± sd	86.09 ± 9.48
Albumin (mg/dl), mean ± sd	4.24 ± 0.39
Hemoglobin (g/dl), mean ± sd	13.4 ± 1.26

The associations between the classification of the nutritional status and laboratory tests of blood glucose, albumin and hemoglobin ($p = 0.7166$, $p = 0.9581$ and $p = 0.5315$, respectively) were not statistically significant.

For the nutritional supplement variable, the rate of CF patients "Without Nutritional Deficit" is statistically lower among those who use supplements than among those who do not use supplements, when considering the American Consensus (13) ($p = 0.0098$) . The Table 2 shows nutritional status and the relationship among biochemical values, use of supplements, PERT, colonization by *P. aeruginosa* cystic fibrosis assisted by the home care enteral nutrition.

Table 2 - Nutritional status and the relationship among biochemical values, use of supplements, PERT, colonization by *P. aeruginosa* cystic fibrosis assisted by the home care enteral nutrition program in Brazil. Period: 2009-2011.

Variables	Nutritional Status American Consensus[13]		p-value
	"Without Deficit" n = 34	"With Deficit" n = 13	
Glucose (mg/dl) Mean ± sd	86.41 ± 8.9	85.18 ± 11,3	0.7166
Albumin (mg/dl) Mean ± sd	4.24 ± 0.41	4.25 ± 0.35	0.9581
Hb (g/dl) mean ± sd	13.50 ± 1.3	13.24 ± 1.01	0.5315
NSu (%)			
Present			
Absent	20 (60.61)	13 (39.39)	**0.0098**
	14 (100.0)	0 (0.00)	
PERT (%)			
Present	27 (67.50)	13 (32.50)	0.1660
Absent	7 (100.0)	0 (0.00)	
P.aeruginosa			
Present	17 (50.00)	9 (69.23)	0.2355
Absent	17 (50.00)	4 (30.77)	

*p-values obtained by tests t student, Fisher exact and chi-square; NSu = Nutritional Supplements ; PERT = Pancreatic Enzyme Replacement Therapy; sd = standard deviation; [13] Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002:35: 246-59;

The statistical analysis did not find significant association between Pancreatic Enzyme Replacement Therapy and American Consensus nutritional status (p = 0.1660).

The variable nutritional status was significantly associated with the types of dietary supplements and frequency of supplementation (p = 0.0445 and p = 0.0266, respectively). The Table 3 shows nutritional status and the types of dietary supplements relations among cystic fibrosis patients.

Table 3 - Nutritional status and the types of dietary supplements relations, frequency of supplementation among cystic fibrosis patients on home enteral nutrition in Brazil. Period: 2009-2011.

Variables	NS American Consensus[13] "Without	NS American Consensus[13] "With	p-value**

	Deficit" n = 34	Deficit" n = 13	
Types of dietary supplements*			**0.0445**
Not use supplements	14 (41.18)	0 (00.00)	
Supplement 1.0 Kcal/ml	8 (23.53)	6 (46.15)	
Supplement 1.25 Kcal/ml	7 (20.59)	5 (38.46)	
Supplement 1.5 Kcal/ml	5 (14.70)	2 (15.39)	
Frequency			**0.0266**
Not use supplements	14 (41.18)	0 (00.00)	
Use 2 times per day	2 (05.88)	2 (15.38)	
Use 3 times per day	17 (50.0)	9 (69.24)	
Use 4 times per day	1 (2.94)	2 (15.38)	

* Supplements with high content of proteins and lipids

**p-value obtained by Fisher exact test; NS = Nutritional status; Kcal = Kilocalories

[13]Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2002: 35: 246-59.

For the variable "presence" of colonization by non-mucoid *Pseudomonas aeruginosa*, the proportion of patients with FEV1 ≥ 80% is statistically lower than the proportion of CF patients with FEV1 <80% (p = 0.0073), however, for the variable colonization by mucoid strain, the proportions were not statistically significant. The Table 4 shows pulmonary function test FEV_1 and colonization by *Pseudomonas aeruginosa* among cystic fibrosis patients.

Table 4- Pulmonary function test FEV_1 and colonization by *Pseudomonas aeruginosa* mucoid and non mucoid among cystic fibrosis patients on home enteral nutrition in Brazil. Period: 2009-2011.

Variables	FEV_1<80%* n = 14	FEV_1≥80%* n = 23	p-value**
Pseudomonas aeruginosa			

Present	12 (85.71)	9 (39.13)	**0.0073**
Absent	2 (14.29)	14 (60.87)	
Pseudomonas aeruginosa mucoid			
Present	2 (16.67)	1 (9.09)	1.000
Absent	10 (83.33)	10 (90.91)	

*In their assessment of spirometry and clinical associations, 37 CF patients were considered and performed in children older than 6 years, due to the peculiar characteristics of the pulmonary function test.

**p-value obtained by Fisher exact test; FEV_1 = Forced expiratory volume in one second.

7.4 DISCUSSION

Malnutrition and progressive pulmonary disease are common in patients with Cystic Fibrosis. Clinical and pulmonary impairments associated with high mortality rates could be prevented with early diagnosis and neonatal screening (20). In this study, the samples were diagnosed when they were, on average, 23 months old, in other words, later. Farias et al. & Rodrigues et al. identified the average age of diagnosis of less than 18 months showing the results of early diagnosis. Clinical observations over the last decade are suggestive as to the favorable results of neonatal screening for cystic fibrosis, especially in relation to nutritional deficits, early identification and treatment of pancreatic disease and number of hospital admissions in the first two years of life (21, 22). In the United States, around 50% of CF patients have the diagnosis confirmed by completing six months of life (23).

Although no changes were observed in biochemical parameters singly nor associations with nutritional status, it is known that albumin in patients with CF is associated with the severity of disease constituting in a prognostic factor in CF patients (24). Forte et al. & Pereira et al. corroborate with the findings of this sample where CF patients have albumin values above 3.5 mg/dl showing a good nutritional status of this sample (25, 26).

The SK score, in this study, indicated a favorable clinical status, because it showed values > 70. Good nutritional status and appropriate clinical status were found in a cross-sectional study similar to this survey conducted with CF patients until 18 years, shown by the value of SS of 83. 6 ± 11. 13, and albumin> 3.5 g/dl (26).

The score is intensely disseminated and used at medical appointments. It is easily applied by physicians and nutritionists offering immediately a global appreciation of the patient. However, most of its categories (general activity, physical examination,

nutrition and radiological findings) is based in subjective information about general clinical status. This score presents a high intra and interobserver reproducibility, but it lacks a category to evaluate the pulmonary function. If applied together with other clinical observations and pulmonary function proof, it allows an adequate monitoring of the patient (7).

In this study, blood glucose levels were remained appropriate, however, glucose metabolism is strongly influenced by the impairment of insulin secretion from the pancreas and the risk increases with age, thus, individuals with CF who develop diabetes suffer accelerated decline in clinical status of the disease and in pulmonary function, as well as the mortality rate is higher than those who do not have diabetes (27, 28).

The negative association between PERT and nutritional status ($p = 0.1660$) may be related to the type of analysis performed for PERT, classified as present and absent, and not the amount used (units lipase per Kilogram body weight per meal/day). It is, therefore, a limitation of the study because pancreatic insufficiency has direct influence on nutritional status. Factors such as the correct or incorrect use of the enzyme, treatment adherence, insufficient doses or higher doses were not evaluated, as well as the method of administration, so the result should be observed carefully (1, 14).

In the assessment of nutritional status (NS) of CF patients, literature has recommended the use of specific consensus of NS classification to ensure an adequate assistance to patients and the prevention and treatment of the nutritional failure effectively, including the use of nutritional supplements. Consensus for this population has detected more cases of malnutrition than nonspecific parameters (13, 14, 19).

When evaluating the association between the use of nutritional supplements and nutritional status, they showed significant correlation ($p = 0.0098$) and these findings are in agreement with the study by Montoya et al. where intervention with nutritional support increased the caloric density of meals and CF patients had weight gain and showed improvements in the nutritional state (30). In a longitudinal research with nutritional supplementation in CF patients, the authors found significant gains in weight and height, as well as increased muscle and fat reserves and, during the follow-up, higher achievement of the nutritional recommendations was remarked with the use of supplements (31).

According to the dietetic prescription, the supplements should be given before or after meals or before bedtime in order to insure that the appetite for normal food is

maintained and that there will not be any substitution of the main meals. The inadequate use of supplements increases the cost, since the formulas are expensive and may reduce the amount of food eaten without improving total energy intake (6, 32).

In this study the using recommendations were followed, and the supplements may have contributed to increasing caloric intake. The types of supplements and the frequency showed a significant association with nutritional status, $p = 0.0445$ and $p = 0.0266$, respectively.

Although the achieved results in this research showed the positive results on nutritional status, at the present moment, we lack evidence to support the use of dietary supplements. A recent systematic review showed that using energy supplements does not improve nutritional status in people with cystic fibrosis (32), however, supplements, according to the dietary guidance nutritionist Reference Center may be used, mainly because they can be consumed away from home, in places such as schools and workplaces, and by sports enthusiasts to complete the energetic support, but should not be regarded as essential.

An intake of dietetic supplements more frequent than three times a day, as observed in a CF patient of this study should not be encouraged, since it may alter the consumption of other essential food, signal the lack of willingness to try new food and encourage the preference for drinks instead of solid foods, especially when consumed by children.

Researches and randomized controlled trials are needed to establish the role of energy supplements for the short–term in people with CF and acute weight loss and also for long-term nutritional management or advanced lung disease or both (32).

Nutritional supplements of the Program of Home Enteral Nutrition Therapy were prescribed for patients to maintain or achieve the nutrition goals set, however, researches, that found a significant association as that one observed in our study, are scarce. Although CF patients receive formulas with no cost facilitating adherence to the treatment, the nutritional needs were not reached, suggesting reorganization in the management and monitoring of the use of nutrition service formulas.

A study about the food consumption among CF patients corroborates with the obtained results in this survey, where most of the CF patients did not reach the recommendations and were observed associations related to age (26).

When evaluating the association between NS and colonization by mucoid and non mucoid *Pseudomonas aeruginosa* on American Consensus (13, 14), no correlation

was found between the variables. In a prospective cohort study conducted with n = 42 CF patients, the researchers also did not identify any association between *P. aeruginosa* and NS. The authors suggest that the few cases colonized by *Pseudomonas aeruginosa* may have contributed to the lack of association, as well as the aggressive eradication therapies with antipseudomonal strategies (33).

Although no association between the NS and colonization has been found, Steinkamp G et al., and Que et al. found through cohorts the relationship between *P. aeruginosa* and FEV1 ($p < 0.05$) and that they are according to the findings of this survey ($p = 0.0073$) showing the negative impact of colonization and deterioration of pulmonary function. No associations were found with the mucoid *P. aeruginosa* which is associated with accelerated rate of decline in pulmonary function (34, 35).

Differently, the longitudinal study in Reference Center for attendance of FC patients found significance in the association of pulmonary colonization by mucoid *Pseudomonas aeruginosa* and FEV1 ($p = 0.010$). It is known that the mucoid strain increases morbidity and mortality in CF patients (25).

Therapeutic intervention in CF remains a challenge, partly because of the number of organs and tissues affected by the lack of a functional cystic fibrosis transmembrane conductance (CFTR) protein. CF was originally regarded primarily as a gastrointestinal (GI) disease because of the failure to thrive and early death from malnutrition in infants with CF. However, successful interventions for the GI manifestations of CF have left chronic lung infections as the primary cause of morbidity and mortality. Despite a complex microbiology within the CF lung, one pathogen, *Pseudomonas aeruginosa*, remains the critical determinant of pulmonary pathology. Treatment and management of this infection and its associated symptoms are the major targets of extant and developing CF therapies (36).

7.5 CONCLUSION

Home care programs which provide nutritional support, clinical and nutritional follow-up of chronic patients such as cystic fibrosis patients may be aroused in Latin American countries and in socio-economic development so that the disease might be treated effectively, with reduced morbidity and mortality and frames of disease exacerbation.

7.6 ACKNOWLEDGMENTS

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ARTIGO 7 – ARTIGO ORIGINAL

Versão em inglês.

Clinical and nutritional aspects of cystic fibrosis patients assisted by a home enteral nutrition program in Brazil. Haack A, Novaes MRG. Revista Chilena de Nutrición. 2013; 40(2): 112-118.

8 ARTIGO ORIGINAL

CLINICAL AND NUTRITIONAL ASPECTS OF CYSTIC FIBROSIS PATIENTS ASSISTED BYA HOME ENTERAL NUTRITION PROGRAM IN BRAZIL

ASPECTOS CLÍNICOS E NUTRICIONALES DE LOS PACIENTES CON FIBROSIS QUÍSTICA COM LA ASISTENCIA DE UM PROGRAMA DE NUTRICIÓN ENTERAL DOMICILIARIA EN BRASIL

Abstract

This study to assessed 47 cystic fibrosis (CF) patients assisted by a program of Home Enteral Nutrition. The following anthropometric measures weight, height, triceps skinfold thickness and circumference of waist were observed, spirometry was performed. Enzymes, nutritional and fat-soluble vitamin supplementations were recorded. No found associations with enzymes and vitamin supplements between groups who did or did not have a nutritional deficit. Spirometry of patients "Without Nutritional Deficit", in European and American Consensus, it was found that the ratio of FEV1 ≥ 80% is statistically greater than the ratio of FEV1<80% (0.0459 and 0.0230, respectively).The percentage of patients “Without Nutritional Deficit” is statistically lower among those who use supplements among those who do not use supplements, than when considers both Consensus (p=0.0210 and 0.0098, respectively).Pulmonary function test FEV1, CF patients with FEV1 <80% and Arm Circumference <5th percentile showed association statistically significant (p=0.0021).The associations between nutritional deficits and altered pattern of spirometry are common situations among CF patients.

Keywords: cystic fibrosis; lung disease; nutritional status; neonatal screening; spirometry.

Resumen

Estudio que evaluó 47 pacientes con fibrosis quística (FQ) con la asistencia de um Programa de Nutrición Enteral Domiciliaria. Se tomaron medidas de antropometría peso, talla, pliegue del tríceps y circunferencia de cintura y espirometria. Enzimas y suplementos de vitaminas solubles em grasa se registraron. No encontraron asociaciones con el uso de suplementos de vitaminas y enzimas entre os grupos que teníam ou no tenían nengún déficit nutricional. Espirometría de lós pacientes "Sin Déficit Nutricional", para el consenso americano y europeo, tiene uma tasa VEF1 ≥ 80% estadísdicamente superior a la tasa de VEF1 < 80% (0.0459 y 0.0230, respectivamente). La tasa de pacientes com FQ "Sin Déficit Nutricional" y usando suplementos es estadísdicamente más bajos que lós que no usan, cuando se consideran los dos consenso (p = 0.0210 y 0.0098, respectivamente). La prueba de función pulmonar de los pacientes con FQ com VEF 1 < 80% y circunferencia del brazo < percentil 5 mostraron una asociación estadísticamente significativa (p = 0.0021). Las asociaciones entre déficit nutricional y espirometria se encuentran muy entre los pacientes con FQ.

Palabras clave: fibrosis quística; enfermedad pulmonar; estado nutricional; cribado neonatal; espirometria.

8.1 INTRODUCTION

Cystic Fibrosis (CF) is a genetic disease that leads to pancreatic insufficiency, chronic obstructive pulmonary disease and malnutrition (1). The nutritional state of the patient and the early introduction of preventive therapy have an important relation to the progress of pulmonary diseases, affecting the quality of life and survival of the patients (2, 3).

The incidence of CF varies according to ethnicity, being more common among Caucasians (4). The longevity of the patients has increased over the years mainly due to effective treatment and currently studies show the possibility of living more than 50 years for CF patients born after 2000 (5).

In 2009, the Health Secretary of the Federal District, Brazil, published the first Technical Regulations for Supply of Home Enteral Nutrition (HEN), bringing benefits to patients diagnosed with CF, and thus providing a greater access to nutritional therapy and improvements in nutritional and clinical status of these patients, users of the Unified National Health System, in which health is a matter of State and everyone's right (6, 7). Public health policies as the supply of HEN and the Neonatal Screening test of broad access to the population can assist in the early detection of CF and in preventing complications. The costs of applying the benefits are coordinated by the State's budget departments (8).

This study aims to assess the socioeconomic, clinical and nutritional profile of CF patients assisted by a program of HEN in a Cystic Fibrosis Reference Center in Brazil.

8.2 METHODS

This cross-sectional, analytic study was carried out with 47 patients, 2-19 years (9.6 mean ± 4.2), from August 2009 to July 2011, all patients of the Home Enteral Nutrition Program (HENP) that was performed in a Cystic Fibrosis Reference Center of the Federal District, Brazil. Although the Reference Center has 66 registered patients, 14 CF patients were excluded because they were adults who were not accompanied by the same team or in breastfeeding. There were two deaths (one child and a teenager) and 3 refused to participate.

The diagnosis of CF was made according to the Guidelines of the Cystic Fibrosis Foundation (9). The research protocol was based on the patient chart formulated by the service staff of the Reference Center and included socioeconomic, clinical and nutritional data.

According to the World Health Organization classification, adolescents aged from 10 to 19 years were taken into account, and the remaining subjects were considered children.

The weight (W) and height (H) were measured as children and teenagers wore only light clothing and no shoes. It was used a platform-type anthropometric scale, brand *Filizola*®, ranking 100g with a maximum capacity of 150 Kg. The height was measured with a stadiometer, accuracy of 0.1 cm and maximum extension of 2 m, brand *Sanny* ®, with the child or adolescent wearing no shoes standing upright with their heels against the wall without a baseboard, staring straight ahead. Measurements of weight and height were used to determine the Body Mass Index (BMI) percentile (11) and W/H % for the definition of acceptable nutritional status (>25th percentile or W/H% above 90%), with risk (10th - 25th percentiles or W/H% 85-89) and nutritional failure (<10th percentile or W/H% <85) according to the recommendations proposed by the American and European Consensus on CF (12, 13).

The measurement of arm circumference (AC) and triceps skinfold thickness (TSF) were observed and analyzed according to standard procedure. The percentiles of AC and TSF <5th show depletion of muscle and adipose tissue, respectively (10). The anthropometric assessment was conducted by a nutritionist at the Center of Reference.

To summarize the statistical analysis of the nutritional status, patients with nutritional failure were referred to as “With Nutritional Deficit” and those in acceptable nutritional status and at risk (without nutritional failure or invasive nutritional support), were considered “Without Nutritional Deficit”.

Spirometry was only performed in children older than 6 years because of the difficulty of conducting the examination in young children and the cutoff predicted point was 80% for height and sex as the lower limit of normality for the parameter of forced expiratory volume in one second (FEV1) (14). The technique of examination followed the recommendation of the American Thoracic Society (ATS) (15) and was held in portable equipment of standardized volume, model *Spida*®. The technician responsible for the spirometry was able to evaluate correctly the curves and maneuvers of pulmonary function test.

It was conducted during a 24-hour dietary recall (24HDR) by a nutritionist in order to register the amount of food consumption and distribution of macronutrients ingested the day before the consultation. The 24HDR was analyzed by Avanutri 4.0 software. For the recommendations of energy intake, they were based on guidelines from 120 to 150% of the established energy for healthy individuals of similar age and sex according to the Recommended Dietary Allowances/*DRIs* (16).

The Pancreatic Enzyme Replacement Therapy (PERT) and fat-soluble vitamin supplementation were recorded and classified as present and absent. The utilized enzymes were CREON® of 10.0000 units, CREON® of 25.000 units and the vitamin supplement ADEKs®.

Data were analyzed using the statistical program SAS 9.2 for Windows. It was used the Student t test for variables with Gaussian distribution. For those which did not present a Gaussian distribution, it was used the Mann-Whitney test. The chi-square or Fisher's exact test was used for the analysis of qualitative variables. In the evaluation, it was used a significance level of 5%.

To evaluate the cystic fibrosis patients on the pulmonary function matter, we used spirometry values. Due to the patient's low social economic situation, in addition to their ages being less than 6 years old, not all patients could go through spirometry, therefore only 37 cystic fibrosis patients' samples were taken into consideration, not 47.

The study was approved by the Ethics Research Comitee of the Health Secretary of the Federal District (Protocol 186/2009). All patients were invited to participate and signed a Free Informed Term of Consent.

8.3 RESULTS

In this study, 59.5% of the patients were male, and the ages of diagnosis and maternal education were 23.3 months and 11.3 years, respectively. 65.9% of the patients had a family income of approximately $464 (four hundred sixty four United State dollars) and it would be classified as low socioeconomic status in Brazil. The Table 1 shows description of sex, age, FEV_1 and antropometric measures of cystic fibrosis patients.

Table 1 - Description of sex, age, FEV_1 and antropometric measures of cystic fibrosis patients on home enteral therapy in Brazil. Period: 2009-2011.

Variable	n = 47
Sex (male/female)	28/19
Age (months), mean ± sd	9.61 ± 4.2
Age diagnostic (months), mean ± sd	23.33 ± 33.81
TST ≥ percentile 5 (frequency, %)	44 (93.62%)
< percentile 5 (frequency, %)	3 (6.38%)
AC ≥ percentile 5 (frequency, %)	36 (76.50%)
< percentile 5 (frequency, %)	11 (23.50%)
Variable	**n = 37**
FEV_1 %, mean ± sd	86.80 ± 22.30

FEV_1 = forced expiratory volume in one second; Spirometry was performed in children older than 6 years (n = 37); TST = triceps skinfold thickness; AC = arm circunference.

Due to the low income of the families and the difficult access to specialized exams such as the gene mutation one, within the 47 studied patients, only 10 did the genetic research and all results were positive to the mutation delta F508. Among them, 90% had pancreatic insufficiency (Confidence Interval – CI 95%, 55,0-99,7) and according to the European and American classification of nutritional condition, 50% of the patients had nutritional deficit with CI 95% (18,71-81,29).

When analyzing the nutritional status in "Without Nutritional Deficit" and "With Nutritional Deficit," according to the American and European Consensus (12,13), the average age of diagnosis and years of maternal education were not statistically significant as seen by the values of p = 0.5220 and p = 0.2487 for European (13), p = 0.3969 and p = 0.5060 for American (12). We also found no connection with family income, use of enzymes (PERT) or vitamin supplements between groups who did or did not have a nutritional deficit. In the analysis of spirometry of CF patients "Without Nutritional Deficit", in both Consensus (13, 12), it was found that the ratio of FEV1 ≥ 80% is statistically greater than the ratio of FEV1 <80% (0.0459 and 0. 0230, respectively).

The rate of CF patients "Without Nutritional Deficit" is statistically lower among those who use supplements than among those who do not use supplements, when considering both the European (13) and American Consensus (12) (p=0. 0210 and 0. 0098, respectively). The Table 2 shows classification of nutritional status in cystic fibrosis patients.

Table 2- Classification of nutritional status and relationship between pulmonary function and the use of nutritional supplement, enzymatic (PERT) and vitamin in cystic fibrosis patients (n=37) enteral nutritional in Brazil.Period: 2009-2011.

Variables	**NS European Consensus [13]**		**p-value***	**NS American Consensus [12]**		**p-value***
	Without deficit n = 34	With deficit n = 13		Without deficit n = 34	With deficit n = 13	
FEV_1						
<80%	7 (53.85%)	6 (46.15%)		7 (50.00%)	7 (50.00%)	
≥80%	20 (86.96%)	3 (13.04%)		20 (86.96%)	3 (13.04%)	
Missing value	7	4		7	3	
			0.0459			**0.0230**
PERT						
Present	27 (69.23%)	12 (30.77%)		27 (67.50%)	13 (32.5%)	
Absent	7 (100.0%)	0 (0.00%)		7 (100.0%)	0 (0.00%)	
Missing value	7	1		7	0	
			0.1648			0.1660
Supplementation of vitamins						
Present	26 (70.27%)	11 (29.73%)		25 (65.79%)	13 (34.21%)	
Absent	8 (88.89%)	1 (11.11%)		9 (100.0%)	0 (0.00%)	
Missing value	0	1		0	0	
			0.4092			0.0906
Nutritional supplementation						
Present	21 (63.64%)	12 (36,36%)		20 (60.61%)	13 (39.39%)	
Absent	13 (100.0%)	0 (0.00%)		14 (100.0%)	0 (0.00%)	
Missing value	0	1		0	0	
			0.0210			**0.0098**

*p-value obtained by chi-square; NS= nutritional status; FEV_1=forced expiratory volume in one second; Spirometry was performed in children older than 6 years (n = 37); PERT= pancreatic enzyme replacement therapy.

The statistical connections between the CF patient age and the age of diagnosis were not significant when related to FEV1 (p = 0.4253 and p = 0.0899, respectively).

In the analysis of pulmonary function test FEV1, CF patients with FEV1 <80% and AC<5th percentile showed association statistically significant (p = 0.0021). The Table 3 shows anthoropometric characteristics and FEV_1 in cystic fibrosis patients.

Table 3 -Anthoropometric characteristics and FEV_1 in cystic fibrosis patients (n = 37) enteral nutrition in Brazil. Period: 2009-2011.

Variables	FEV_1<80%	FEV_1≥80%	p-value*
	n = 14	n = 23	
Weight (mean ± sd)	35.63 ± 15.74	33.25 ± 14,09	0.6370
Height (mean ± sd)	1.44 ± 0.21	1.36 ± 0,18	0.2522
BMI (mean ± sd)	16.34 ± 2.91	17.02 ± 3,23	0.5278
AC			**0.0021**
<percentile 5	7 (87.50)	1 (12.50)	
≥percentile 5	7 (24.14)	22 (75.86)	
TST			
<percentile 5	2 (14.29)	0 (0.0)	0.1366
≥percentile 5	12 (85.71)	23 (100.0)	

*p- values obtained by student's t test and chi-square, BMI=body mass index; AC=arm circunference; TST= triceps skinfold thickness; FEV_1=forced expiratory volume in one second; SD=standard deviation

The average percentage of achievement of the *Recommended Dietary Allowances/DRIs* (16) among CF patients was of 104.51 ± 34.53%, below the recommended 120 to 150%. In the study, 72.34% of the CF patients were below the recommended dietary intake and 19.15% had an ideal consumption. The carbohydrate intake was adequate, ≥ 50%; however, the protein intake was high (21.95%) and lipid one, below the recommended ≥ 35% (26.10%), as described in Figure 1.

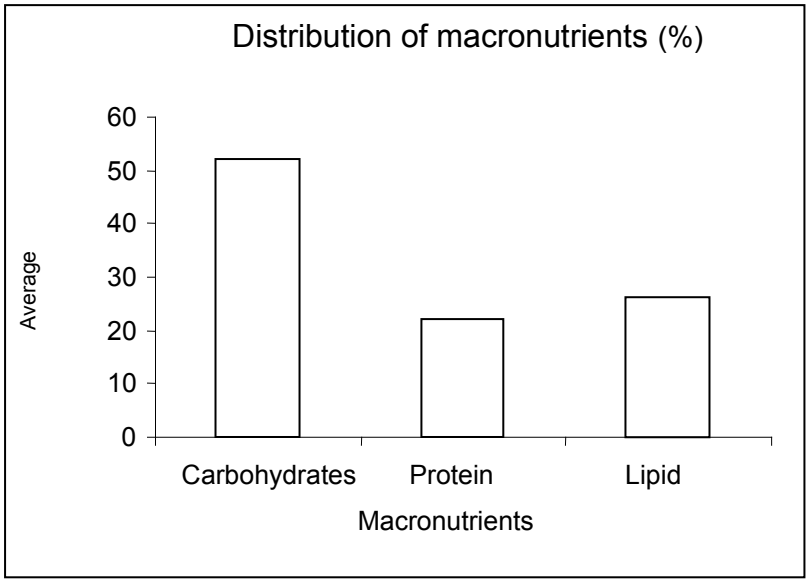

Figure 1- Distribution of macronutrients ingested by cystic fibrosis users an enteral therapy program in Brazil. Period: 2009-2011.

8.4 DISCUSSION

Over the past 50 years, the longevity in patients with CF has increased significantly and the improvements have been attributed to multiple factors such as early diagnosis, improvements in nutrition, infection control, body mass index (BMI), socioeconomic status, among others (17, 5, 18).

In this study, the subjects were diagnosed when they were, on average, 23 months old and this result does not corroborate with the surveys performed in the Cystic Fibrosis Reference Center. Chakr et al. (19) and Pereira et al. (20) verified that cystic fibrosis infant patients were diagnosed before they were 12 months old, 11,7 and 4,5 respectively.

This result indicates that the neonatal screening should be expanded and effective in Brazil aiming the early diagnosis of this disease, the prevention of pulmonary complications, nutritional disorders, and assistance in growth (18, 21). In the United States, around 50% of CF patients have the diagnosis confirmed by completing six months of life (22).

The analysis found low-income and low maternal education among the guardians for patients. Although the literature is scarce in socio-economic data releases from individuals with CF, income and maternal education, it is known that the favorable

socioeconomic status allows a greater degree of maternal education and higher income and, thus, it contributes directly to a better treatment adherence and better nutritional status. The nutritional profile is directly linked to the better clinical status and fewer number of hospital infections (23). CF patients in the most advantageous economic situation can be better informed and, therefore, get better health care and access to services while in attendance at the clinics. Schechter et al. (17) highlighted in a study in the U.S. that the socioeconomic level is associated to 3.6 higher risk of death, and also to a set of harmful environmental factors such as pollution, exposure to passive smoking, individual and familiar stress, besides the lowest values of weight, height and FEV1. The impact proved to be so obvious that the authors considered the socioeconomic profile as a potential confounder in clinical researches (24).

The use of consensuses on clinical evaluation of CF patients is recommended in the literature to ensure an adequate assistance to patients and the prevention and treatment of nutritional failure effectively. Consensus directed to this population has detected more cases of malnutrition than nonspecific parameters (12, 13, 25).

Many patients in this study had nutritional deficit and altered pattern of spirometry, a common situation in adolescents and adults with cystic fibrosis, because the nutritional status, body mass, BMI follow the pulmonary function and indicate a better prognosis (26, 27). The use of percentile of BMI in this research is consistent with the literature, because in children over 2 years this indicator is related to adequate growth, besides a lower risk of death (28). A cohort study from 1990 to 2007 showed improvement in survival of CF patients with low pulmonary function when there is monitoring of BMI. Researchers say that these findings may help patients, relatives and teams in the appropriate individual management and inform the managers of public policies about the right time of interventions and allocation of financial resources (29).

The statistical association found in this survey between the AC and FEV 1 was expected, because it is common the link between pulmonary function decline and loss of muscle mass due to the high energy expenditure of these patients (30). In a prospective cohort conducted with children during 3,5 years, the authors presented results that corroborate with our research, because it was observed an important deficit of lean body mass due to an increase in muscle protein catabolism common in CF (31). Low-cost techniques and of good applicability to body assessment as measures of folds and circumferences are ordinaries in Reference Centers and contribute to the service evaluation as verified by the study of Pereira et al., held in 2010, where values were

below 10% of depletion of adipose and muscle tissue among CF patients indicating good adherence to dietary treatment (20).

When evaluating the association between the enzyme replacement therapy, the use of fat-soluble vitamins and nutritional status were not observed statistically significant results, although the exogenous replacement of enzymes and vitamins is necessary in many cases of CF due to pancreatic insufficiency in 85% to 95% of CF patients and excessive loss of lipids that leads to malabsorption of vitamins A, D, E and K. Pancreatic sufficient children become insufficient as they get old and this can be observed by laboratory tests, signs of malabsorption of fats and insufficient weight gain (32,33,34). Martinez Costa et al. (35) found in a sample of adolescents and children specific deficiencies to the carotenoids (63%) and vitamin E (47%). The replacement of fat-soluble vitamin in CF patients can be made by multivitamin designed in the water soluble form due to the difficulty of absorption of these vitamins. However, it should also take care about its use, because they can cause nauseas (32).

CF patients have energy recommendations of 120 to 150%, with high levels of fats (16). To achieve the recommendations provided and improve the nutritional status, nutritional supplements were used in this study, and they showed significant correlation with the nutritional profile of patients ($p = 0.0098$). The use of polymeric, oligomeric, hypercaloric and hyperlipidic formulas were suggested by the Nutrition Service due to high energy demand observed by the pulmonary disease and enzyme replacement therapy, besides the possibility of accessing and registering on Program of Home Enteral Nutrition Therapy, where the FC patients receive the formulas with no cost which facilitates the use and adherence to treatment, because most of the patients consist in low-income population.

Although patients are users of a Brazilian government program of enteral nutritional therapy, it was noticed a percentage of achievement of DRIs (16) below the recommended intake and profile of ideal lipid consumption was not achieved. The literature is not consensual about the effectiveness of the use of supplements in FC patients, (36) however; its use is recommended for patients with nutritional deficiency, contributing to a higher caloric intake.

Studies that evaluated the dietary intake among CF patients corroborate with the results obtained in this work, where most of the CF patients did not reach the recommendations.

For improvements in the program of enteral nutritional therapy to FC patients, health public policies in Brazil must be planned and restructured to happen improvements in nutritional and clinical assistance, in addition to promoting the prognosis and quality of CF patients' life.

8.5 ACKNOWLEDGMENTS

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9 CONCLUSÕES

No presente trabalho foram avaliados e descritos aspectos epidemiológicos, clínicos- nutricionais e farmacológicos de pacientes atendidos no ambulatório de fibrose cística em um centro de referência (hospital público) do Distrito Federal. Com os resultados obtidos, concluiu-se que:

- Práticas como atendimento multidisciplinar, intervenção clínico-nutricional e estímulo à atividade física devem ser incentivados nos pólos de atendimento e acompanhados para que a assistência seja precoce e a mais efetiva possível;

- Manifestações no trato digestório e respiratório podem comprometer o estado nutricional na Fibrose Cística. A suplementação enzimática e vitamínica, assim como, o uso de fármacos como antibióticos, mucolíticos entre outros são necessários para tratar e prevenir complicações;

- O estudo mostrou uma associação positiva entre o uso de suplementos (tipo e frequência) nutricionais e a variável déficit nutricional entre os pacientes fibrocísticos. Alterações nas provas de função pulmonar também foram encontradas e foram associadas com medidas antropométricas como a circunferência de braço;

- O acesso aos suplementos, fármacos e a assistência clínica por meio de políticas públicas e financiamento pelas instituições governamentais, como programas domiciliares, podem contribuir para a menor morbidade e maior sobrevida dos fibrocísticos;

- Embora a literatura apresente relato sobre a colonização por *P.aeruginosa* nos pulmões com o estado nutricional, o estudo não mostrou estes achados, possivelmente pelo número de casos acometidos pela colonização das cepas mucóide e não mucóide;

Com base nos estudos realizados, sugerimos que sejam mantidas equipes de atuação multidisciplinar no acompanhamento e tratamento da fibrose cística e que modelos de serviço baseados em triagem neonatal e no auxílio com fármacos, suplementos nutricionais, vitamínicos e enzimáticos sejam estimulados e ampliados evitando-se quadros de exarcebação da doença que podem culminar com a necessidade de transplante e prejudicar a qualidade de vida de todos os envolvidos.

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ANEXOS

Anexo A – Documento de Aprovação do Comitê de Ética

Anexo B – Termo de Consentimento Livre e Esclarecido

Anexo C – Carta de aprovação da Revista Comunicação em Ciências da Saúde

APÊNDICES

Apêndice 1 – Artigo intitulado ”**Multidisciplinary care in cystic fibrosis; a clinical-nutrition review** publicado na revista **Nutrición Hospitalaria 2012; 27 (2): 362-371.**

Apêndice 2 – Artigo intitulado “ **Pathophysiology of cystic fibrosis and drugs uses in associated digestive tract diseases** publicado no periódico **World Journal of Gastroenterology 2013 ; 19(46): 8552-8561.**

Apêndice 3 – Artigo intitulado “**Clinical and nutritional aspects of cystic fibrosis patients assisted by a home enteral nutrition program in Brazil** publicado na **Revista Chilena de Nutrición 2013; 40(2): 112-118.**

Apêndice 4 – Artigo intitulado “**Cystic fibrosis patients assisted by a program nutrition therapy: assessment of the use of supplements in patients colonized and non colonized by *P. aeruginosa*** publicado na revista **Revista de Investigacion Clinica 2014; 66(2).**