The complexity of malnutrition in cystic fibrosis

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The Complexity of Malnutrition in Cystic Fibrosis

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ABBREVIATIONS

% IBW – percentage of ideal body weight

ASL – airway surface layer

BAL – bronchoalveolar lavage

BMI – body mass index

CF – cystic fibrosis

CFLD – cystic fibrosis-associated liver disease

CFRD – cystic fibrosis-related diabetes

CFTR – cystic fibrosis transmembrane regulator

CRP – C-reactive protein

FEV_1 – forced expiratory volume in 1 second

FFM – fat free mass

GERD – gastroesophageal reflux disease

IBD – inflammatory bowel disease

ICS – inhaled corticosteroids

IL-1β – interleukin-1β

IL-6 - interleukin-6

MI – meconium ileus

PERT - pancreatic enzyme replacement therapy

PI – pancreatic insufficient

REE – resting energy expenditure

RMR – resting metabolic rate

TNF-α - tumor necrosis factor-α

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ABSTRACT

The Complexity of Malnutrition in Cystic Fibrosis. Romana Prskalo

Cystic Fibrosis (CF) is the most common life-limiting genetic disease of Caucasian populations. It is a disease inherited in an autosomal recessive fashion, and the defect lies in the gene encoding the cystic fibrosis transmembrane regulator (CFTR) - a chloride channel regulating ion transport across the apical surface of secretory epithelial cells. The main clinical manifestations are pancreatic insufficiency and progressive obstructive pulmonary and gastrointestinal disease. Malnutrition in patients with CF is a common clinical feature in patients of all ages, and a common cause of failure to thrive and growth failure in both infancy and childhood. Although it is not as common of a problem as it was in the past, it still contributes to increased morbidity and premature death in patients with CF.

Malnutrition in CF is a result of the complex interaction of various interrelated and unrelated factors, which lead to increased energy requirements, increased energy losses, and a decreased caloric intake- resulting in a negative energy balance. The organ dysfunction caused by the systemic manifestations of the disease also contribute to malnutrition. Exocrine pancreatic insufficiency is a major cause of maldigestion and malabsorption. It can be treated with pancreatic enzyme replacement therapy (PERT), but even with optimal therapy, it does not always result in optimal nutrition and growth. This indicates that pancreatic insufficiency does not account for all of the nutritional issues in CF, as was once thought, pointing to other factors such as progressive lung disease, gastrointestinal disease, psychosocial issues, and comorbid conditions, among others, that may contribute and influence the development of malnutrition in patients with CF.

The challenge with malnutrition is that there is an absence of a specific, etiological treatment for patients with CF and in the meantime, there exists only enzyme replacement therapy and supportive treatment, which may help reduce energy losses, but do not eliminate the problem. Specific etiological and genetic therapy is still far in the future, and for now, the solution is to vigilantly monitor nutritional status and growth and follow patients on a lifelong basis.

Key words: cystic fibrosis, malnutrition

SAŽETAK

Složenost pothranjenosti u cističnoj fibrozi. Romana Prskalo

Cistična fibroza (CF) najčešća je nasljedna bolest u bjelačkoj populaciji koja bitno skraćuje životni vijek. Nasljeđuje se autosomno recesivno, a posljedica je mutacije gena CFTR (od engl. *cystic fibrosis transmembrane regulator* ili hrv. transmembranski regulator povodljivosti za cističnu fibrozu). CFTR funkcionira kao kloridni kanal koji regulira prijenos iona preko apikalne površine sekretornih epitelnih stanica. Simptomi i težina bolesti značajno variraju od bolesnika do bolesnika, no osnovne kliničke manifestacije CF su kronična plućna bolest i bolest probavnog sustava. Malapsorpcijski sindrom prisutan je u svim dobnim skupinama i glavni je uzrok slabijeg napredovanja u dječjoj dobi. Malapsorpcija nije toliko veliki terapijski problem kao u prošlosti, no još uvijek značajno pridonosi morbiditetu i preuranjenoj smrti bolesnika s CF.

Pothranjenost u CF rezultat je složene interakcije različitih povezanih i nepovezanih čimbenika, koji zajedno dovode do povećanih energetskih potreba, povećanih gubitaka energije i smanjenog unosa kalorija s posljedičnom negativnom energetskom ravnotežom. Disfunkcija organa uzrokovana sustavnim pojavama bolesti također pridonosi neishranjenosti. Insuficijencija egzokrine gušterače osnovni je uzrok poremećene digestije i malapsorpcije. Može se liječiti nadoknadom enzima, no čak ni optimalna supstitucijska terapija ne dovodi uvijek do optimalne kontrole malapsorpcije. To upozorava na to da insuficijencija gušterače nije jedini uzrok malnutricije u CF, kao što se nekoć mislilo, ukazujući na druge dodatne potencijalne čimbenike koji mogu pridonijeti i utjecati na razvoj pothranjenosti u bolesnika s CF. To su između ostalog progresivna plućna bolest, gastrointestinalna bolest, psihosocijalne okolnosti ili simultana prisutnost jedne ili dvije kronične bolesti.

Izazov u liječenju malnutricije u CF leži u nedostatku specifične, etiološke terapije za bolesnike oboljele od CF. Trenutno je osnovno liječenje supstitucijska terapija pankreasnim enzimima i potporne mjere koje pomažu kontroli gubitaka energije, ali često ne rješavaju problem uhranjenosti u potpunosti. Specifična etiološka i genetska terapija stvar je budućnosti, a za sada je rješenje da se pažljivo prati nutritivni status i rast pacijenta, i to doživotno.

Ključne riječi: cistična fibroza, neishranjenost

1 INTRODUCTION TO CYSTIC FIBROSIS

1.1 Epidemiology of Cystic Fibrosis

Cystic fibrosis (CF) is the most common, life-limiting autosomal recessive disease occurring in Caucasian populations. [1] It is characterized by the production of thick, viscous secretions affecting all organs and tissues with mucus-secreting glands, for example, the airways, pancreas, gastrointestinal tract, biliary tract, reproductive tract, and sweat glands.
The prevalence of the disease varies by ethnicity and is considered to be between 1,500-3,000 cases per 100,000 live births in Caucasian populations [2], such as those found in Europe, Northern America, and Australia. Approximately 1 in 25-30 people of Caucasian descent are asymptomatic carriers of the disease [3] CF can affect people of all racial and ethnic groups, although the prevalence is low in African Americans and very low in those of Asian descent. [4] It must be noted, however, that there are great variations in prevalence among different geographical areas and subsets of populations even among Caucasians.

The association between CF and malnutrition is a strong one. A cross-sectional analysis performed by the German CF quality assurance group has revealed that the prevalence of malnutrition in children aged 2-6 years old is 19%. This percentage increased significantly with age up to 38% in adults, [5] indicating that malnutrition is not just a feature of disease in childhood, but appears to be a lifelong issue, especially now that the mean life expectancy of CF patients has increased well beyond what it used to be several years ago.

1.2 Genetics of Cystic Fibrosis

CF is a rare, multisystem genetic disease that is inherited in an autosomal recessive pattern. The mutation involves a defective single large gene located on chromosome 7q31.2 that encodes the cystic fibrosis transmembrane regulator (CFTR) protein. [6] This encoded protein functions as a regulated chloride channel which, in turn, may regulate the activity of other ion channels at the apical surface of the cell. [7, 8, 9]

CFTR is normally present on the apical surface of the cell membrane of exocrine glands and several other tissues (including the lungs, biliary tract, intestinal epithelium, epididymis, vas deferens, and cervix, among others). Expression of clinical disease requires defective

mutations in both alleles of the CFTR gene, altering the structure of the CFTR protein, and causing dysfunction of the chloride ion channel. This leads to failure of exchange of chloride and sodium ions as well as bicarbonate and water molecules in and out of the cell, and changes in the composition of secretions secreted by and lining epithelial surfaces in the lungs, pancreas, intestines, liver, exocrine sweat glands, bile ducts, and epididymis. [7]

There are currently over 2,000 mutations of the gene encoding the CFTR protein listed in the CFTR mutation database [10], but only a minority, around 300, cause cystic fibrosis. [11] The single most common mutation is ΔF508 (also known as delta F508, delF508, c.1521_1523delCTT, or p.Phe508del,), caused by the deletion of three base pairs resulting in the absence of phenylalanine at position 508 of the CFTR protein. [6] This deletion results in CFTR protein misfolding, impaired cellular processing of the protein, and defective delivery of CFTR to the cell surface. [8] Literature shows that approximately 70% of Caucasian CF patients have one copy of the ΔF508 mutation while 50% are homozygous for this mutation. [6] In 2013, 86.4% of patients in the CF Registry were found to have at least one copy of the ΔF508 mutation, with homozygotes making up 46.5% and heterozygotes making up 39.9% of this number. [12] The remaining percentage of cases were caused by many of the other disease-causing mutations, which occur at a much lower frequency and are individually rare; for example, the next most common mutation, G542X, was found in only 4.6% of patients. [12]

While the predominant mutation in Caucasians, particularly of Northern European origin, is ΔF508, it must be emphasized that certain mutations are found at a different frequency in certain ethnic groups. For example, in Ashkenazi Jews, the ΔF508 was found at a considerably lower frequency (31%) compared to North American and Northern European populations. The predominant CF mutations in Ashkenazi Jews were found to be W1282X (48%), ΔF508 (30%) and G542X (12%) [13], in contrast to Northern European and North American populations in which the ΔF508 mutation accounted for over 70% of all mutations, followed by G551D (2.6%), G542X (2.3%), and hundreds of other infrequent variants. [14, 15] Moreover, the frequency of the ΔF508 mutation varies greatly from country to country, even within European populations. For example, the ΔF508 mutation was found at a prevalence of 87.5% in Denmark compared to only 31.0% in Lithuania. [16]

Different mutations cause different defects in the CFTR protein, resulting in a spectrum of disease severity ranging from mild to severe phenotypes. [17] There are five, or in some newer literature, six, classifications of gene mutations causing CF based on the level or the degree of dysfunction of CFTR activity; with (generally) more severe disease phenotype caused by mutations in classes I-III, and milder disease in classes IV-V/VI [18] - see table 1.

Table 1. Classification of CFTR* mutations [18]

Class	Effect on CFTR protein	Functional CFTR	CFTR apical expression	Examples of mutations
I	Defective production (absent synthesis)	No	No	G542X, W1281X, 1717-1G>A
II	Impaired processing	No	No	F508del, I507del, N1303K
III	Defective regulation of CFTR chloride channel	No	Yes	G551D, G1349D, V520F
IV	Altered conductance of CFTR chloride channel	Reduced	Yes	R117H, R347P, R334W
V	Reduced synthesis of CFTR protein	Reduced	Reduced	A445E, D565G, 3849+10kbC>T
VI	Less stable CFTR protein	Reduced	Reduced	c.120del123

*CFTR = *cystic fibrosis transmembrane regulator*

Aside from the mutations in the CFTR protein, various other genetic and environmental factors, including mutations in other genes excluding CFTR as well as various gene modifiers [8] of the CF phenotype, may influence the expression of clinical disease. Therefore, it must be noted that mutation analysis does not always provide accurate prognostic information. It is also known that the interaction between a certain genetic predisposition and the environment plays a role in the development as well as the heterogeneity in the severity of the disease, although the exact mechanisms for how this occurs are not yet fully understood.

1.3 Phenotypic variation in Cystic Fibrosis

One of the main characteristics of CF is that it is a disease of variable severity and course between and within affected individuals. Today, newborn screening can be performed for CF allowing the possibility to diagnose the disease at the beginning of the child's life, allowing therapeutic intervention, particularly nutritional support, to be arranged before serious complications of the disease arise. The currently available newborn screening method measures the raised serum concentration of immunoreactive trypsinogen using the Guthrie blood spot test. [19] An abnormal newborn screen requires further diagnostic testing to confirm the disease and this is performed using a chloride sweat test (the "gold standard" for diagnosing CF) and molecular DNA analysis. The majority of genetic tests screen for the most common CF mutations occurring in a specific population. According to the Consensus Guidelines from the Cystic Fibrosis Foundation, diagnosis of CF can be made when the individual has a positive newborn screen along with evidence of CFTR dysfunction, in the form of a positive sweat chloride test (sweat chloride level ≥60 mmol/L), and the presence of 2 CFTR disease-causing gene mutations on genetic analysis. It is not enough to make a diagnosis based on clinical suspicion alone. Other tests of CFTR function may also be performed in specialized centres if indicated. [20]

Currently, approximately 60% of CF patients are diagnosed through newborn screening, [20-22] while around 20% of those not diagnosed by NBS develop their first presentation of disease shortly after birth, in the form of meconium ileus (MI), a type of intestinal obstruction caused by inspissated meconium. [23] Other affected patients commonly present early in life, usually within the first year, with the classical symptoms of CF such as failure to thrive, steatorrhea, cholestatic jaundice, and chronic respiratory infections, among others. [6] These symptoms may also be found in patients who have been screened for CF. Other CF patients with milder disease phenotypes may exhibit subclinical forms or atypical features of the disease and may be diagnosed at a later age or even proceed undiagnosed. Patients with milder CFTR genotypes (see table 1) generally have milder lung disease and pancreatic insufficiency to a lesser degree, with delayed expression and slower progression of disease. [24]

The most common CFTR mutation, ΔF508, which is found in the majority of patients with the severe form of disease, has a strong correlation with PI, particularly in a patient who has inherited two severe alleles. An individual that is homozygous for the ΔF508 mutation

usually has PI, [25] which is relevant because most of these patients will need aggressive and lifelong nutritional support to prevent growth failure and malnutrition. 85% of all CF patients have PI leading to maldigestion, which is defined by evidence of steatorrhea following 72-hour fecal fat testing. [26] The pancreatic sufficient (PS) phenotype, on the other hand, is associated with the presence of one or two "mild" CFTR mutations (see table 1) including R117H, R334W, R347P, A455E, and P574H. [27]

Thus, as a result of the vast number of different CFTR gene mutations and resulting spectrum of disease phenotypes, all categories of disease severity may be present within the population. There exists a broad variability of clinical expression between patients, both in terms of the various modes of disease presentation as well as the onset of progression of the disease, and it is this wide spectrum of disease variability that makes the disease unpredictable, in terms of diagnosis and possibly treatment.

1.4 Pathogenesis of Cystic Fibrosis

The pathophysiological cascade of CF begins with a genetic mutation encoding the CFTR protein, which leads to altered ion channel flux, leading to abnormally viscous and dehydrated epithelial secretions in many tissues as well as impaired mucociliary clearance in the respiratory system. [18] While the exact pathogenesis of CF leading to organ dysfunction is not completely understood, it can be said that the defective composition of secretions significantly contributes to the clinical manifestations of the disease. In the lungs, the respiratory epithelium becomes impermeable to chloride ions and reabsorbs excessive sodium leading to a relative dehydration of airway secretions, leading to obstruction, chronic inflammation and eventual fibrosis. A similar manifestation occurs in other organ systems, including the pancreas, gastrointestinal tract, hepatobiliary tract, and genitourinary tract, among others. The pathophysiological mechanisms of some of these systems will be discussed separately and in more detail later on, with regard to how they contribute to the disease and their association with malnutrition.

In the sweat glands of patients with CF, there is no presence of obstruction or pathologic abnormalities like in the other organ systems, but rather an abnormality of sodium chloride homeostasis. The sweat ducts are unable to reabsorb chloride ions due to the absence or

dysfunction of CFTR, and therefore, sodium is also poorly reabsorbed. The resulting sweat contains concentrated secretions high in sodium and chloride ions, contributing to excessive sweating and the "salty" sweat described by parents of children with CF. [8] This pathology of the sweat glands as a result of CFTR dysfunction is the basis of the chloride sweat test used in the diagnosis of CF.

Ultimately, the phenotype of CF determines the disease severity and progression, and as there is such a wide spectrum of severity in CF, disease presentation can be diverse. However, the "classical" form of CF - the fully expressed disease - is characterized by the following predominant features; progressive lung disease, pancreatic dysfunction leading to intestinal malabsorption, elevated sweat electrolytes, and infertility in males or subfertility in females.[23] These features begin early on in life and contribute to the state of malnutrition observed in a majority of CF patients. The "classical" form is what this review will primarily be dealing with, as malnutrition plays a significant role in the "classical", severe form of CF.

2 THE ENERGY IMBALANCE

The precise etiology of malnutrition in CF is unclear, and it can be said, therefore, that it is the result of a complex interaction of both related and unrelated factors that alter the energy balance. This includes reduced energy intake, increased energy expenditure, impaired digestion and absorption, and excessive energy losses. The total energy balance in any individual is based on the input versus the output, and in the case of CF, patients often have a predominantly negative energy balance. Specifically, malnutrition in CF is a consequence of an imbalance between high energy requirements, reduced intake, and excessive energy losses. The energy imbalance is further aggravated by the cycle of inflammation, obstruction, and infection in the respiratory and gastrointestinal systems.

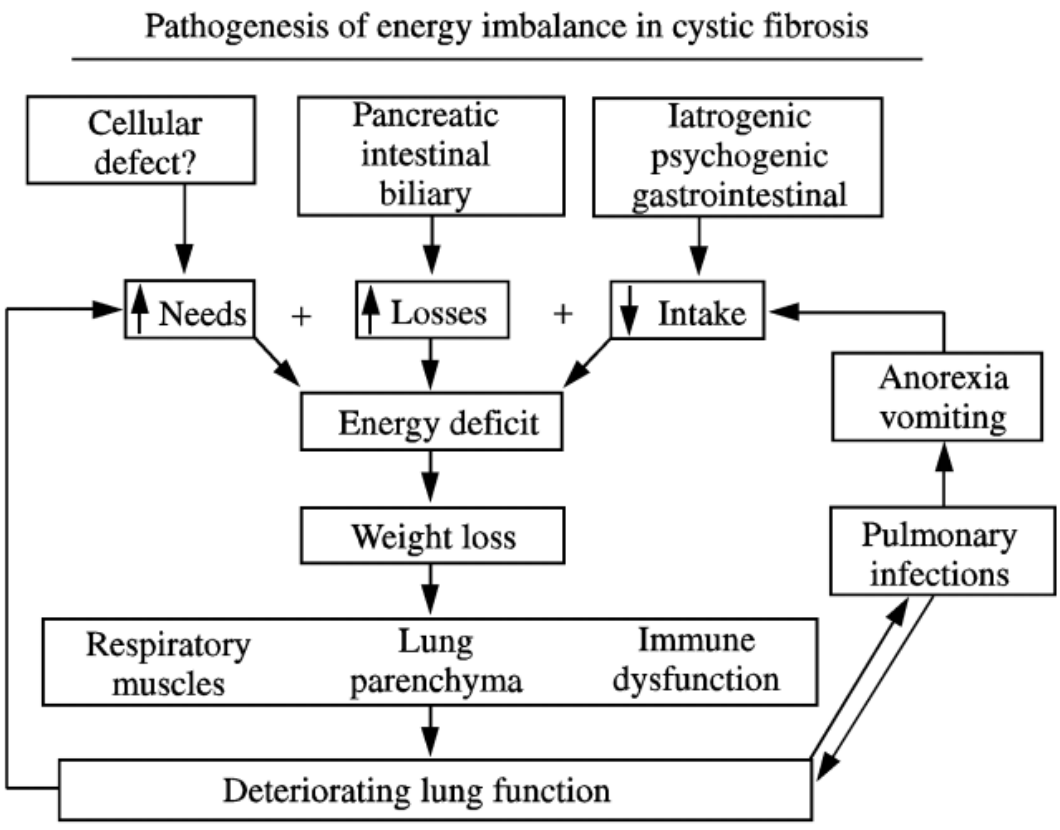

Figure 1. The interconnected factors leading to an energy deficit and weight loss as lung function deteriorates [28]

2.1 Increased energy requirements

The increased energy requirements are primarily due to acute pulmonary exacerbations, superimposed on the presence of chronic pulmonary infection and inflammation, all leading to increased work of breathing and the presence of a hypermetabolic state. Currently, it is recommended for a patient with CF to have an energy intake between 110-200% of the recommended daily intake (RDA) compared to the general population. CF patients also require a greater fat intake, between 35-40% of calories, compared to the general population. [29] These greater energy requirements are mostly due to the presence of an increased resting metabolic rate (RMR) in CF patients, leading to an increased resting energy expenditure (REE). [30-32]

The energy balance is further aggregated by acute pulmonary exacerbations which additionally increase RMR and energy requirements from an estimated 50-100% of normal. [33] Furthermore, the RMR remains elevated for some weeks even after the inflammation is resolved before returning back to the baseline level. Additionally, progression of obstructive lung disease, even in clinically stable CF patients, has been shown to lead to increases in RMR as lung function, in the form of forced expiratory volume in 1 second (FEV_1), declines. [34]

It has also been suggested that dysfunction of the CFTR gene itself may have a direct effect on basal metabolism and lead to higher energy requirements at the cellular level. [35] The mechanism behind this appears to be a defect in the mitochondrial energy transporter, which as a result of the CFTR mutation, leads to a two-to three-fold increase in oxygen consumption in the affected tissues of patients with CF, compared to unaffected tissues. [36] It can be said, therefore, that increased energy requirements are a consequence of both dysfunction at the cellular level, as well as at the somatic level of the organism, due to the pathologic consequences of the disease. [34]

2.2 Increased energy losses

The increased energy losses occur in the form of intestinal malabsorption, caused mainly by pancreatic exocrine insufficiency, which leads to fecal energy losses in the form of both steatorrhea and diarrhea. As a result of pancreatic endocrine dysfunction, there are energy

losses through the urine in the form of glucosuria, a manifestation of cystic fibrosis-related diabetes (CFRD). Other losses in the stool include carbohydrates, proteins, bile salts and mucus, but to a lesser extent than fats. Even with optimal pancreatic enzyme replacement therapy (PERT) in CF patients, these losses are not normalized, and it has been shown that children with CF have stool energy losses ranging from 5-20% of oral energy intake even when using pancreatic enzyme replacement, compared to 1-6% losses in healthy controls. [37] Furthermore, the influence of certain drugs, particularly antibiotics, on the colonic flora, may cause alterations that lead to changes in digestion – including decreased fermentation of carbohydrates, deconjugation of bile acids, and diarrhea. The role of comorbid conditions such as celiac disease, inflammatory bowel disease (IBD), irritable bowel syndrome, and cystic fibrosis-related liver disease (CFLD) may also influence energy losses, further aggravating digestion and malabsorption.

2.3 Decreased energy intake

The decreased energy intake occurs in the form of reduced appetite which is influenced by a variety of factors and can be divided into chronic suboptimal intake and acute suboptimal intake. Chronic suboptimal intake is a result of several factors, most importantly, perhaps, due to the psychological aspect of the disease, causing anorexia, anxiety, and depression. The influence of cytokines and presence of a chronic inflammatory state also contribute to the reduced intake and lead to mechanisms contributing to the development of cachexia. Several somatic symptoms including gastroesophageal reflux disease (GERD), abdominal pain, colic, gas, nausea, vomiting, and chronic cough may all contribute to the reduced intake of food and decreased appetite. Acute pulmonary exacerbations may cause anorexia both during and following the episodes and result in an acute suboptimal intake. Furthermore, medications used in CF may contribute to reduced appetite and caloric intake.

3 SYSTEM-SPECIFIC MANIFESTATIONS OF CYSTIC FIBROSIS CONTRIBUTING TO MALNUTRITION

3.1 Lung disease

The presence of severe pulmonary disease is one of the main features of CF contributing to malnutrition. Several studies, including a longitudinal analysis performed by the German CF quality assurance (CFQA) group [5], have exhibited the co-dependant relationship between malnutrition and lung function in CF. It was shown that a decrease in weight was associated with a corresponding decrease in lung function (in the form of FEV_1, as measured by spirometry) whereas patients who were of normal weight and who had improved nutrition remained at the same or even improved their FEV_1 values. Furthermore, the presence of malnutrition has been recognized as an independent negative prognostic factor and main predictor of impaired survival in CF. [38] In the study, low % ideal body weight (IBW) and low % of predicted FEV_1 were shown to be independent and highly accurate prognostic indicators for the probability of death within 5 years in patients with CF. Additionally, progressive pulmonary disease is recognized as the main negative prognostic factor in patients with CF. [2] Malnutrition in patients in CF is important because it is related to lung function; in so that there is a strong positive correlation between degree of malnutrition and severity of lung disease; the presence of malnutrition parallels the decreases in lung function. Hence, severity of lung disease is an indicator of prognosis and survival, with decreasing lung function leading to decreased survival and an increase in morbidity and mortality. [5, 38] More importantly, it has been shown that nutritional status has a significant effect on pulmonary disease progression and survival in CF patients, and that malnutrition developing from an early age could influence lung development and function later in life. Indexes of growth and nutrition, including height for age (HFA), weight for age (WFA), %IBW, and body mass index (BMI) in early childhood can be used as strong predictors of pulmonary function in later childhood, with weight loss being associated with worse pulmonary function and symptoms and signs of lung disease. [39] This data demonstrates the importance of malnutrition in regards to lung function and how the two factors are interrelated.

Pulmonary disease in CF patients generally follows a course of chronic and recurrent infections, inflammation, and obstruction within the airways. The pathophysiological mechanism behind the pulmonary disease seen in patients with severe phenotypes of CF is

the result of a CFTR mutation leading to defective or absent CFTR expressed in respiratory epithelial cells of the bronchi and bronchioles. [40, 41] Dysfunction or absence of CFTR leads to altered ion flux as well as impaired fluid secretion leading to the production of abnormal respiratory secretions lining the epithelial cells, collectively referred to as the airway surface layer (ASL). Normal, healthy airway epithelia have the ability to absorb or secrete ions and fluid through various ion channels including epithelial sodium channel (ENaC), CFTR, and calcium activated chloride channels (CaCCs). [42] In patients with CF, altered ion transport leads to decreased chloride and bicarbonate ion secretion as well as enhanced absorption of sodium ions. The reduced bicarbonate concentration leads to acidification of the ASL, which may negatively influence microbial killing and host defences. [18] Fluid exchange is also impaired as a result of the altered ion transport, leading to excessive dehydration of secretions composing the ASL. Furthermore, there is also excessive mucin production [41], resulting in thick and viscous secretions that coat the airways and cannot be adequately removed by mucociliary clearance as they are in normal, healthy lungs. [8] The accumulation of mucus leads to narrowing and obstruction of the airways and as a result, increased work of breathing. The hyperviscous secretions lead to mucus plugging within the airways, which creates an anaerobic environment and predisposes the airway epithelium to chronic microbial colonization with various microorganisms including *Staphyloccocus aureus, Pseudomonas aeruginosa, Burkholderia cepacia, Haemophilus influenza*, and *Aspergillus fumigatus*, among others. [6]

Consequently, as microbial colonization ensues, activated neutrophils are recruited and begin to infiltrate the airways, releasing various cytokines and factors, including interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), and leukotriene β4 that contribute and further aggravate the pro-inflammatory milieu. Reduced levels of anti-inflammatory cytokines and proteases have also been found in the airways of CF patients. [8] Thus, the cycle of pulmonary obstruction, infection and inflammation ensues.

The presence of a chronic inflammatory state accompanied by chronic infection in the pulmonary system play a particularly large role in the contribution to malnutrition because the subsequent decreased lung function and increased work of breathing result in an increase in energy expenditure both at rest, in the form of an increased RMR, as well as during activity. As a result, both REE and total energy expenditure are increased. Energy

expenditure increases further in the presence of an acute exacerbation, which further increases the RMR and energy requirements for patients with CF. Exacerbations are frequently accompanied by acute weight loss, which can be attributed to a decreased appetite along with a reduced caloric intake [28], in addition to increased energy losses, in the form of increased RMR. Moreover, acute pulmonary exacerbations are frequently accompanied by a decline in pulmonary function which can be, in part, attributed to the amplification of the inflammatory cascade due to the additional production of various pro-inflammatory factors, cytokines [43], and C-reactive protein (CRP) [44]. Patients in the terminal stages of pulmonary disease often have chronic anorexia [28], which contributes to malnutrition and weight loss. Therefore, lung inflammation and infection, both chronic as well as acute exacerbations, increase the work of breathing and contribute to the increased total energy expenditure seen in CF patients.

The production of highly viscous mucus that causes airway obstruction, impaired mucociliary clearance, as well as chronic microbial colonization are the main drivers of the chronic pulmonary disease in CF. These features further contribute to the recurrent pulmonary infections and eventual destruction of lung parenchyma, as well as to the chronic, persistent inflammatory state within the pulmonary system. [18] Progressive obstruction, infection, and inflammation eventually leads to tissue destruction and fibrosis.
It is well recognized that severe lung disease is the main cause of morbidity and mortality in CF. End-stage lung disease in CF patients ultimately leads to respiratory failure, which is responsible for approximately 80% of patient mortality. [22]

3.2 Pancreatic dysfunction

Pancreatic dysfunction is one of the main features contributing to malnutrition in CF. The pathogenesis behind pancreatic exocrine dysfunction in CF includes impaired pancreatic fluid secretion as well as altered composition of the secretions. In the pancreas, CFTR is expressed primarily at the apical surface of the ductal epithelial cells. [45] Under normal circumstances, pancreatic fluid contains various digestive enzymes released by the pancreatic acinar cells, suspended in an alkaline solution high in bicarbonate and chloride, released by the ductal cells. The pancreatic fluid, when stimulated, is released into the small intestine and contributes to the digestion of fats, proteins, and carbohydrates within the duodenal contents.

The alkaline pH of the pancreatic fluid is essential, as an alkaline medium is needed in the duodenum and rest of the small intestine for optimal functioning of the digestive enzymes, as well as for the neutralization of gastric acid. [18]

In patients with the pancreatic insufficient (PI) phenotype of CF (around 90% of all CF patients) [26, 46], however, the composition of pancreatic secretions differs. Absent or impaired function of CFTR in pancreatic ductal cells leads to altered ion transport across the ductal epithelium and leads to decreased chloride [47] as well as bicarbonate secretion [48] within the ductal lumen. The altered ion flux also influences the fluid secretion across the ductal epithelium, leading to impaired movement of fluid into the lumen resulting in dehydrated secretions. Normally, acinar cells release proteins (primarily pancreatic enzymes) which become suspended within the dilute, alkaline (and bicarbonate-rich) fluid in the pancreatic lumen. In CF, the impaired anion transport leads to production of fluids that are more acidic and of smaller volume than normal. This causes hyperconcentration and precipitation of the proteins within the ducts, leading to obstruction and destruction of the duct lamina, and ultimately results in pancreatic insufficiency. [47]

The change in composition of the pancreatic secretions influences the digestive process within the small intestine and contributes to maldigestion and malabsorption. As a result of the decreased concentration of bicarbonate in the pancreatic secretions, the pH within duodenum is decreased, and the acid from the incoming gastric contents is not neutralized by the normally alkaline, bicarbonate-rich pancreatic fluids. The hyperacidic pH within the duodenum impairs digestion by causing denaturation of the digestive enzymes, particularly lipase. Decreased lipase activity is the driving force behind steatorrhea and subsequent fat malabsorption [47], which is responsible for the great fecal energy losses seen in CF patients with PI.

Another element of pancreatic dysfunction in CF is the deficiency of pancreatic enzymes. As a result of the production of dehydrated pancreatic fluid, mucin concentration increases and contributes to obstruction within the ducts. The thick secretions block the passage of pancreatic enzymes moving through the ducts and prevents the delivery of pancreatic enzymes to the duodenum. This results in an inability of the gut to adequately digest food and absorb nutrients from it, resulting in malabsorption. The obstruction of the ducts with pancreatic enzymes also results in “auto digestion” of the pancreatic ducts and acini, leading

to progressive dysfunction and damage of ductal and acinar cells. [18] This leads to progressive acinar destruction and decreased enzyme production over time. [49] Exocrine pancreatic insufficiency occurs in the majority of CF patients early on in the course of disease, due to destruction of pancreatic acini as well as ductular obstruction. These inflammatory and destructive processes in the pancreas usually begin in utero, and progress after birth during which time the infant is usually asymptomatic. Currently, approximately 90% of CF patients progress to pancreatic insufficiency and require PERT early on in childhood. [46]

In addition to the progressive destruction of the pancreatic ducts and acini, there may be subsequent damage to β cells. [18] Destruction of the endocrine portion of the pancreas ultimately leads to impaired glucose tolerance and CF-related diabetes mellitus (CFRD), which is present in around 25% of children and 40% of adult patients, making it the most common comorbidity in patients with CF. [33] The relevance of CFRD in regards to malnutrition is the loss of energy through the urine (glucosuria). Associated metabolic features and complications of diabetes mellitus may further contribute

3.3 Gastrointestinal disease

There is a myriad of elements within the gastrointestinal system that contribute to malnutrition in patients with CF. Several components have already been mentioned. The best known are a direct consequence of pancreatic insufficiency, which leads to maldigestion and malabsorption in the intestines leading to energy losses (primarily fats) through the stool. Another key component is the presence of hyperacidity in the duodenum. The reason for the lower duodenal pH is primarily due to decreased bicarbonate in pancreatic secretions. However, it is also in part due to decreased bicarbonate secretion by the duodenal epithelium itself [47] where there is abnormal CFTR expression in CF patients. The decreased duodenal pH leads to denaturation of pancreatic enzymes (if present) [50], which contributes to steatorrhea and fat malabsorption.

Furthermore, the absorption of fats in the intestine is also dependant on the presence of bile salts, and in the case of CF, bile salts are denatured and precipitated as a result of the decreased duodenal pH. [51] Moreover, there is an increased loss of bile salts in the stool and

impairment of enterohepatic recirculation due to impaired ileal reabsorption, possibly due to the thick, mucus secretions lining the epithelium or to small intestinal bowel overgrowth (SIBO). [18] Impaired reabsorption of bile acids leads to excessive levels within the intestines, and their loss through the stool, which may even lead to secretory diarrhea in some patients.[52] Bile salts are normally required to emulsify and solubilize lipids in the intestinal lumen, so their dysfunction and excretion further impairs lipid digestion and absorption and contributes to fat malabsorption and fecal energy losses.

CFTR within the gastrointestinal tract is relatively weakly expressed in the gastric mucosa and highly expressed in both the small and large intestinal epithelium. [53] CFTR dysfunction in the intestine, as in other secretory organs (excluding the sweat glands), leads to reduced volume of secretions within the lumen and overproduction of mucins, that contribute to obstruction within the gut.

The accumulation of thick, viscid mucus is one of the main pathological features of CF, and contributes to many sequelae of the disease. Furthermore, thick sluggish bile from the hepatobiliary system, once it enters the intestines, may contribute to the development of various intestinal obstructive syndromes as well as chronic constipation. In extreme cases, acute obstruction within the intestinal lumen may manifest as MI at birth, and distal intestinal obstruction syndrome (DIOS) seen in older children or young adults. [54] In the long-term, the thick, viscid secretions throughout the intestinal tract may contribute to constipation and obstipation [51]. Although these pathologies do not contribute to malnutrition per say, they are vital in the manifestation of disease.

Furthermore, the thick, viscous mucus that accumulates in the intestinal lumen further limits absorption of nutrients from the intestinal epithelium, contributing to malabsorption. Excess mucus may also lead to bacterial overgrowth in the small intestine. SIBO is frequent in CF, and may contribute to malabsorption and maldigestion, and subsequent symptoms such as bloating, flatulence, abdominal pain, diarrhea and steatorrhea. [55] These bacteria in the small intestine may compete with the host for ingested nutrients, and may also deconjugate bile salts, decreasing their ability to emulsify lipids. [56] Alterations in the colonic bacterial flora may also occur as a result of the chronic, as well as short-term, use of antibiotics as well as other medications. [51]

Altered motility also contributes to malabsorption in CF, and includes both rapid gastric emptying as well as decreased small intestinal transit time. [49] This leads to inadequate mixing of food with pancreatic secretions and bile, and decreased time for nutrients to be absorbed within the small intestine, both of which contribute to maldigestion and malabsorption.

Regarding the presence of chronic inflammation within the gastrointestinal tract, several studies have demonstrated the increased expression of inflammatory markers and cytokines within the intestinal lumen of CF patients. [57] The presence of chronic inflammation within the intestines contributes to the hypermetabolic state found in patients with CF, and leads to increased energy expenditure. Other causes contributing to inflammation include the presence of IBD (including Crohn's disease and ulcerative colitis) and celiac disease. [18] These conditions act as comorbidities in patients with CF and further aggravate the presence of malnutrition by contributing to maldigestion, malabsorption, and a chronic inflammatory state. One should also consider the possibility of acute bacterial, viral, and parasitic infections in some patients as contributing factors (although short-term) to malabsorption and malnutrition.

Furthermore, the presence of fibrosing colonopathy, a complication of prolonged treatment with excessive doses of PERT, may contribute to malnutrition. Fibrosing colonopathy is of variable presentation, and may include features such as abdominal pain and distention, altered bowel habits, and failure to thrive. It may also lead to formation of strictures causing recurrent bowel obstruction, and if clinically significant, require colonic resection. [58]

In conclusion, a variety of entities within the gastrointestinal tract may contribute to the presence of malnutrition in patients with CF. The majority cause maldigestion and malabsorption and lead to increased energy losses through the stool. Furthermore, abdominal complaints such as pain, bloating, constipation, and GERD may contribute to a reduced appetite and result in a decreased caloric intake, additionally worsening the energy imbalance. The presence of comorbid conditions affecting the gastrointestinal tract as well as infections may further contribute to malabsorption and increased energy losses.

3.4 Hepatobiliary disease

CFLD is present in around 30% of patients with CF, and encompasses a variety of manifestations ranging from neonatal cholestasis to persistent elevations of transaminases, hepatomegaly, steatosis, biliary obstruction, and focal biliary cirrhosis – the characteristic hepatic lesion. [59] Eventually, there may be progression to fibrosis and finally, portal hypertension and cirrhosis. The development of CFLD is associated with presence of a more severe phenotype of the disease (mutation classes I-III), although it also appears to be associated with other gene polymorphisms. [33, 60]

CFLD is considered an important cause of morbidity as well as mortality in patients with CF, as it accounts for 2.9% of the overall mortality in patients with CF, making it the third most common [61] (after cardiorespiratory and transplant-related causes) and significant non-pulmonary cause of death. [12] Liver disease in CF has even been hypothesized as an independent risk factor for mortality [62], in addition to lung disease and malnutrition.

The expression of CFTR in the liver is restricted to the apical surface of the biliary epithelium [63]; there is no CFTR expression on the hepatocyte. As a result, abnormal secretions are produced by the epithelium lining the biliary ducts and cause ductal obstruction, similar to that observed in the pancreas. Due to impaired anion transport across the apical membrane, combined with the overproduction of mucus by the biliary epithelial cells, there is production of viscous and inspissated bile by the ductal epithelium. This inspissated bile causes obstruction within the intrahepatic biliary ducts, and with time leads to chronic damage, inflammation and fibrosis of the liver. [18]

The clinical manifestations of malnutrition are further aggravated by deterioration of liver disease because the abnormal bile is unable to emulsify lipids in the intestines. Furthermore, the bile salts become deconjugated and precipitate in the intestines as a result of lowered duodenal pH, further aggravating fat malabsorption and steatorrhea. Cholestasis, together with pancreatic insuffiency, contributes to fat malabsorption [64] which predisposes to deficiencies of fat-soluble vitamins in the liver. Steatosis, or fatty liver, has also been associated with malnutrition in some patients, as well as with deficiencies of essential fatty acids choline and carnitine. [65]

The development of portal hypertension may also contribute to malnutrition in a multifactorial way, leading to limited nutrient absorption, increased resting energy expenditure, anorexia, and reduced caloric intake. [65] Patients with cirrhosis may also progress to liver synthetic failure characterized by hypoalbuminemia, vitamin K dependent coagulopathy, and high bilirubin. [62]

In conclusion, presence of CFLD has been shown to negatively affect nutritional status in CF in a multifactorial way. It includes increases in resting energy expenditure, fat malabsorption (due to the combination of cholestasis and pancreatic insufficiency), reduced nutrient intake, and abnormal metabolism of nutrients. [64] It has also been shown that severe liver disease appears to significantly increase the risk of developing CFRD, [66] which may contribute to the complexity of malnutrition in CF.

3.5 Cytokine activity

Chronic infection and inflammation within the respiratory and gastrointestinal tracts are associated with the presence of a chronic inflammatory and hypermetabolic state in CF patients. In the lungs, chronic airway colonization and infection with persisting microorganisms are thought to trigger the cells of the immune system and promote migration of activated neutrophils to the airways. The mechanisms leading to inflammation in the CF lung include the interactions between various immune and cellular components, as well as release of numerous pro-inflammatory mediators and cytokines which cause tissue inflammation and destruction. These processes progressively lead to declining lung function and ultimately premature death in a majority of CF patients. [67]

The presence of a chronic inflammatory state in patients with CF is demonstrated by increased levels of inflammatory markers and pro-inflammatory cytokines, including TNF-α, CRP, interleukin 1β (IL-1β) and IL-6, as well as certain “stress-response” hormones such as catecholamines and cortisol. [43] In the lung, it was found that patients with CF had significantly increased levels of pro-inflammatory cytokines, including IL-1β, 6, 8, and TNF-α, in samples of bronchoalveolar lavage (BAL) fluid compared to healthy controls. It was also shown that CF patients had decreased concentrations of natural cytokine antagonists

such as IL-1 receptor antagonist (IL-1Ra) and soluble TNF receptors (TNF-sR) compared to healthy controls. [68]

Macrophages seem to play a crucial role in the inflammatory processes within the chronically infected lung, as demonstrated by Bonfield et al. [68] It was shown that the majority of pro-inflammatory cytokines are produced by alveolar macrophages in the lungs of patients with CF in response to chronic infection with various microorganisms (in particular *S. aureus* and *P. aeruginosa*). Other cell types, including activated neutrophils as well as T-lymphocytes may also contribute to the production of pro-inflammatory mediators. A study by Tiringer et al. [69] demonstrated significant upregulation of Th1- (interferon-γ), Th2- (interleukins-5 and 13), Th17- (interleukin-17A), and Th17-related cytokines (IL-1β, IL-6) in the BAL fluid of patients with CF.

Increased levels of inflammatory mediators in the lungs as well as GI tract [57, 70] contribute to the chronic inflammatory and catabolic state found in patients with CF. Many cytokines, particularly TNF-α, have the ability to stimulate lipolysis, muscle catabolism, and to increase REE in patients with CF. [31, 71] Pro-inflammatory cytokines may also have a negative influence on bone mineral density, which can further contribute to a low body weight and malnutrition. It was found that circulating levels of inflammatory mediators, such as IL-6 and TNF-α, were higher in patients with a low fat free mass (FFM) compared to patients with a normal FFM, indicating that patients with low body weight were more prone to a catabolic state than patients of a healthy body weight. Patients with a reduced FFM were also shown to have decreased bone mineral density, in the presence of an inflammatory and catabolic state. [43]

Therefore, release of pro-inflammatory cytokines and factors promotes the presence of a chronic inflammatory state that leads to progressive worsening of lung function and tissue destruction. Moreover, worsening lung function further exacerbates malnutrition, leading to a vicious cycle of increased energy requirements and increased energy losses. Furthermore, inflammatory mediators and cytokines may directly activate pathways leading to the development of a catabolic state, and may cause a similar presentation to that of cachexia found in many patients with other chronic or malignant diseases. As a result, patients with CF

have increased energy requirements and resting energy expenditure compared to healthy peers. [31]

3.6 Medications

Certain medications used in the treatment of CF may have an influence on the metabolic state of the patient as well other physiological consequences. They may decrease appetite, cause changes in taste, or have abdominal side effects, [72] and so lead to a decreased caloric intake. Inhaled β_2-adrenergic agonists (ex. salbutamol, salmeterol) are medications commonly used in CF patients in treatment of lung disease, in conjunction with physiotherapy, especially during pulmonary exacerbations. They have a sympathomimetic effect, and are used to produce bronchodilation by directly acting on the β_2-adrenoreceptors on the bronchial smooth muscle. They also inhibit the release of inflammatory mediators from mast cells and monocytes, and increase mucus clearance by acting on the cilia. [73] Long-term use of salbutamol (a β_2-agonist) in patients with CF has been shown to increase REE, although the mechanism of action behind this is not fully understood. Also, REE increased by 10% within the first hour after administration of salbutamol [74], indicating that the long-term effect of β_2-agonist therapy may be significant in relation to malnutrition if it is used several times a day, as it may lead to a chronically increased REE, increasing total daily energy expenditure and energy requirements.

Corticosteroids, both inhaled and systemic, are also frequently used during periods of acute pulmonary exacerbations. Corticosteroid use in clinical doses has been shown to negatively influence skeletal muscle strength by inducing myopathy, leading to limb muscle weakness and reduced muscle mass in patients with CF. [75] Treatment with inhaled corticosteroids (ICS) in children with CF has proven to not be beneficial, with no positive effect on lung function, and may also negatively affect growth. [76] The study by De Boeck et al. showed that children using high doses of inhaled fluticasone (an ICS) grew less than children in the placebo group, and had growth impairment which persisted for 12-24 months after the medication was discontinued.

3.7 Psychosocial issues

As CF is a chronic and multifactorial disease, most patients require various lifelong therapies and treatments in order to delay disease progression and improve quality of life. A strong emphasis is placed on maintaining adequate nutrition, chest physiotherapy, PERT, and medications to control disease, which be difficult for patients and their families to deal with. The burden of performing all the therapies, and the particularly strong focus on food intake, may make the process of eating and mealtimes stressful, and may cause stress, anxiety, and depression [72], particularly in the adolescent population. A strong focus is also placed on weight gain, often from the diagnosis of the disease, which may lead to body image issues and disordered eating behaviors. [77] Currently, the target BMI is 22 for female patients with CF and 23 for males. [78] It is not readily acceptable for adolescents and young adults with CF to purposefully maintain a low weight and insist on dieting because these patients at the time of pulmonary exacerbations have lower or no nutritional reserve and deteriorate much more rapidly and become undernourished much faster in comparison to their well-nourished counterparts. This may strongly compromise their disease progression and alter their prognosis in the long-term.

It has been shown that patients with CF have higher rates of anxiety and depression compared to the general population [79], with anxiety being more prevalent than depression across the lifespan. One international epidemiological study has shown the prevalence of anxiety and depression to be two-to-three times higher in patients with CF and their caregivers than in the community [80]. Symptoms of anxiety and depression have both been shown to lead to poorer disease outcomes, increased morbidity, and decreased quality of life. Although no direct associations have been found, it can be postulated that mental health symptoms may affect health outcomes, such as nutrition and lung disease, and worsen disease severity by leading to poor adherence and management of disease. [79]

Although eating disorders are not more prevalent in adolescents with CF compared to their healthy counterparts, eating disturbances are, with around 53% of CF adolescents showing disturbed eating attitudes compared to 40-47% in the general population. Out of this number, 18.8% of females and 7.1% of males reported participating in weight-loss behaviours, although the average BMI of the sample group was already at the lower limit of the “healthy” weight range. [81] This indicates that the higher levels of behavioural and psychological

problems present in the CF population may be even more detrimental to the development of malnutrition.

Another aspect of CF that may contribute to psychological distress is CF-related pain. A study looking at the prevalence of pain in CF patients found that 59% of children and 89% of adults had at least one episode of pain during the last month [82]. This pain may be related to the disease itself, and involve the abdomen, back, head or chest, or to procedures. Pain may be a potential complication of CF and may lead to consequences such as decreased quality of life, limited physical activity, and psychological distress.

Various psychosocial issues may lead to a decreased caloric intake in patients with CF, and it has been shown that patients with severe pulmonary disease are prone to depression and other psychological issues, which may lead to chronic anorexia. [28] Pulmonary exacerbations as well as acute infections lead to anorexia and a decreased caloric intake, often resulting in acute weight loss.

CONCLUSION

The causes of malnutrition in CF are complex and multifactorial. As a consequence of the genetic mutation causing CFTR dysfunction in various organs and tissues, abnormal secretions are produced which lead to inflammation, obstruction, and organ dysfunction. As a result, patients with the severe, “classical” form of CF suffer from pancreatic insufficiency, chronic respiratory disease, recurrent respiratory infections, intestinal malabsorption, and CFLD which may lead to the development of malnutrition and low body weight. Various other comorbidities and factors affecting food intake may worsen malnutrition including CFRD, psychosocial aspects of the disease, and medications, among others. Furthermore, symptoms such as chronic cough, nausea and vomiting, GERD, and abdominal pain, may further contribute to a decreased food intake and contribute to malnutrition. In addition, patients with CF are often hypermetabolic and in a state of chronic inflammation. Cytokine activity and various immune and endocrine factors contribute to increased energy expenditure, often leading to weight loss. Acute infections involving the respiratory and gastrointestinal tracts further aggravate the hypermetabolic state and decrease energy intake by causing anorexia and catabolism.

Malnutrition, although an expected clinical feature of CF, should never be accepted as an untreatable condition. Not only does malnutrition worsen the patient’s prognosis and disease outcome, by influencing their lung function, it also affects their quality of life. Therefore, after optimizing PERT and vitamin supplementation, one should always look for other possible contributing causes of malnutrition and attempt to detect and control them and target these issues therapeutically.

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BIOGRAPHY

I was born in Rijeka, Croatia on the 6th of June 1993. Shortly after, my family and I moved to Kuwait and lived there for seven years before moving to Dubai, U.A.E. in 2001. In 2009, I moved to Zagreb, Croatia and graduated from "XV. Gimnazija" high school with an International Baccalaureate (IB) diploma in 2011. I enrolled in the Medical Studies in English programme at the University of Zagreb, School of Medicine in 2011 and am due to graduate in July 2017. I am grateful to have been able to gain clinical knowledge and experience and to do my clinical rotations in both Uppsala, Sweden and London, England. My plan for the future, after graduating, is to undergo specialist training in Europe, preferably in the field of Internal Medicine.