Cystic fibrosis-related diabetes mellitus

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CYSTIC FIBROSIS-RELATED DIABETES MELLITUS

GRADUATE THESIS

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ABBREVIATIONS

BM- Body mass

BMI- Body mass index

CF- Cystic fibrosis

CFRD- Cystic fibrosis-related diabetes

CFTR- Cystic fibrosis transmembrane conductance regulator

CGM- Continuous glucose monitoring

FEV1- Forced expiratory volume

GI- Gastrointestinal

TDID- Total daily insulin dose

Index

SUMMARY

Title: Cystic fibrosis-related diabetes mellitus

Background: Cystic fibrosis (CF) is autosomal recessive genetic disorder caused by mutations in the CFTR gene. It leads to multisystem complications such as persistent pulmonary infections, pancreatic insufficiency with diabetes, and liver damage, significantly decreasing the quality of life and contributing to morbidity and mortality. This study aims to investigate the prevalence and age of diagnosis of cystic fibrosis-related diabetes (CFRD) in Croatia and explore the connection between the age of CFRD diagnosis, insulin therapy, and body mass index (BMI).

Participants and Methods: This retrospective study analyzes the medical data of 123 patients diagnosed with CF and followed at the Croatian Referral Centre of the Ministry of Health for cystic fibrosis. Data were retrieved from the hospital information system. Among the 123 patients, 17 (6 males, 11 females) were identified with CFRD. The median age was 23 years (range 13-38, SD 6,91), and the median BMI was 22.73 (range 13.55-29.59 SD 3,61) kg/m^2.

Results: The prevalence of CFRD was 4.49% in the pediatric CF population and 38.24% in the adult CF population. The median age of CFRD diagnosis was 13 years (range 9-24, SD 4.43), with the majority diagnosed between 10 and 15 years ($p=0.021$; $p<0.05$). An earlier age of CFRD diagnosis (9-13 years) was associated with higher insulin doses required for therapy, peaking at age 10 with an average of 1.32 IU/kg. Additionally, those diagnosed at a younger age (4-15 years) had a notably lower mean BMI.

Conclusion: This first study investigating CFRD in Croatia establishes that the median age of diagnosis is predominantly between 10 and 15 years. The prevalence of CFRD aligns with findings from other research. An earlier age of CFRD diagnosis is associated with higher insulin doses required for therapy and a lower BMI, highlighting the importance of early detection and management of the disease to improve the health outcomes of CF patients.
Keywords: cystic fibrosis, cystic fibrosis-related diabetes, diagnosis, prevalence

SAŽETAK

Naslov: Šećerna bolest pridružena cističnoj fibrozi

Uvod: Cistična fibroza (CF) je autosomno recesivna genetska bolest uzrokovana mutacijom CFTR gena. CF dovodi do multisistemskih komplikacija kao što su učestale plućne infekcije, insuficijencija rada gušterače s dijabetesom te oštećenje jetre. CF značajno smanjuje kvalitetu života te pridonoseći morbiditetu i mortalitetu. Cilj ove studije je istražiti prevalenciju i dob dijagnoze dijabetesa povezanog s cističnom fibrozom (CFRD) u Hrvatskoj te istražiti povezanost između dobi dijagnoze CFRD-a, terapije inzulinom i indeksa tjelesne mase (BMI).

Ispitanici i metode: Radilo se o retrospektivnoj studiji u kojoj su analizirani medicinski podatci 123 bolesnika s dijagnozom CF-a koji su praćeni u Referalnom centru Ministarstva zdravstva Republike Hrvatske za cističnu fibrozu. Podaci su prikupljeni iz bolničkog informacijskog sustava. Identificirano je ukupno 17 bolesnika (6 muškaraca, 11 žena) s CFRD-om. Medijan dobi bio je 23 godine (raspon 13-38, SD 6,91), a medijan BMI bio je 22,73 (raspon 13,55-29,59, SD 3,61) kg/m^2.

Rezultati: Prevalencija CFRD-a bila je 4,49% u pedijatrijskoj populaciji i 38,24% u odrasloj populaciji s CF-om. Medijan dobi dijagnoze CFRD-a bio je 13 godina (raspon 9-24, SD 4,43), s većinom dijagnosticiranih između 10 i 15 godina ($p=0,021$; $p<0,05$). Ranija dob dijagnoze CFRD-a (9-13 godina) bila je povezana s većim dozama inzulina u liječenju CFRD-a, s vrhuncem u dobi od 10 godina s prosjekom od 1,32 IU/kg. Osim toga, oni dijagnosticirani u mlađoj dobi (4-15 godina) imali su značajno niži prosječni BMI.

Zaključak: U studiji u kojoj je po prvi puta evaluiran CFRD u Hrvatskoj ustanovljeno je da se dijagnoza postavlja najčešće u dobi između 10 i 15 godina. Prevalencija u hrvatskoj populaciji s CF-om slična je onima u drugima istraživanjima. Ranija dob dijagnoze CFRD-a povezana je s većim dozama inzulina i nižim BMI, što ukazuje na važnost ranog otkrivanja i liječenja bolesti kako bi se poboljšali zdravstveni ishodi pacijenata s CF-om.

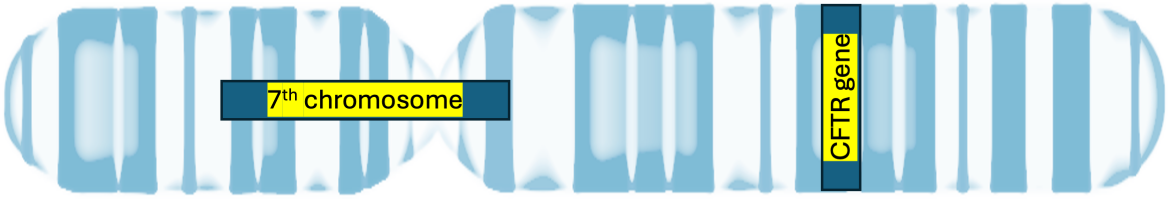
Ključne riječi: cistična fibroza, dijabetes povezan s cističnom fibrozom, dijagnoza, prevalencija

INTRODUCTION

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive genetic multisystem disorder of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, with symptoms of persistent pulmonary infection, loss of pancreatic exocrine function, elevated intestinal and liver damage and elevated sweat chloride levels (Ratjen, Döring 2003; De Boeck 2020). CF greatly decreases life quality and contributes to morbidity and mortality. There are many serious research efforts to improve CF patient monitoring and treatment regarding the disease complications (Kirigin Biloš et al. 2024). That approach enhances the quality of life in CF patients.

CF is the most common life-threatening monogenic disease afflicting Caucasian people. CF is a genetic disorder most commonly found in individuals of European descent due to a higher frequency of the CFTR gene mutation in this population. Diagnosing cystic fibrosis as early as possible is crucial for starting treatment promptly. Newborn screening enables early detection of the disease, helping to prevent complications and improve survival. This is why CF should be included in European newborn screening programs. The CF has progressed significantly over the years. Early intervention with medications like Advances in gene therapy and personalized medicine continue to offer hope for more effective treatments and improved quality of life for individuals with CF



- Figure 1: Presentation of CFTR gene location on 7th chromosome. (Cystic Fibrosis Western Australia. Available at: https://www.cfwa.org.au/cf-overview/. Accessed 28 June 2024.)

Epidemiology of cystic fibrosis

The population of CF patients is multi-ethnic and counts at least 100,000 patients globally (Shteinberg et al. 2021). CF affects approximately 1 in every 3000 to 6000 live births in the European population, (Scotet et al. 2020). Today number of CF patients in Europe exceeds 54000 (Cystic Fibrosis Foundation 2021). Life expectancy of CF patients increases due to advanced diagnostic technologies, improved therapy management, and execution of newborn screening programs. The later led to earlier detection of CF, providing on-time interventions that improved life quality and survival rates of CF patients. The life expectancy of patients with CF has immensely increased. The measured values of the median age of survival in CF patients is 52.1 years (The Canadian Cystic Fibrosis Registry 2018). While improvement has led to the prolonged lifespan of CF patients, the new non-pulmonary complications of the disease become prominent, such as cystic fibrosis-related diabetes (CFRD) (Putman et al. 2023). CFRD is present in 20% of adolescent, and 30% - 50% of adult CF patients (Moran et al. 2010). This disease complicates status of CF patients with additional symptoms of this rare form of diabetes (Lurquin et al. 2023a).

Pathophysiology of cystic fibrosis

CF develops because of mutations on the CFTR gene located on the longer arm of chromosome 7 (see Figure 1). CFTR gene produces CFTR protein, which plays a critical role in regulating chloride channels that regulate chloride (and bicarbonate) transport across epithelial membranes. Dysfunction of this transport causes production of thick, viscous mucus in numerous organs. In the respiratory tract mucus obstructs airways and enables bacterial colonization resulting in chronic infections. Subsequently patient develops bronchiectasis and progressive lung damage. In the pancreas, mucus blockages cause exocrine pancreatic insufficiency, impairing digestion and nutrient absorption that results in patients' malnutrition and growth deficiencies (Rowe et al. 2005; Riordan et al. 1989)

Clinical Presentation of cystic fibrosis

CF usually starts in early childhood. The most frequent symptoms are respiratory symptoms (45%), failure to thrive (28%), and meconium ileus (20%) (Accurso et al. 2005). Patients with later CF onset have mostly gastrointestinal symptoms, additional diagnosis of diabetes mellitus and fertility problems. (Yankaskas et al. 2004; Gilljam et al. 2004; Rodman et al. 2005). Combined CF symptoms can be divided according to the dysfunction of certain organic

systems during the illness. Respiratory symptoms in CF include chronic cough, wheezing, dyspnea, and recurrent lung infections, leading to respiratory failure. Gastrointestinal (GI) symptoms are connected to pancreatic dysfunction and hepatobiliary disease. The most common GI symptoms are malabsorption and steatorrhea. (Elborn 2016; De Boeck, Amaral 2016).

Treatment of cystic fibrosis

CF has been considered a deadly childhood disease for a long time. Better prognosis for CF patients started in 90s with new CF centers formed. Medical treatment for CF was focused on frequent supervision of the patient's medical condition and alleviating of present CF symptoms. The successful symptomatic treatment of CF patients included: airway clearance techniques, bronchodilator inhalation, corticosteroid therapy, pancreatic enzyme replacement therapy, nutritional supplementation, antimicrobial therapy for pulmonary infections etc. Because of the above-mentioned symptomatic treatments, the approach to CF patients became multidisciplinary. New hopes in CF therapy started with the discovery of the CFTR gene in 1989. Further research about the different mutations in the CFTR gene studied its product, the chloride channel. The research on chloride channels induced the idea of innovative therapy with CFTR modulators. These small molecules change cell processing, restore the expression and functionality of the chloride channel, and likewise folding and stability of the mutant CFTR. CFTR modulators complement CF standard medical care. CFTR modulator therapy improves lung function. CF patients on CFTR modulators have fewer pulmonary exacerbations and better nutritional status. CF patient survival is generally increased, especially if the CFTR modulator therapy has started early in childhood. In the year 2012 first CFTR modulator ivacaftor was approved. Ivacaftor was later combined with new CFTR modulators lumacaftor and tezacaftor in dual combination therapy. The new triple therapy of ivafactor, tezafactor and elexafactor is applicable for 90% of CF patients. CFTR modulators are confirmed as standard care for CF in many countries including Croatia (from year 2021.). Besides CFTR modulators there are other promising therapies in the development phase; gene therapy and activation of alternative ion channels to bypass CFTR. Development of patient-derived cell models' specimens with different mutations allow ex vivo testing of new therapeutic formulas on CFTR function. These models can be used for personalized therapy management in CF (Tješić Drinković et al. 2022).

Cystic fibrosis-related diabetes

Cystic fibrosis-related diabetes (CFRD) is a frequent complication in people with CF. Viewed separately, CFRD is considered as a special form of diabetes (Moran et al. 1998). Primary cause of developing CFRD is relative insulin deficiency, although insulin resistance can also influence hyperglycemia. When CF patients develop CFRD, it usually encompasses worse lung function and poorer nutritional status than of CF diagnosed population in general. Since discovery of CFRD in 1980s, risk of CF death rate is in decline (Moran et al. 2009) due to earlier screenings, diagnosis and introducing insulin as treatment.

Epidemiology of cystic fibrosis-related diabetes

CFRD is a complication of CF that usually develops in school-aged kids and older (Cystic Fibrosis Foundation 2021). The occurrence of CFRD increases with age. At ages of 20 to 40, the CFRD prevalence in CF population is 20% to 40% respectively. (Ode et al. 2022). The function level of the endocrine part of the pancreas is directly related to its exocrine function. Therefore, pancreatic exocrine function level can be used as a risk marker. Other risk factors include severe CFTR genotype, age, female sex, and type 2 diabetes family history.

Pathophysiology of cystic fibrosis-related diabetes

The pathophysiology of CFRD is complex, with multifactorial pathological processes in the background. Insulin deficiency is the main defect represented by a continuous decrease of insulin secretion in CF patients. This can eventually lead to the development of diabetes mellitus. Not all CF patients develop CFRD. Abnormalities in the development of CF patients may also contribute to its onset. (Bogdani et al. 2017). Eventually, the destruction of pancreatic tissue due to viscous plugs forming leads to pancreatic exocrine and endocrine dysfunction. It is considered that interleukin-1 beta immunoreactivity can be a factor that contributes to this process in the early part of CFRD development (Hull et al. 2018). In some patients' side effects of hyperglycemia during glucocorticoid therapy, and liver dysfunction can contribute to the developing and worsening of CFRD.

Clinical presentation of cystic fibrosis-related diabetes

CFRD clinical picture is often subtle, where the patient's weight and lung function decline slowly over time. The lung function in CFRD patients is additionally diminished. CFRD patients

have an increased risk of respiratory symptoms exacerbations than CF patients without CFRD. Poor nutritional status in CFRD patients is often present even before establishing diagnosis. Insulin has strong anabolic effect that helps in maintaining body weight. A catabolic state appears when insulin levels are low, contributing to poor nutritional status. In CFRD patients, there is wide spectrum of glucose intolerance levels that can range from impaired glucose tolerance to advanced diabetes. Hyperglycemia and insulin insufficiency have been established as major factors for the prediction of clinical outcomes in CF patients. (Granados et al. 2019). The oral glucose tolerance test (OGTT) is a golden standard in diagnosis of CFRD and its prediabetic stages.

Treatment of cystic fibrosis-related diabetes

Treatment for CFDR is essentially the same as for CF with the addition of insulin in the therapy of the patient. Usually, high-calorie diet is required, however, if the patient is under CFTR modulatory therapy some caloric restriction can be implemented if needed. (Ode et al. 2022). Insulin therapy is introduced to the patient's regular therapy immediately after the CFRD is diagnosed. With normal insulin levels, CFRD patients can mitigate complications. The compliance of patient regarding insulin therapy application is needed, but sometimes very hard to achieve. The new CFTR modulator therapy regarding nutritional status, helps CF patients to gain and maintain weight. Therefore, it is recommended to have personalized and individualistic approach when setting nutritional goals. CFTR modulator therapies are still being investigated in regards of their impact on glucose levels. Triple combined CFTR modulator therapies, elexacaftor/tezacaftor/ivacaftor, have shown some promising results in reducing insulin dose requirements and improving forced expiratory volume 1 (FEV1) and body mass index (BMI) in CFRD patients (Lurquin et al. 2023b).

Cystic fibrosis-related diabetes in Croatia

Studies in Croatia have provided valuable insights into CFRD prevalence, clinical characteristics, and up-to-date management strategies within the Croatian CF population (Tješić Drinković et al. 2023). The review emphasizes the importance of multidisciplinary care and tailored interventions to optimize outcomes for Croatian CF patients with diabetes. The integration of international guidelines and advancements in CFTR modulator therapies further shape CFRD management in Croatia: The care for CFRD patients is personalized by addressing the unique challenges posed by CFRD in different individuals and aiming to enhance patient life quality and long-term prognosis (Dickinson, Collaco 2021). These efforts should be enriched with further research localized at CF centers on regional or country level. This study purpose is to contribute to such research of CF/CFRD patients within the Croatian population.

HYPOTHESIS

The diagnosis of CFRD in analyzed CF patients is most frequently established from 10 to 15 years of age, its prevalence is similar to other European countries.

OBJECTIVES

1. The primary objective of this study is to investigate the prevalence and age of diagnosis of CFRD in Croatia.
2. The second objective was to explore the connection between the age of diagnosis of CFRD with insulin therapy.
3. The third objective was to explore the connection between the age of diagnosis of CFRD with BMI.

PATIENTS AND METHODS

Patients

This retrospective study analyzes the medical data of 123 patients diagnosed with CF (most of the patients were treated with elexacaftor/tezacaftor/ivacaftor for at least 2 years) and followed at the University Hospital Centre Zagreb, the State Referral Centre for CF. The study identified 17 patients with CFRD. Type 1 diabetes was excluded.

The study was approved by the University Hospital Centre Zagreb Ethical Committee. This approval confirms the study's adherence to medical research ethical guidelines, ensuring the protection of patient data confidentiality and patient integrity throughout the research process.

Methods

For data analysis, the hospital information system was utilized, extracting relevant details from patient medical records, including medical history and hospital checkups. The collected data included age (years), sex (M/F), height (meters), body mass (BM, kg), body mass index (BMI, kg/m^2), CFTR gene mutation (homozygous/heterozygous), age at diagnosis of CFRD (years), age at initiation of insulin therapy (years), total daily insulin dose (TDID, IU.), and total daily insulin dose/body mass (TDID/BM, IU/kg).

The values of interest were collected and analyzed as quantitative variables. While gender data was collected, it was not used as a grouping variable. The CFTR gene mutation data was used only for the descriptive analysis of the study group.

Statistical processing was performed using Microsoft Excel software for descriptive data analysis. Numerical variables were described according to data distribution, including mean value, standard deviation, minimum, median, and maximum. To confirm the statistical significance of the study hypothesis and for further analysis, parametric tests such as the Student T-test and z-test were used.

RESULTS

Patients' characteristics

The obtained results and additional data of 17 selected patients are summarized in Table 1 and Table 2.

Table 1 presents the clinical examination values, including actual age (years), height (meters), body mass (kg), BMI (kg/m²), sex (M/F), and confirmed genotype. At the time of analysis median age of all analyzed patients was 23 (range 13 -38, SD 6,91) years, and the median BMI was 22,73 kg/m^2 (range 13.55 - 29.59, SD 3,61) kg/m². Of all 17 patients, there were 6 males and 11 females. At the time of analysis males had a median age of 21 (range 16-24, SD 2,86) years and females had a median age of 27 (range 13-38, SD 8,10) years. In males, the median BMI value was 22,92 (range 22,73-23,10, SD 3,00) kg/m^2 and in females, the median value was 22,71 (range 13,55-26,86, SD 3,73) kg/m^2.

Among the selected 17 patients, the most prevalent CFTR gene mutation was homozygous (F508del). However, a heterozygous mutation appeared in 3 of the 17 patients (F508del/Y1092X, F508del/N1303K, F508del/p.Ser466*).

Table 2 presents data for patients diagnosed with CFRD and their insulin therapy details. In all cases except for patient No. 12, insulin therapy began immediately upon CFRD diagnosis; patient No. 12 commenced therapy 3 years later. The medina value of total daily insulin doses (TDID) was 26 (range 0-82 SD 27,80) IU and the median total daily insulin doses adjusted to body mass (TDID/BM) was 0,53 (range 0-1,32 SD 0,44) IU/kg.

Table 1: Data collected from CFRD patients included in the study. Each row presents individual patient values. Columns from left to right show recorded variables: sex (M/F), age (years), height (m), body mass-BM (kg), body mass index BMI (kg/m^2) and CFTR gene mutation. Mean value, standard deviation, min. median and max. are presented at the bottom of the table.

CFRD Patient(n)	**Sex M/F**	**Actual age (years)**	**Height (m)**	**Body mass BM (kg)**	**BMI (kg/m^2)**	**CFTR gene mutation**
1	M	20	1,82	71,30	21,53	Hom F508del
2	M	20	1,82	75,30	22,73	Hom F508del
3	M	23	1,79	74,00	23,10	Hom F508del
4	M	22	1,77	92,70	29,59	Hom F508del
5	M	24	1,57	59,50	24,14	F508del/Y1092X
6	F	23	1,59	48,70	19,26	Hom F508del
7	F	27	1,61	60,00	23,15	Hom F508del
8	F	23	1,57	62,30	25,27	Hom F508del
9	F	32	1,72	72,10	24,37	Hom F508del
10	F	31	1,50	51,10	22,71	Hom F508del
11	F	33	1,50	52,30	23,24	Hom F508del
12	F	24	1,62	70,50	26,86	Hom F508del
13	F	38	1,72	59,00	19,94	F508del/N1303K
14	M	16	1,60	55,40	21,64	Hom F508del
15	F	16	1,47	37,80	17,49	F508del/p.Ser466*
16	F	15	1,59	56,00	22,15	Hom F508del
17	F	13	1,63	36,00	13,55	Hom F508del
Mean	/	23,53	1,64	60,82	22,40	/
SD	/	6,91	0,11	14,25	3,61	/
Min	/	13,00	1,47	36,00	13,55	/
Median	/	23,00	1,61	59,50	22,73	/
Max	/	38,00	1,82	92,70	29,59	/

Table 2: Data collected from CFRD patients included in the study. Each row presents individual patient values. Columns from left to right show recorded variables: age of the patient when CFRD diagnosis was established (years), age of insulin therapy introduction (years), total daily insulin dose TDID (IU.), total daily insulin dose/body mass TDID/BM (IU/kg). Mean value, standard deviation, min. median and max. are presented at the bottom of the table.

CFRD Patient	Age CFRD diagnosis(years)	Age of insulin introduction(years)	TDID (IU)	TDID/BM (IU/kg)
1	13	13	82	1,15
2	17	17	0	0,00
3	15	15	54	0,73
4	13	13	82	0,88
5	10	10	66	1,11
6	13	13	26	0,53
7	23	23	6	0,10
8	22	22	0	0,00
9	19	19	0	0,00
10	9	9	22	0,43
11	21	21	13	0,25
12	15	18	14	0,20
13	15	15	25	0,42
14	13	13	59	1,06
15	10	10	50	1,32
16	12	12	38	0,68
17	9	9	26	0,72
Mean	14,65	14,82	33,12	0,56
SD	4,43	4,50	27,80	0,44
Min	9,00	9,00	0,00	0,00
Median	13,00	13,00	26,00	0,53
Max	23,00	23,00	82,00	1,32

Age of cystic fibrosis-related diabetes diagnosis

The median age of diagnosis of CFRD was 13 (9-23, SD 4,43) years. Statistical analysis revealed that the majority of CFRD patients were diagnosed within a specific age range, predominantly between 10 to 15 years ($p=0.021$; $p<0.05$). Figure 2 illustrates the distribution of CFRD patients based on the age at diagnosis, with four distinct groups represented on the x-axis. Notably, the group diagnosed with CFRD between 10 to 15 years of age is significantly larger compared to other age groups ($p<0.05$).

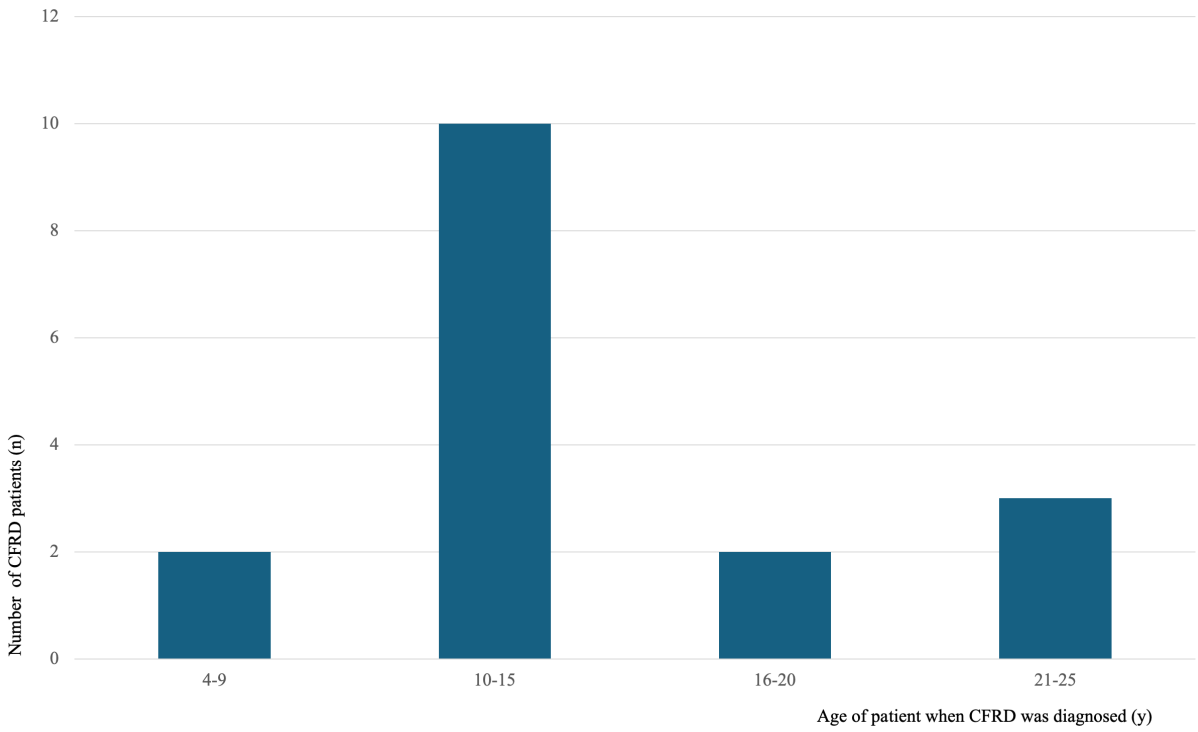


Figure 2: Graphical presentation showing the distribution of patients with CFRD according to the age when the CFRD diagnosis was established. On the x-axis age groups of patients (according to the age when CFRD diagnosis was set) are presented as columns. The number of CFRD patients is presented on the y-axis.

The prevalence of cystic fibrosis-related diabetes

Total prevalence of CFRD in the population of 123 CF patients was 13,82%. The study categorized patients into two main groups based on age: children (aged 17 years and less) and adults. The prevalence of CFRD in the pediatric population was 4,49% while the prevalence of CFRD in the adult population was 38,24% (including those diagnosed in childhood). Figure 3 illustrates the prevalence of CFRD within these groups. Patients diagnosed with both CF and CFRD are depicted in orange within the columns, while those without CFRD are shown in blue. Despite a higher number of children diagnosed with CF compared to adults, adults show a higher prevalence of CFRD than children . Statistical analysis using a z-test confirmed this observation across common significance levels ($\alpha = 0.05$, $\alpha = 0.01$, $\alpha = 0.001$), where the calculated z-value (-4.86) exceeded the critical value (approximately ±3.29).

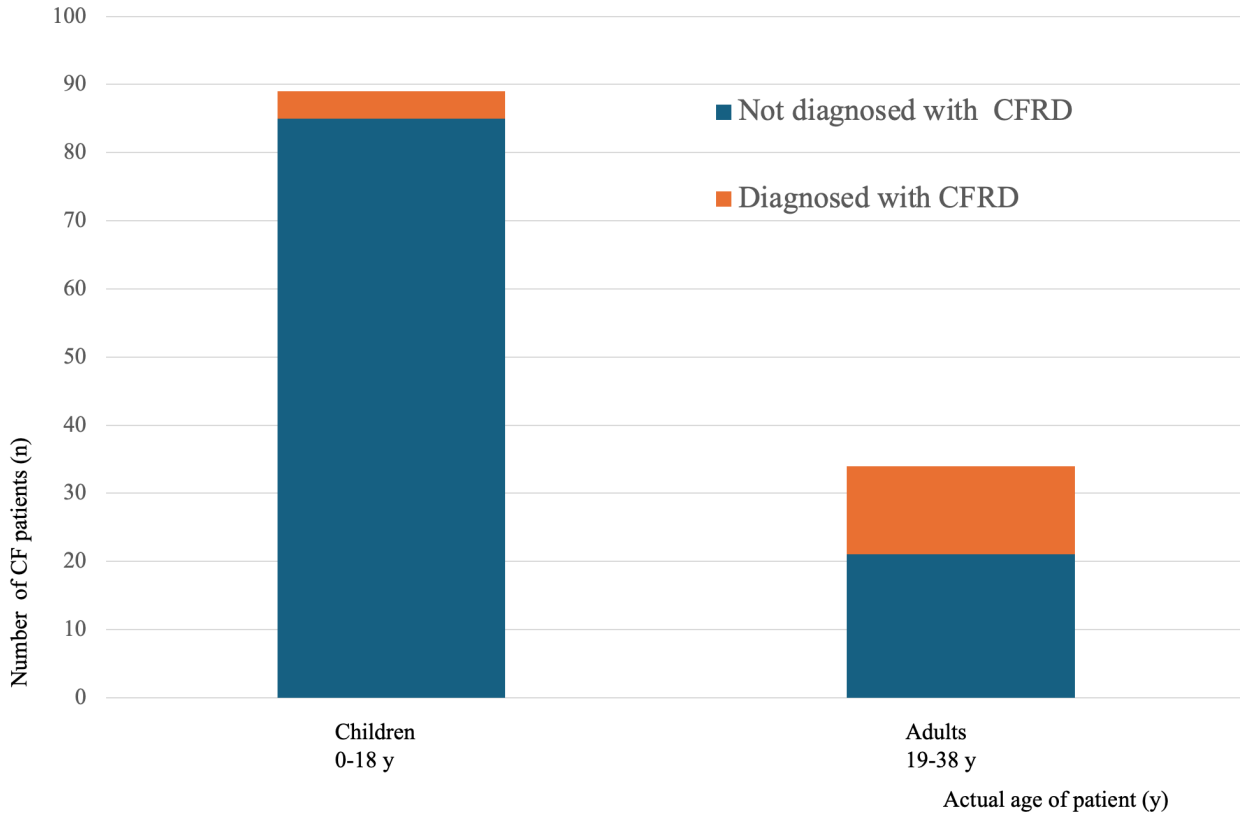


Figure 3: Graphical presentation of CFRD prevalence in CF patients according to two major age groups presented on the x-axis. Left column represent children group (0-18 y) and right column represent adult group (19-38 y). Total number of CF patients is presented on y-axis. Blue colored part of columns represents CF patients not diagnosed with CFRD. Orange part of columns represent CF patients diagnosed with CFRD.

Age of cystic fibrosis-related diabetes diagnosis and insulin therapy

Figure 4 presents a comparison between two variables for each patient: the age at which CFRD diagnosis was established (depicted by the height of blue columns on the left y-axis) and the Total Daily Insulin Dose per Body Mass (TDID/BM) shown on the right y-axis). Each patient is represented by an individual blue column, and a linear graph connects the TDID/BM values across patients. Patients diagnosed with CFRD at age 10 exhibited the highest TDID/BM values, which decrease as the age of CFRD diagnosis increases. Conversely, the lowest TDID/BM value was recorded in a patient diagnosed with CFRD at age 23. This linear trend in Figure 4 illustrates that insulin therapy dosage tends to increase when CFRD is diagnosed at an earlier age in CF patients. Statistical analysis confirmed this relationship as significant ($p < 0.001$).

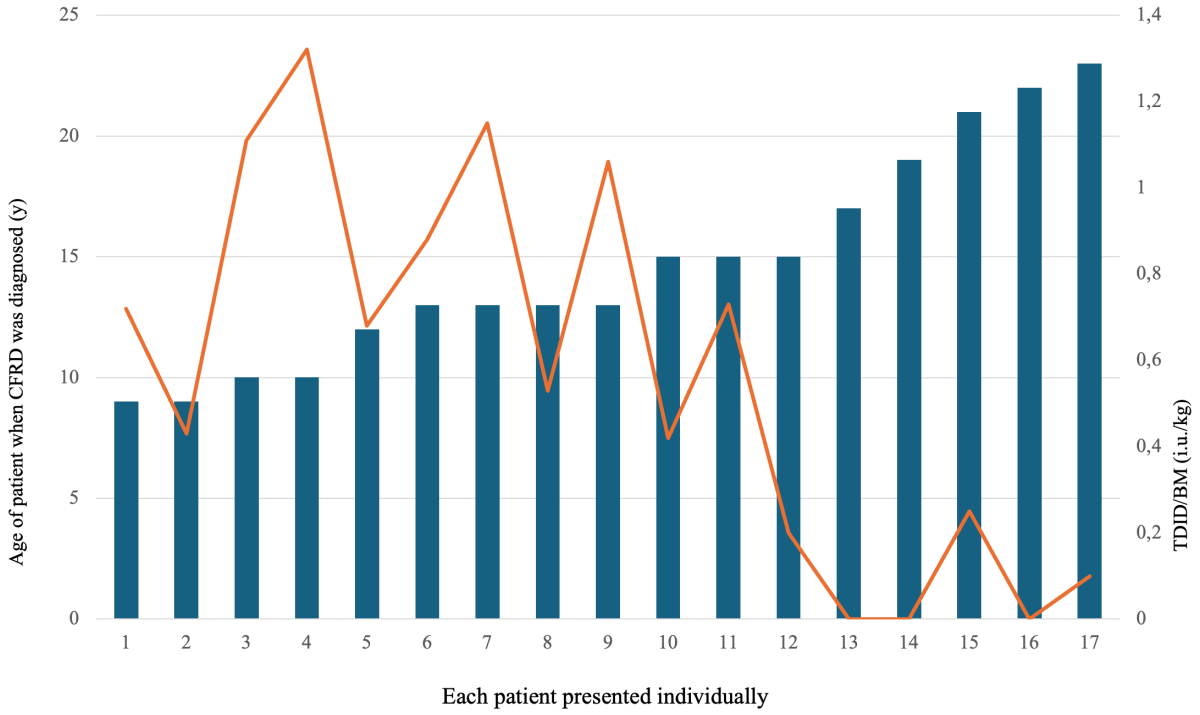


Figure 4: Graphical presentation of correlation between patient age when CFRD diagnosis was established and TDID/BM values for each patient individually. On x-axis, each patient is represented as a column. The left y-axis presents the age of the patient when CFRD diagnosis was established (y). The height of the column presents those values. The right y-axis shows related values of TDID/BM (IU/kg). The linear graph presents connected individual TDID/BM values.

Age of cystic fibrosis-related diabetes diagnosis and body mass index

Figure 5 illustrates the analysis of BMI values among CFRD patients based on the age at which diagnosis was established, segmented into four distinct groups. The mean BMI value is notably lower in the group diagnosed at a younger age (4-15 years). This difference was statistically significant ($p=0.03$; $p<0.05$). As the age at CFRD diagnosis increases, the mean BMI value progressively rises.

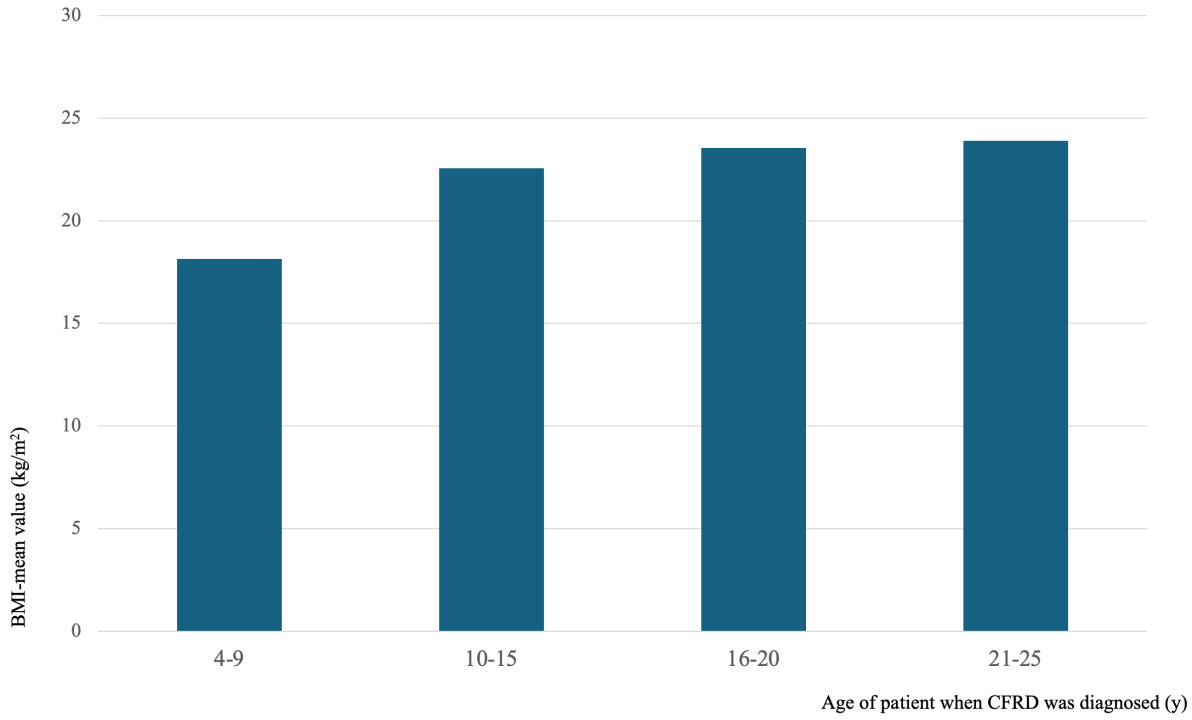


Figure 5: Graphical presentation of BMI according to age intervals when CFRD was diagnosed. Age groups formed according to the age of the patient when CFRD was diagnosed are presented on the x-axis. The mean value of BMI for each age group of patients is presented on the y-axis.

DISCUSSION

This retrospective study analyzes the medical data of 123 patients diagnosed with CF and followed at the Croatian Referral Centre of the Ministry of Health for cystic fibrosis. With approximately 150 CF patients in Croatia, this sample is representative of the country. From the observation of collected data, it is obvious that majority of CFRD patients are grouped around the certain age interval in which CFRD diagnosis was established. Since hypothesis assumes that in most cases CFRD diagnosis is established in analyzed CF population between 10-15 years of age, the initial hypothesis is confirmed. The median age of CFRD diagnosis is 13 years, but with big individual differences and SD of 4,43. Other studies with CFRD data did not have the same result. Their median age was 21 - 22 years which is significantly bigger than my median age (Lek N, Acerini CL, 2010; Scheuing N et al. 2013)

The prevalence of CFRD in the pediatric population was 4,49% while the prevalence of CFRD in the adult population was 38,24% (including those diagnosed in childhood). That corresponds with epidemiology studies of CFRD prevalence stating that 2% of children, 19% of adolescents and 40%-50% of adults are affected. (Granados et al. 2019; Moran et al. 2009).
Therefore, as the age of the CF patient increases, complications that can cause the CFRD onset increase as well. However, in the latest overview of Iafusco et al. the expected onset of CFRD is shifted to the age group of 18-24 years (Iafusco et al. 2021). Our hypothesis confirms the establishment of CFRD diagnosis in the Croatian population at a younger age. Some authors consider that CFDR-diagnosed patients are asymptomatic in the early stages of the disease (Granados et al. 2019). It is possible that due to the good screening for CFDR within the Croatian CF population, otherwise asymptomatic patients or patients with mild pancreatic dysfunction, were discovered earlier. Confirming of study hypothesis implicates that more frequent screening for CFDR within CF population should start from 10 years of age, that is also recommended in guidelines issued by American Diabetes Association (Clinical Care Guidelines for Cystic Fibrosis–Related Diabetes 2010.)

Further study research was focused on each particular patient's characteristic. The connection between patient age when CFRD diagnosis was established and further insulin therapy management, was evaluated through TDID/BM. Patients had a wide range of TDID/BM with a maximal value at the age of 10. Typically, average TDID/BM in CFRD patients is in range <0.5-

0.8 IU/kg (Ode et al. 2019). It is still uncertain why, however, there are some possibilities for having TDID/BM values higher than average in those patients who were diagnosed with CFRD earlier in life. For example, those patients who are diagnosed with CFRD at an early age may have more health-related complications that can contribute to having diminished BM. The possibility of taking higher doses of steroids for their pulmonary inflammations as one of the therapy options can cause this change. Also, there is the possibility that beta-cell function declines from an earlier age, causing the lack of endogenous insulin and creating a catabolic environment for patients. For patients that have lower TDID/BM values, CFRD was diagnosed at age 17 and further on. Therefore, it can be suggested more frequent insulin therapy controls and dosage adjustments for those patients who have been diagnosed with CFRD at the age of 9-13. Developing and using modern technology, for example, continuous glucose monitoring (CGM) can contribute to a better understanding of glycemic levels and maybe contribute to early diagnosis of CFRD development and better management using less insulin (Kirigin Biloš et al. 2024)..

The third objective of the study was to analyze BMI values concerning the age of the patient when CFRD diagnosis was established. Usually, BMI in CFDR patients is lower than in patient with CF without diabetes (Marshall et al. 2005, Sutharsan et al. 2023). A progressive increase in BMI with the rising of age when diagnosis of CFDR was established, suggests that older patients currently diagnosed with CFRD have better overall nutritional status and potentially less severe CF-related complications at the time of CFRD diagnosis. Almost all CFRD patients in this study are on CFTR modulator therapy and some of them gained a lot in their BM since starting the treatment. However, patients diagnosed with CFRD at younger ages (4-15 years) have lower BMI values compared to those diagnosed later in life, possibly as a consequence of insulinopenia and catabolism. That corresponds to clinical research of other authors, which states that CFRD patients who did not complete their growth had BMI lower than controls by 5-11%. (Marshall et al. 2005) This finding confirms that early onset of CFRD can adversely affect nutritional status and growth. This observation underscores the importance of early nutritional intervention and vigilant monitoring of growth parameters in younger CF patients (focused on patients 4-15 years of age) to mitigate the impact of CFRD.

The weakness of this retrospective study is the number of patients with CFRD diagnosis compared to countries with a larger CF population. Still, they are all followed uniformly in one centare by a multidisciplinary team, particularly by one diabetologist and the data have fewer

confounding variables. Kaminski et al. emphasize the importance of multidisciplinary care and tailored interventions to optimize outcomes for CF patients with diabetes. (Kaminski et al. 2019). Studies on the Croatian population have confirmed that and provided a valuable understanding of CFRD prevalence, clinical pictures, and therapy strategies.

CONCLUSION

In this retrospective study of 123 CF patients monitored at the Croatian Referral Centre of the Ministry of Health for cystic fibrosis, we identified 17 patients with CFRD. For the first time the median age of CFRD diagnosis in Croatia was established, it is 13 years, with the majority diagnosed predominantly between the ages of 10 and 15, a statistically significant time range compared to other age groups.

Also for the first time the prevalence of CFRD in the Croatian CF population was found, 38.24% in adults and 4.49% in children, consistent with findings from other research.

Notably, an earlier age of CFRD diagnosis (9-13 years) was associated with higher insulin doses required for therapy, peaking at age 10 with an average of 1.32 IU/kg. Additionally, early onset of CFRD was linked to poorer nutritional status and a lower BMI.

These findings highlight the crucial need for early detection and effective management of CFRD to mitigate its impact on the health and nutritional well-being of CF patients.

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BIOGRAPHY

I was born in 1995 in Zagreb, Croatia.

My high school education was accomplished at XV. Mathematical Gymnasium- International Baccalaureate program (IB) in Zagreb. After finishing high school education, I took the Scholastic Aptitude Test (SAT) and SAT subject tests in biology, physics and chemistry, where my score was in 90th percentile.

Afterwards, I began my higher education at the School of Medicine, University of Zagreb, studying in an English program. I joined our faculty water polo team where we won 2 times 3rd place in the Zagreb University tournament. During my study years, I became more attracted towards internal medicine, specifically endocrinology.

I am fluent in English, French, and German.