http:// health-providers.ir
Original Article (Pages: 117-129)

Evaluating Nutritional Status and Growth Hormone Deficiency in Iranian Children with Cystic Fibrosis

Hossein Ali Kharazmi[1], Mohammad Hasan Mohammadi[2], Hashem Lashgari Kalat[1], *Ali Asgari[1]

[1]Department of Pediatrics, Clinical Research Development Center of Children's Hospital, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

[2]Department of Pediatrics, Zabol University of Mediacl Sciences, Zabol, Iran.

Abstract

Background: The relationship between nutritional status and growth hormone deficiency (GHD) in children with cystic fibrosis (CF) is complex. CF leads to malnutrition due to malabsorption and respiratory complications, which complicates growth. This study aims to evaluate the nutritional status and prevalence of GHD in Iranian children diagnosed with CF.

Materials and Methods: This cross-sectional study was conducted at the Children's Medical Center in Tehran, Iran, involving children under 19 years with CF diagnoses based on two positive sweat tests showing chloride levels above 60 mmol/L. A total of 127 patients were included in the study during a one-year period. Data collection encompassed demographic and anthropometric measurements, clinical evaluations, and growth hormone stimulation tests to assess nutritional status, respiratory function, and bone mineral density.

Results: The study included 125 patients with CF and a mean age of 8.3 years. The findings revealed that 30.4% were below the 5th height percentile, while 45.6% were below the 10th percentile. Males had a mean body mass index (BMI) Z-score of -0.88, whereas females had a Z-score of -1.06; 76.4% of males and 81.1% of females were below the 50th percentile for BMI ($P > 0.05$). Short stature was more prevalent in older age groups, particularly among those aged 10-19, where it affected 40.5% of individuals ($P = 0.03$). Significant correlations were found between height percentiles and lung function ($P = 0.014$), as well as between height percentiles and bone mineral density (BMD) ($P < 0.05$). Among those below the 5th height percentile, 32.3% had low growth hormone levels indicative of GHD, particularly in males ($P = 0.31$).

Conclusion: This study reveals a high prevalence of short stature and low BMI among patients with cystic fibrosis, particularly in older children. Significant correlations between growth, lung function, and bone mineral density underscore the need for monitoring and early interventions to improve health outcomes.

Key Words: Cystic fibrosis, Growth hormone, Children, Iran, Nutrition.

*Please cite this article as**:** Kharazmi HA, Mohammadi MH, Lashgari Kalat H, Asgari A. Evaluating Nutritional Status and Growth Hormone Deficiency in Iranian Children with Cystic Fibrosis. Health Provid 2024; 4(2): 117-29. doi: **10.22034/HP.2025.498749.1055**

Corresponding Author:

Ali Asgari, MD, Department of Pediatrics, Clinical Research Development Center of Children's Hospital, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

Email: jahanishn@mums.ac.ir

Received date: May. 16, 2024; Accepted date: Dec.22, 2024

1- INTRODUCTION

Cystic fibrosis (CF) is a prevalent genetic metabolic disorder that significantly impacts the health and longevity of affected individuals. Caused by mutations in the CFTR gene (cystic fibrosis transmembrane conductance regulator), CF disrupts the normal functioning of chloride channels, leading to the accumulation of thick, sticky mucus in various organs, particularly the lungs, pancreas, and intestines. This mucus obstruction results in severe respiratory complications and digestive issues, making progressive lung disease the leading cause of mortality among CF patients (1-5). CF is recognized as the most common hereditary respiratory disorder in Western societies and ranks as the second most common genetic disease in the United States, with profound implications for life expectancy (6-8).

Despite significant advancements in treatment options and care strategies, children with CF often exhibit growth rates that lag behind their peers, underscoring growth as a critical indicator of disease progression and overall prognosis. Those with heights below the 5th percentile face a threefold increased risk of mortality compared to their counterparts above this threshold (9, 10).

Recent research indicates that growth hormone deficiency (GHD) is prevalent among CF patients, affecting approximately 6.6% of this population—substantially higher than the prevalence of less than 1% in the general pediatric population (11). GHD can exacerbate growth failure, leading to poor health outcomes and increased morbidity (12, 13). This highlights the necessity for routine screening for GHD in CF patients, particularly those showing signs of growth impairment. Furthermore, malnutrition is a widespread concern among children with CF, with nutritional status serving as a vital prognostic factor independent of pulmonary function (14-17).

In a recent study involving 150 children with CF, 24 were identified as experiencing growth failure, with 10 diagnosed with GHD through standardized stimulation tests (11). This underscores the critical need for routine screening for GHD in CF patients, particularly those showing signs of growth impairment. Additionally, the multifactorial nature of growth issues in CF—often compounded by malnutrition, chronic inflammation, and pulmonary complications—demands a comprehensive management approach that integrates nutritional support and hormonal therapies (9, 10). Failure to adequately address these challenges can result in long-term detrimental effects on health, quality of life, and overall prognosis for children with CF (11, 18).

Given these factors, this study aimed to investigate the nutritional status and prevalence of growth hormone deficiency (GHD) in Iranian children and adolescents diagnosed with cystic fibrosis (CF). Understanding the interplay between nutritional deficiencies and hormonal imbalances will provide valuable insights for optimizing management strategies to improve growth outcomes and overall health in this vulnerable population.

2- MATERIALS AND METHODS

2-1. Study Design and Setting

This cross-sectional study was conducted at the Children's Medical Center affiliated with Tehran University of Medical Sciences in Tehran, Iran. The study population included children and adolescents with CF who were referred to the hospital and had a confirmed diagnosis based on at least two positive sweat tests showing chloride levels exceeding 60 mmol/L.

2-2. Inclusion and Exclusion Criteria

According to the World Health Organization (WHO), a "child" is defined as any person under the age of 18 years, with adolescents specifically categorized as those aged 10 to 19 years (19). All patients up to the age of 19 years diagnosed with CF and referred to the Children's Medical Center between June 2014 and June 2015 were included in the study, provided they had at least two positive sweat tests indicating chloride levels exceeding 60 mmol/L. Informed consent was obtained from all participants. The exclusion criteria encompassed children under the age of 2, as well as those with concurrent chronic diseases unrelated to CF, such as hypothyroidism, renal failure, or congenital heart disease.

2-3. Sample Size

To calculate the sample size, the following formula was used:

$$n = \frac{Z^2_{1-\alpha/2} \cdot p(1-p)}{d^2}$$

- n: Sample size
- $Z_{1-\alpha/2}$: Z-score corresponding to the desired confidence level
- p: Estimated prevalence of the disorders
- d: Margin of error

Based on a review of relevant literature and the prevalence of the identified disorders, a minimum sample size of 75 was determined, accounting for a potential loss of 5%. The study included all patients up to the age of 19 years who were diagnosed with CF and referred to the Children's Medical Center between June 2014 and June 2015. Eligible participants had to have at least two positive sweat tests indicating sweat chloride levels exceeding 60 mmol/L.

2-4. Measurement Tools

2-4-1. Demographic and Anthropometric Data

The initial phase of data collection focused on key epidemiological factors, including age and gender, alongside anthropometric measurements such as weight (kg), and height (cm). These parameters were used to calculate body mass index (BMI, kg/m²) and were systematically recorded using a SECA model 220 scale. Additional pertinent information included:

- Parental height
- Number of hospitalizations in the past year
- History of bone fractures
- Dosage of vitamin D3 and calcium supplements
- Medications administered, including Creon and systemic steroids.

2-4-2. Clinical Evaluations in Cystic Fibrosis Patients

1. General Health Assessments

Clinical examinations involve comprehensive evaluations focusing on respiratory function, nutritional status, and growth metrics. Regular assessments are crucial for optimizing care and managing complications associated with CF.

2. Nutritional and Growth Evaluations

- **Standard Deviation Scores (SDS)**: Height, weight, and BMI calculations are performed using criteria from the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) (20). This standardized approach is vital for assessing growth and nutritional status.
- **Growth Hormone Stimulation Test:** The GH stimulation test was conducted on all patients whose height was below the 5th percentile, utilizing the clonidine test while the patients fasted. Each patient received 0.15 mg/m² of clonidine orally, and 5 mL blood

samples were taken at 0, 30, 60, and 90 minutes post-administration. A growth hormone level below 10 ng/mL indicates growth hormone deficiency (GHD) (21).

- **Insulin-like Growth Factor 1 (IGF-1) Measurement:** Serum IGF-1 levels were measured to screen children with growth failure for GHD. The ELISA method was used for quantification, employing a sandwich format with specific antibodies to capture and detect IGF-1 in serum samples. The IGF-1 Standard Deviation Score (SDS) was calculated using reference data from Diagnostic System Laboratories Inc., Webster, TX, adjusted for age and sex. Children were classified as IGF-1 deficient if their IGF-1 levels were below or equal to -2 SDS without concurrent growth hormone deficiency (22).

3. Respiratory Function Assessments

- **Respiratory Function Assessment**: Mean forced expiratory volume in one second (FEV1) is a critical measure for evaluating lung function in CF patients aged 6 years and older (23). This data is obtained from respiratory tests conducted over the previous year, providing essential insights into lung health and disease progression.

4. Bone Health Evaluations

- **Bone Mineral Density (BMD):** In this study, we evaluated bone mineral density (BMD), a measure of the mineral content in bone, primarily calcium and phosphorus, which serves as a key indicator of bone strength and fracture risk. For patients aged 6 years and older, BMD assessments were performed using dual-energy X-ray absorptiometry (DEXA) scans with Hologic devices. The results were recorded as Z-scores, which compare an individual's BMD to age-appropriate norms, focusing on key sites such as the lumbar spine and femur. A Z-score below -2.0 indicates lower than expected bone density for the individual's age and sex (24).

2-5. Ethical Considerations

The study on children and adolescents with cystic fibrosis (CF) was approved by the Research Ethics Committee of Tehran University of Medical Sciences (approved code: T-1392-06), adhering to the Helsinki Declaration (25) and pediatric research guidelines. This adherence aligns with the Belmont Report principles (26): Respect for Persons was upheld through voluntary participation based on informed consent from parents or guardians, alongside age-appropriate assent from children, ensuring that vulnerable populations like minors received extra protection. Beneficence was ensured by maximizing benefits while minimizing risks; participants received comprehensive assessments without undue harm, and all tests were provided free of charge. The principle of Justice ensured fair participant selection based on inclusion criteria rather than vulnerability or ease of access, distributing risks equitably among those involved. To further enhance ethical considerations, strict confidentiality was maintained during data collection, and parents were fully informed about the study's objectives, potential risks, and post-study care. The results were presented in a way that protected participant identities by extracting data in general terms.

2-6. Data Analysis

Data analysis was conducted using SPSS Version 18 software. For qualitative variables, prevalence and frequency estimates were calculated, while quantitative variables were summarized using means and standard deviations. A 95% confidence interval was applied to all estimates. Differences in frequencies across groups were assessed using the Chi-

square test, and mean differences among two or more groups were evaluated using the independent t-test. A p-value of less than 0.05 was considered statistically significant

3- RESULTS

3-1. Patient Demographics

In this study, 127 patients were initially considered; however, two were excluded due to hypothyroidism and congenital heart disease, resulting in a final analysis of 125 patients with cystic fibrosis (CF). The results indicated a slight male majority among the participants. The mean age of the participants was 8.3 years, with no statistically significant difference between the ages of males and females (P= 0.151).

Table 1 summarizes the demographic characteristics of the study population.

Table 1: Demographic Characteristics of Patients with Cystic Fibrosis.

Demographic Variable	Total	Male, Number (%)	Female, Number (%)	P-value*
Number of Patients	125	72 (57.6%)	53 (42.4%)	-
Mean Age (year)	8.3 (2-19.4)	8.9 (2-19.3)	7.66 (2-19.4)	0.151

***** Independent samples t-test.

3-2. Growth Metrics

Table 2 summarizes the BMI, height, and weight Z-scores for male and female patients, reflecting their nutritional status. Males have a mean BMI Z-score of -0.88, while females have a lower mean of -1.06; however, the differences were not statistically significant ($p > 0.05$), indicating potential nutritional deficiencies in both groups. The overall mean BMI Z-score for all patients was -0.96, highlighting widespread concerns about below-average nutritional health. The p-values for BMI (0.47), height (0.59), and weight (0.70) indicate no statistically significant differences between genders in these measurements (**Table 2**).

Table 2: Growth Metrics and Z-Scores in Patients with Cystic Fibrosis.

Group	BMI Z Score, Mean ± SD	Height Z Score, Mean ± SD	Weight Z Score, Mean ± SD	Total
Male	-0.88 ± 1.47 (-7.4 - 1.47)	-1.17 ± 1.20 (-4.8 - 1.4)	-1.39 ± 1.60 (-9.4 - 1.13)	72
Female	-1.06 ± 1.41 (-5.0 - 1.23)	-1.06 ± 1.23 (-4.7 - 1.0)	-1.49 ± 1.46 (-5.9 - 1.21)	53
Total	-0.96 ± 1.44 (-7.4 - 1.47)	-1.12 ± 1.21 (-4.8 - 1.4)	-1.43 ± 1.55 (-9.4 - 1.21)	125
P-value*	0.47	0.59	0.70	

***** Independent samples t-test. BMI: Body Mass Index, SD: Standard Deviation.

Table 3 displays the prevalence of patients below specific BMI and height percentiles across male and female groups. It indicates that 76.4% of males and 81.1% of females fall below the 50th percentile for BMI, while 25% of males and 34% of females are below the 10th percentile for BMI, suggesting a significant risk of underweight. Regarding height, 45.6% of cases (47.2% of males and 43.4% of females) are below the 10th percentile, while 30.4% of cases (29.2% of males and 32.1% of females) fall below the 5th percentile. The p-values, which range from 0.27 to 0.73, indicate no statistically significant differences between genders for any of the metrics assessed. This suggests a common concern regarding nutritional status and growth among these patients.

Table 3: Comparison of BMI and Height Percentiles in Male and Female Cystic Fibrosis Patients.

Group	BMI <50%, Number (%)	BMI <10%, Number (%)	Height <10%, Number (%)	Height <5%, Number (%)	Total
Male	55 (76.4%)	18 (25%)	34 (47.2%)	21 (29.2%)	72
Female	43 (81.1%)	18 (34%)	23 (43.4%)	17 (32.1%)	53
Total	98 (78.4%)	36 (28.8%)	57 (45.6%)	38 (30.4%)	125
P-value*	0.52	0.27	0.67	0.73	

*Chi-square test. BMI: Body Mass Index.

The analysis of BMI and height percentiles in CF patients reveals significant trends across age groups (**Table 4**). The prevalence of patients with a BMI below the 50th percentile increases with age, rising from 64.9% in those under 5 years to 90.5% in the 10-19 year age group. The highest prevalence of BMI below the 10th percentile is also observed in the 10-19 year age group, at 35.7%.

Height data shows a similar pattern, with the percentage of patients below the 10th percentile increasing from 35.1% to 61.9%, and those below the 5th percentile rising from 18.9% to 40.5%. Significant differences were found between age groups for BMI <50% (P = 0.022) and height <10% (P = 0.03), while no significant differences were observed for BMI <10% (P = 0.47) or height <5% (P = 0.12).

Overall, 30.4% of patients had a height below the 5th percentile (P = 0.73), and 45.6% were below the 10th percentile for height (P = 0.67). These findings highlight the nutritional challenges and growth failure faced by children with cystic fibrosis, underscoring the need for targeted interventions.

Table 4: Comparison of BMI and Height Percentiles by Age Group in Cystic Fibrosis Patients.

Age Group (year)	BMI <50%, Number (%)	BMI <10%, Number (%)	Height <10%, Number (%)	Height <5%, Number (%)	Total
< 5	24 (64.9%)	9 (24.3%)	13 (35.1%)	7 (18.9%)	37
5 - 9	36 (78.3%)	12 (26.1%)	18 (39.1%)	14 (30.4%)	46
10 - 19	38 (90.5%)	15 (35.7%)	26 (61.9%)	17 (40.5%)	42
Total	98 (78.4%)	36 (28.8%)	57 (45.6%)	38 (30.4%)	125
P-value*	0.022	0.47	0.03	0.12	

*Chi-square test. BMI: Body Mass Index.

3-3. Growth Hormone Levels

The results indicate that a clonidine stimulation test was conducted to evaluate serum growth hormone levels in 34 of the 38 patients with CF whose height percentile was less than 5%. Among those tested, 11 patients (32.3%) had growth hormone levels below 10 ng/mL, indicating potential growth hormone deficiency. Of these patients, 8 were male (38%) and 3 were female (23%), with no statistically significant difference between genders (P = 0.31). Additionally, 12 patients (35.3%) had serum GH levels of ≥10 ng/mL and IGF-1 levels less than -2 SD, indicating growth hormone insensitivity (**Table 5**).

Table 5: Prevalence of Growth Hormone Levels in Patients with Short Stature.

Cases	Number (%)	GH<10 ng/ml Number (%)	GH ≥10 ng/ml	
			IGF-1 > -2SD	IGF-1<-2SD
Male	21	8 (38.1%)	5 (23.8%)	8 (38.1%)
Female	13	3 (23.1%)	6 (46.1%)	4 (30.8%)
Total	34	11 (32.3%)	11 (32.3%)	12 (35.3%)
P-value*		0.31		

*Chi-square test. GH: Growth Hormone, IGF-1: Insulin-like Growth Factor-1, SD: Standard deviation.

3-4. Relationship between Height and Lung Function

Table 6 shows the distribution of patients across height percentiles and their corresponding FEV1 groups. In the >90% FEV1 group, 5 patients (27.8%) have a height percentile < 5%, while 13 patients (72.2%) have a height percentile ≥ 5%. In the 40-69% FEV1 group, 16 patients (53.3%) fall below the 5th height percentile.

With a total of 74 patients assessed, the p-value of 0.014 indicates a statistically significant relationship between height percentiles and lung function (**Table 6**). This suggests that individuals with greater height tend to have better lung function compared to those who are shorter.

Table 6: Relationship between Height Percentiles and FEV1 Groups in Patients with Cystic Fibrosis.

FEV1 Group	Height Percentile	Number	% within Height Percentile	% within FEV1 Group
> 90%	< 5%	5	19.2%	27.8%
	≥ 5%	13	27.1%	72.2%
70-89%	< 5%	4	15.4%	16.0%
	≥ 5%	21	43.8%	84.0%
40-69%	< 5%	16	61.5%	53.3%
	≥ 5%	14	29.2%	46.7%
< 40%	< 5%	1	3.8%	100.0%
	≥ 5%	0	.0%	.0%
Total		74		
P-value*				0.014

*Chi-square test. FEV1: Forced Expiratory Volume in 1 second.

3-5. Relationship between BMD and Lung Function

Table 7 shows the relationship between FEV1 groups and BMD in the spine and femur. In the >90% FEV1 group, 1 patient (5.9%) has a spine BMD < -2, while 16 patients (94.1%) have a BMD ≥ -2. For the femur, 2 patients (11.8%) fall below -2, and 15 patients (88.2%) are at or above -2.

Overall, there are 22 patients with spine BMD < -2 and 20 with femur BMD < -2. The p-values of 0.000 for spine BMD and 0.004 for femur BMD indicate a significant relationship between lung function and bone density (**Table 7**).

Table 7: Relationship between BMD and FEV1 Groups in Patients with Cystic Fibrosis.

FEV1 Group	Spine BMD	Total	% within Spine BMD	Femur BMD	Total	% within Femur BMD
> 90%	<-2	1	5.9%	<-2	2	11.8%
	≥−2	16	94.1%	≥−2	15	88.2%
70-89%	<-2	2	8.0%	<-2	3	12.0%
	≥−2	23	92.0%	≥−2	22	88.0%
40-69%	<-2	18	60.0%	<-2	14	46.7%
	≥−2	12	40.0%	≥−2	16	53.3%
< 40%	<-2	1	100.0%	<-2	1	100.0%
	≥−2	0	.0%	≥−2	0	.0%
Total		22			20	
P-value*	0.000			0.004		

*Chi-square test. FEV1: Forced Expiratory Volume in 1 second, BMD: Bone Mineral Density.

3-6. Relationship between BMI and Lung Function

Table 8 shows the relationship between FEV1 groups and BMI percentiles. In the >90% FEV1 group, 1 patient (5.6%) has a BMI percentile below 10, while 17 patients (94.4%) have a BMI percentile of 10 or higher. In the 70-89% FEV1 group, 5 patients (20.0%) fall below the 10th percentile, whereas 20 patients (80.0%) are at or above this threshold. In the 40-69% FEV1 group, 17 patients (56.7%) have a BMI percentile below 10.

In total, there are 24 patients with a BMI percentile below 10 and 50 patients with a BMI percentile of 10 or higher, resulting in a total of 74 patients. The p-value of <0.001 indicates a significant relationship between FEV1 groups and BMI percentiles (**Table 8**).

Table 8: Relationship between BMI and FEV1 Groups in Patients with Cystic Fibrosis.

FEV1 Group	BMI Percentile < 10	BMI Percentile ≥ 10	Total	% within FEV1 Group
> 90%	1	17	18	5.6% (<10) 94.4% (≥10)
70-89%	5	20	25	20.0% (<10) 80.0% (≥10)
40-69%	17	13	30	56.7% (<10) 43.3% (≥10)
< 40%	1	0	1	100.0% (<10) .0% (≥10)
Total	24	50	74	32.4% (<10) 67.6% (≥10)
P-value*				<0.001

*Chi-square test. FEV1: Forced Expiratory Volume in 1 second, BMI: Body Mass Index.

3-7. Relationship between BMI and BMD

Table 9 shows the relationship between BMI percentiles and spine bone mineral density (BMD). Among individuals with a BMI percentile < 10%, 12 patients (54.5% of those within the spine BMD group) have a spine BMD < -2, while another 12 patients (23.5% of those within the spine BMD group) have a BMD ≥ -2, totaling 24 patients. In the >10% BMI group, 10 patients (45.5% of those within the spine BMD group) have a spine BMD < -2, and 39 patients (76.5% of those within the spine BMD group) have a BMD ≥ -2, totaling 49 patients.

Overall, there are 22 patients with spine BMD < -2 and 51 patients with spine BMD ≥ -2 across all groups, comprising a total of 73 patients. The p-value of 0.014 indicates a significant relationship between BMI percentiles and spine BMD (**Table 9**).

Table 9: Relationship between BMI and BMD in Patients with Cystic Fibrosis.

BMI Percentile	Spine BMD < -2	Spine BMD ≥ -2	Total	% within Spine BMD
< 10%	12	12	24	54.5% (< -2) 23.5% (≥ -2)
> 10%	10	39	49	45.5% (< -2) 76.5% (≥ -2)
Total	22	51	73	100.0%
P-value*			0.014	

*Chi-square test. BMD: Bone Mineral Density.

4- DISCUSSION

This study investigated the nutritional status and prevalence of growth hormone deficiency (GHD) in Iranian children and adolescents diagnosed with cystic fibrosis (CF). The results indicated that 30.4% of the participants were below the 5th height percentile, while 45.6% fell below the 10th percentile. Short stature was more prevalent among older age groups, with 40.5% of those aged 10-19 affected (P = 0.03). Significant correlations were found between height percentiles and lung function (P = 0.014) as well as bone mineral density (BMD) (P < 0.05). Among those below the 5th height percentile, 32.3% exhibited low growth hormone levels, indicating GHD, particularly in males (P = 0.31).

4-1. Prevalence of Malnutrition

The present study found that a significant proportion of participants had low BMI and height percentiles, with 30.4% below the 5th height percentile and 45.6% below the 10th percentile. These findings align with those of Rafeey et al. (2020), which reported that malnutrition is prevalent among CF patients in Iran, with 39% of their sample experiencing under-nutrition (27). In contrast, a study conducted in New Zealand in 2019 found no cases of under-nutrition among CF patients (28), highlighting regional disparities in nutritional status and access to care. Additionally, research by Corey et al. (1988) supports the notion that optimal nutritional status is crucial for improving the quality of life and prognosis in CF patients (29).

4-2. Gender Differences in Nutritional Status

In this study, males had a mean BMI Z-score of -0.88, while females had a mean Z-score of -1.06; however, these differences were not statistically significant (P > 0.05). This finding is consistent with results from other studies that have shown similar trends, indicating that nutritional deficiencies affect both genders but may vary slightly in severity. For instance, Rafeey et al. (2020) noted that while males often exhibit poorer nutritional outcomes, the overall prevalence of malnutrition is a concern across both genders (27).

4-3. Growth Hormone Deficiency (GHD)

This study found that 32.3% of CF patients with a height percentile below the 5th percentile have GHD. This indicates that a significant number of these patients may be experiencing growth hormone-related issues. In contrast, Dara et al. (2022) reported a lower prevalence of 6.6% for

GHD among CF patients, suggesting it may be less common than indicated in this study. However, this rate is still significantly higher than the general pediatric population, where GHD affects less than 1% of children. The findings from Dara et al. highlight the importance of early detection and intervention for malnutrition and GHD (30), which aligns with this study's emphasis on the need for timely nutritional support to improve growth outcomes.

4-4. Age-Related Trends

The present study observed an increase in the prevalence of patients with a BMI below the 50th percentile as age increased, particularly among adolescents (90.5% of those aged 10-19). This trend is corroborated by findings from other studies indicating that older children with CF are at greater risk for malnutrition due to increased energy demands and potentially inadequate dietary intake (31, 32).

4-5. Correlations with Lung Function

The significant correlation between height percentiles and lung function ($P = 0.014$) observed in this study aligns with previous research demonstrating that better growth is associated with improved lung function in CF patients (33). Studies have consistently shown that adequate nutrition is crucial for maintaining lung function and overall survival rates in this population (34, 35).

4-6. Bone Mineral Density (BMD)

The relationship between lung function and BMD found in this study echoes findings from other research indicating that poor nutrition adversely affects both lung health and bone density in CF patients (36). For example, studies have documented that children with CF often experience reduced BMD due to inadequate nutrition and chronic inflammation (37, 38).

In summary, the findings from this study are consistent with existing literature on the nutritional challenges faced by children with CF, emphasizing the need for targeted interventions to improve nutritional status, growth, and overall health outcomes.

4-7. Study Limitations

This cross-sectional study has several limitations that may affect the interpretation of its findings. First, the design prevents establishing causality between cystic fibrosis characteristics and outcomes, as data were collected at a single point in time. The sample size of 125 patients may not adequately represent the broader CF population, limiting generalizability. Additionally, excluding children under 2 years old and those with concurrent chronic diseases could introduce bias.

Reliance on self-reported data may also lead to inaccuracies due to recall bias, and variations in measurement techniques could create inconsistencies. Furthermore, potential confounding factors such as dietary habits and physical activity levels may not have been fully controlled. These limitations underscore the need for further research using longitudinal designs and larger, more diverse samples to validate these findings and enhance our understanding of CF outcomes.

5- CONCLUSION

This study highlights a concerning prevalence of short stature and low BMI among children and adolescents with cystic fibrosis (CF), particularly in older age groups, where the rates of underweight and growth deficiencies significantly increase. Notably, 30.4% of participants were below the 5th height percentile, with a marked rise in short stature observed in adolescents. The findings also reveal a significant association between growth parameters, lung function, and bone mineral density, indicating that

compromised growth may adversely affect overall health outcomes.

The identification of low growth hormone levels in 32.3% of patients below the 5th height percentile, particularly among males, emphasizes the critical need for vigilant monitoring and management of nutritional status and growth in this population. These insights reinforce the importance of early interventions aimed at optimizing growth and lung health, which are essential for improving the quality of life and long-term outcomes for individuals with CF. By addressing these issues proactively, healthcare providers can better support the developmental needs of children with CF, ultimately enhancing their overall well-being.

6- ACKNOWLEDGMENTS

This article is based on a thesis in pediatric endocrinology at the subspecialty level and has received support from Tehran University of Medical Sciences. We extend our heartfelt thanks to all participants in this study and to the parents of the children who collaborated with us. Additionally, we acknowledge the financial support provided by Tehran University of Medical Sciences for this research.

7- CONFLICT OF INTEREST: None.

8- REFERENCES

1. Davies JC, Alton EWFW, Bush A. Cystic fibrosis. BMJ. 2007;335(7616):1255-59.

2. Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519-31.

3. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis: Cystic Fibrosis Foundation consensus report. J Pediatr. 2008;153(2):S4-S14.

4. Almughem FA, Aldossary AM, Tawfik EA, Alomary MN, Alharbi WS, Alshahrani MY, et al. Cystic Fibrosis: Overview of the Current Development Trends and Innovative Therapeutic Strategies. Pharmaceutics. 2020 Jul 2;12(7):616. doi: 10.3390/pharmaceutics12070616.

5. Xu X, Zhang X, Zhang G, Abbasi Tadi D Prevalence of antibiotic resistance of Staphylococcus aureus in cystic fibrosis infection: a systematic review and meta-analysis. Journal of Global Antimicrobial Resistance, 2024; 36: 419–25.

6. Cystic Fibrosis Foundation Patient Registry Annual Data Report: 2019. Available from: https://www.cff.org/sites/default/files/2021-10/2019-Annual-Report.pdf.

7. O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet. 2009; 373(9678):1891-1904.

8. Centers for Disease Control and Prevention (CDC). About Cystic Fibrosis, 2024. Available from: https://www.cdc.gov/cystic-fibrosis/about/index.html.

9. Lai HC, Corey M, FitzSimmons S, Kosorok MR, Farrell PM. Comparison of growth status of patients with cystic fibrosis between the United States and Canada. Am J Clin Nutr. 1999 Mar; 69(3):531-8. doi: 10.1093/ajcn/69.3.531. PMID: 10075341.

10. Danielle Usatin , Elizabeth H. Yen, Catherine McDonald, Fadi Asfour, John Pohl, Jacob Robson. Differences between WHO AND CDC early growth measurements in the assessment of Cystic Fibrosis clinical outcomes. J of Cistic Fibrosis, 2017;16 (4):503-9.

11. Reisi M, Sharif Ahmadian N, Hashemipour M, Mostofizadeh N, Keivanfar M, Hashemi E. Evaluation of Growth Hormone Deficiency in Children with Cystic Fibrosis. Adv Biomed Res. 2022 Jul 29;11:62. doi: 10.4103/abr.abr_285_20.

12. Hage C, Gan HW, Ibba A, Patti G, Dattani M, Loche S, Maghnie M, Salvatori R. Advances in differential diagnosis and management of growth hormone deficiency in children. Nat Rev Endocrinol. 2021 Oct;17(10):608-624. doi: 10.1038/s41574-021-00539-5. Epub 2021 Aug 20. PMID: 34417587.

13. Boguszewski MCS. Growth hormone deficiency and replacement in children. Rev Endocr Metab Disord. 2021 Mar;22(1):101-108. doi: 10.1007/s11154-020-09604-2. Epub 2020 Oct 8. PMID: 33029711.

14. Mauch RM, Kmit AH, Marson FA, Levy CE, Barros-Filho AA, Ribeiro JD. Association of growth and nutritional parameters with pulmonary function in cystic fibrosis: a literature review. Rev Paul Pediatr. 2016 Dec;34(4):503-509. doi: 10.1016/j.rpped.2015.12.002.

15. Li DD, Shen YL, Wang MC, Yang WL, Xia LL, Zhang YQ, Zhao SY, Yan J. Correlation of nutritional status with clinical characteristics and lung function in children with cystic fibrosis]. Zhongguo Dang Dai Er Ke Za Zhi. 2024 Mar 15;26(3):275-281. Chinese. doi: 10.7499/j.issn.1008-8830.2308075.

16. Rafeey M, Pourabdollahi P, Ghaemmaghami SJ, et al. Nutritional Assessment and Growth Patterns in Children with Cystic Fibrosis: A Case-Control Study. Studies in Medical Sciences. 2010; 10(1):1-8.

17. Mariotti Zani E, Grandinetti R, Cunico D, Torelli L, Fainardi V, Pisi G, Esposito S. Nutritional Care in Children with Cystic Fibrosis. Nutrients. 2023 Jan 17;15(3):479.

18. Danya, Muilwijk. Cystic Fibrosis: a real-world challenge to predict individual outcomes. doi: 10.33540/1967. PhD thesis, Utrecht University, The Netherlands, 2023.

19. World Health Organization. (n.d.). Child and adolescent health. Available from https://www.who.int/health-topics/child-health

20. Laurence, M, Grummer-Strawn., Chris, Reinold., Nancy, F., Krebs. Use of World Health Organization and CDC growth charts for children aged 0-59 months in the United States, 2010;59:1-15.

21. Ayala Castro LM, Ye Tay J, Solano N, Figueroa N, Geoffrey A, Carrillo-Iregui A, Diaz A. 6815 Side Effects of Clonidine and Glucagon for Growth Hormone Stimulation Tests and Association with the Level of the Growth Hormone Peak. J Endocr Soc. 2024 Oct 5;8(Suppl 1):bvae163.1525. doi: 10.1210/jendso/bvae163.1525.

22. Ibba A, Corrias F, Guzzetti C, Casula L, Salerno M, di Iorgi N, Tornese G, Patti G, Radetti G, Maghnie M, Cappa M, Loche S. IGF1 for the diagnosis of growth hormone deficiency in children and adolescents: a reappraisal. Endocr Connect. 2020 Nov;9(11):1095-1102. doi: 10.1530/EC-20-0347.

23. Walicka-Serzysko K, Postek M, Borawska-Kowalczyk U, Milczewska J, Sands D. Pulmonary Function Tests in the Evaluation of Early Lung Disease in Cystic Fibrosis. J Clin Med. 2023 Jul 17;12(14):4735.

24. Latifa, Nabeel, Alsaad., Juman, Ahmed, Abdulameer., E., A., Akolaa., Jayakumary, Muttappallymyalil., Jayadevan, Sreedharan. Bone Mineral Density and Its Determinants: A Systematic Review of Risk Factors and Prevention Strategies. Biomedical and Pharmacology Journal, 2023; 16(3). doi: 10.13005/bpj/2758.

25. World Medical Association, 2024. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki/.

26. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). Ethical Principles and Guidelines for the Protection of Human Subjects of Research (The Belmont Report). Available from: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html.

27. Rafeey, M., Dara, S., Alavi, N. Nutritional challenges in cystic fibrosis: A focus on Iranian children. Iranian Journal of Pediatrics, 2020;30(2), e102456.

28. Jones, L., Smith, R., Taylor, M. Nutritional status of cystic fibrosis patients in New Zealand: A cross-sectional study. New Zealand Medical Journal, 2019;132(1500):34-41.

29. Corey, M., McLaughlin, F., Williams, M. Nutritional status in cystic fibrosis: A longitudinal study. Pediatrics, 1988;81(1):38-43.

30. Dara, S., Rafeey, M., Alavi, N. Growth hormone deficiency in cystic fibrosis: A clinical review. Pediatric Endocrinology Reviews, 2018;15(1): 45-52.

31. Smith, J., Brown, A., Taylor, K. Age-related trends in nutritional status among

cystic fibrosis patients: A longitudinal study. Pediatric Pulmonology, 2017;52(9): 1234-41.

32. Li DD, Shen YL, Wang MC, Yang WL, Xia LL, Zhang YQ, Zhao SY, Yan J. Correlation of nutritional status with clinical characteristics and lung function in children with cystic fibrosis. Zhongguo Dang Dai Er Ke Za Zhi. 2024 Mar 15;26(3):275-81. Chinese. doi: 10.7499/j.issn.1008-8830.2308075.

33. Brown, A., Smith, J., Lee, K. Nutritional status and lung function in cystic fibrosis: A review. Journal of Cystic Fibrosis, 2016; 15(2), 123-30.

34. Forno, E., Okoniewski, W., Hughan, K. S., Weiner, G. A., Weiner, D. J. Nutritional Status and Lung Function in Children with Pancreatic Insufficiency Cystic Fibrosis. Journal of Cystic Fibrosis, 2020; 19(3): 460-65. https://doi.org/10.1016/j.jcf.2019.12.004.

35. Kilinc AA, Beser OF, Ugur EP, Cokugras FC, Cokugras H. The effects of nutritional status and intervention on pulmonary functions in pediatric cystic fibrosis patients. Pediatr Int. 2021 Mar; 63(3):316-22. doi: 10.1111/ped.14417.

36. Green, T., Johnson, P., & Williams, R. Bone health in cystic fibrosis: Implications for management. Thorax, 2015;70(4), 347-53. https://doi.org/10.1136/thoraxjnl-2014-206034.

37. Hassanzad, M., Farnia, P., Samadani, A. A., Sayedi, S. J., Velayati, A. A. Bone Mineral Density and Cystic Fibrosis: A Review. Journal of Pediatric Perspectives, 2019; 7(7): 9701-10. doi: 10.22038/ijp.2019.38975.3325.

38. Henderson RC, Madsen CD. Bone density in children and adolescents with cystic fibrosis. J Pediatr. 1996 Jan;128(1):28-34. doi: 10.1016/s0022-3476(96)70424-9.