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Original Article

Relation of Serum IGF-1 and IGFBP-3 Levels with Acute Exacerbation in Cystic Fibrosis

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ABSTRACT

Aim: Cystic fibrosis (CF) is an autosomal recessive genetic disorder primarily affecting the lungs and it is a leading cause of morbidity and mortality. Progressive lung disease and acute pulmonary exacerbations (PEx) are significant contributors to poor patient outcomes. Early detection and management of PEx are critical in improving prognosis. Biomarkers have gained interest due to their role in diagnosing, monitoring, and evaluating treatment responses in PEx. This study investigated fluctuations in serum levels of insulin-like growth factor-1 (IGF-1) and its IGF binding protein-3 (IGFBP-3) during CF exacerbations in order to assess their potential as clinical biomarkers.

Materials and Methods: A total of 37 CF patients (16 females, 21 males, mean age 96.95±62.56 months), hospitalized for PEx and receiving intravenous antibiotic treatment, were included. Serum levels of IGF-1 and IGFBP-3 were measured at baseline, at the onset of exacerbation, and at the end of the exacerbation. Additionally, for 16 of the patients, serum levels were reassessed one month post-treatment. Forced expiratory volume (FEV1) measurements were performed for those patients who were able to complete the spirometry test.

Results: At baseline, serum IGF-1 and IGFBP-3 levels were significantly lower than those of the normal population ($p<0.001$). Marked decreases in IGF-1 and IGFBP-3 levels were observed at the onset of exacerbation compared to the baseline ($p<0.05$). These levels increased significantly following treatment at the end of the exacerbation ($p<0.05$), although no significant difference was found between the baseline and post-treatment levels. FEV1 values also showed significant differences between the baseline and exacerbation periods ($p<0.05$).

Conclusion: Serum levels of IGF-1 and IGFBP-3 in the CF patients were lower than in healthy age-matched controls, with significant fluctuations corresponding to the progression and treatment of acute exacerbations. These fluctuations offer valuable insight into the diagnosis and monitoring of treatment response. Therefore, IGF-1 and IGFBP-3 levels are potentially useful biomarkers for the clinical management of CF exacerbations.

Keywords: Cystic fibrosis, acute pulmonary exacerbation, IGF-1, IGFBP-3, biomarker

Introduction

Cystic fibrosis (CF) is a genetic disorder caused by *CFTR* gene mutations, leading to impaired chloride ion transport and thickened mucus secretions. While it affects multiple organs, the lungs are the most impacted. Its pathophysiology involves chronic inflammation, recurrent infections, and progressive lung damage, often resulting in respiratory failure (1).

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Pulmonary involvement in CF is a major factor in morbidity and mortality. Acute pulmonary exacerbations (PEx), marked by a sudden worsening of respiratory symptoms, are a significant complication. Often triggered by infections, PEx accelerates lung function decline and causes long-term damage. Early diagnosis and effective management are vital for improving outcomes (2).

The treatment of PEx includes pharmacological options such as antibiotics and anti-inflammatory agents, alongside non-pharmacological methods such as chest physiotherapy. While clinical assessment, respiratory function tests, and imaging are standard for evaluating exacerbations, interest is growing in biomarkers to detect onset, assess severity, and monitor treatment response. Numerous inflammatory and immune-related biomarkers have been studied for their potential roles in managing acute exacerbations (3,4).

Insulin-like growth factor-1 (IGF-1) and its IGF binding protein-3 (IGFBP-3) are potential markers for disease severity and treatment response in CF. CF patients generally have lower serum IGF-1 and IGFBP-3 levels, likely due to nutritional deficiencies and systemic inflammation. Studies indicate that their levels vary during acute exacerbations, reflecting inflammation severity and treatment effectiveness (5-7).

This study investigated the relationships between serum IGF-1 and IGFBP-3 levels and PEx in CF patients. By analyzing their fluctuations during exacerbations and treatment, we aimed to assess their role in diagnosing and monitoring therapy responses.

Materials and Methods

Between January 2016 and June 2017, 37 CF patients aged 0-18 years, followed by the Department of Pediatric Pulmonology, Marmara University Faculty of Medicine, were prospectively included in this study. The participants, hospitalized for PEx and treated with intravenous (IV) antibiotics, were enrolled after obtaining informed consent from their legal guardians. Ethics approval was obtained from the Marmara University Faculty of Medicine, Clinical Research Ethics Committee (date: 06/11/2015, approval no.: 09.2015.291).

As there are no universally accepted criteria for diagnosing CF-related PEx, the diagnoses were based on clinical symptoms and signs. Only hospitalized patients requiring IV antibiotic therapy were included, and those patients treated on an outpatient basis were excluded from this study. Patients without legal guardian consent were excluded. Patients without blood samples at baseline, exacerbation onset, or end of exacerbation, as well as those who withdrew or had baseline samples but no PEx episodes, were also excluded. Serum IGF-1 and IGFBP-3 levels were measured at four-time points: Baseline, exacerbation onset, exacerbation end, and post-treatment. Blood for baseline samples was taken from patients without any active lung infection or recent PEx. Blood samples for exacerbation onset were collected upon hospitalization, and for exacerbation end, on the discharge day after treatment. A total of 37 patients meeting the criteria were included in this study. During the post-treatment follow-up, 21 patients missed their hospital appointments, preventing blood sample collection. Consequently, 37 patients were evaluated over three periods, while 16 patients with follow-up samples were separately assessed across four periods.

For each period, 5 mL of blood was collected in serum separation tubes, centrifuged at 4,000 rpm for 5 minutes, and the serum was stored at -80 °C. IGF-1 and IGFBP-3 levels were measured using the chemiluminescence method on an "immulite 2000" device at the Central Biochemistry Laboratory of Marmara University Faculty of Medicine, Pendik Training and Research Hospital.

Patient data included age at CF diagnosis, age during PEx, gender, height-for-age, weight-for-age, and body mass index (BMI)-for-age z-scores. Spirometry tests were evaluated for those patients capable of performing this procedure.

Statistical Analysis

Data recording and analysis were performed using "SPSS 20." Descriptive statistics, such as mean, standard deviation, median, frequency, percentage, range, and percentiles (25^{th}, 50^{th}, 75^{th}), were calculated. The Friedman test was used to compare serum IGF-1, IGFBP-3, and FEV1 levels across the baseline, exacerbation onset, end, and post-treatment periods, with $p<0.05$ considered statistically significant. The Wilcoxon test was used to compare the four periods, and p-values were adjusted with the Bonferroni correction. Spearman's correlation coefficients were used to analyze the relationships between serum IGF-1, IGFBP-3, and FEV1. For all tests, except those with Bonferroni correction, $p<0.05$ was considered statistically significant.

Results

This study included 37 CF patients [16 females (43.2%) and 21 males (56.8%)] hospitalized for PEx and treated with antibiotics at the Department of Pediatric Pulmonology, Marmara University Faculty of Medicine.

The mean, standard deviation, median, minimum, maximum, and percentile values for the patients' ages, ages at diagnosis, height-for-age z-scores, weight-for-age z-scores, and BMI-for-age z-scores are presented in Table I. For serum IGF-1 and IGFBP-3 values, which were not normally distributed, descriptive statistics including mean, standard deviation, median, and interquartile range were calculated for the four clinical periods, and these are presented in Table II. Figures 1 and 2 present the minimum, maximum, median, 25th, and 50th percentiles of the IGF-1 and IGFBP-3 levels for three periods as boxplots.

During the serum IGF-1 and IGFBP-3 measurement periods, FEV1% values were recorded for the 20 patients (54.1%) who were able to perform spirometry. In the follow-up period, 9 out of 16 patients were able to perform spirometry (Table II).

The serum IGF-1 and IGFBP-3 levels of 37 patients were compared across baseline, onset of exacerbation, and end of exacerbation, revealing statistically significant differences between periods ($p<0.001$). Pairwise comparisons of the three periods using the Wilcoxon test (Bonferroni correction applied, $p<0.017$) revealed significant differences between

Table I. Descriptive data for age, age at diagnosis, and age-adjusted height, weight, and BMI Z-scores

		Age (months)	Age at diagnosis (months)	Height-for-age Z-score	Weight-for-age Z-score	BMI-for-age Z-score
n		37	37	37	37	37
Mean		96.95	22.35	-0.88	-0.96	-0.71
SD (±)		62.56	47.91	0,93	1.35	1.47
Median		96	3	-1.03	-0.98	-0.78
IQR		95	5	1.21	2.06	2.27
Minimum		2	1	-3.51	-3.54	-3.94
Maximum		207	187	1.14	2.03	1.86
Percentile	**25th**	45	2	-1.42	-2.02	-1.82
	50th	96	3	-1.03	-0.98	-0.78
	75th	139.5	7	-0.20	0.04	0.45

SD: Standard deviation, IQR: Interquartile range, BMI: Body mass index

Table II. Distribution of serum IGF-1, IGFBP-3 levels, and FEV1 measurements across different clinical periods

		n (%)	Mean ± SD	Median (IQR)
IGF-1	Baseline	37 (100)	128.28±89.54	101 (81.20)
	Onset of exacerbation	37 (100)	98.91±76.16	76.40 (62.70)
	End of exacerbation	37 (100)	139±87.52	109 (99.80)
	Post-treatment control	16 (43.2)	125.15±94.10	75.30 (133.53)
IGFBP-3	Baseline	37 (100)	3.49±1.37	3.17 (2.11)
	Onset of exacerbation	37 (100)	2.93±1.51	2.65 (1.51)
	End of exacerbation	37 (100)	3.90±1.52	3.55 (2.53)
	Post-treatment control	16 (43.2)	3.39±1.61	2.73 (2.80)
FEV1	Baseline	20 (54.1)	78.7±21.98	82 (30.5)
	Onset of exacerbation	20 (54.1)	59.5±15.73	59.5 (27.25)
	End of exacerbation	20 (54.1)	74.5±20.34	74 (28.25)
	Post-treatment control	9 (24.3)	76±19.33	82 (32.5)

Serum IGF-1 unit is ng/mL, IGFBP-3 unit is µg/mL and FEV1 values are given as percentages (%)
IGF-1: Insulin-like growth factor-1, IGFBP-3: Insulin-like growth factor binding protein-3, FEV1: Forced expiratory volume, IQR: Interquartile range, SD: Standard deviation

the baseline and exacerbation onset (p<0.001 for IGF-1, and p=0.001 for IGFBP-3). The differences between onset of exacerbation and end of exacerbation values were also found to be significant (p<0.001). When comparing changes between the baseline and post-treatment periods, no statistically significant differences were found (p=0.216 for IGF-1, and p=0.032 for IGFBP-3) (Table II).

In the post-treatment follow-up, the serum IGF-1 and IGFBP-3 levels of 16 patients were compared across the baseline, onset of exacerbation, end of exacerbation, and follow-up periods using the Friedman test, revealing statistically significant differences (p<0.001 for IGF-1, and p=0.002 for IGFBP-3). Pairwise comparisons using the Wilcoxon test (Bonferroni correction, p=0.008) showed no significant differences in serum IGF-1 and IGFBP-3 levels between the baseline and post-treatment periods (IGF-1: p=0.642, and IGFBP-3: p=0.938). The comparison between the onset of exacerbation and post-treatment periods showed significant differences (p=0.004 for IGF-1 and IGFBP-3), while no significant difference was observed between the exacerbation end and post-treatment periods (p=0.278 for IGF-1, and p=0.66 for IGFBP-3).

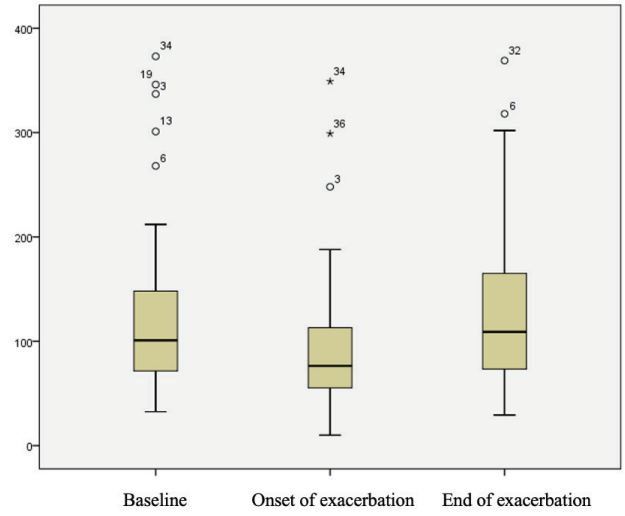

Figure 1. Serum IGF-1 levels at baseline, onset of exacerbation, and end of exacerbation
[x-axis: clinical periods; y-axis: IGF-1 levels (ng/mL)]
IGF-1: Insulin-like growth factor-1

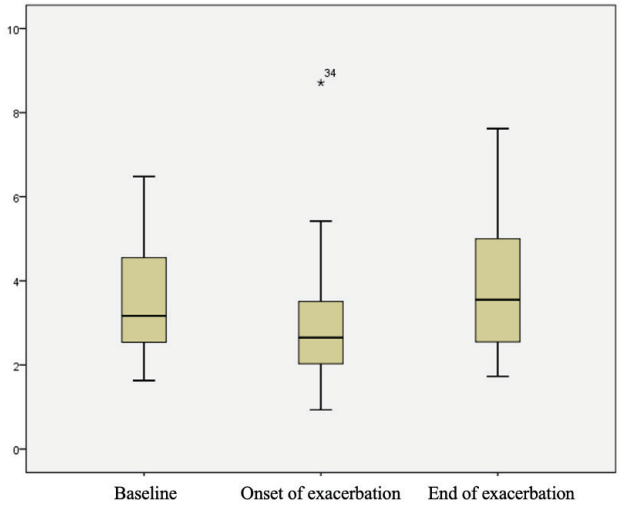

Figure 2. Serum IGFBP-3 levels at baseline, onset of exacerbation, and end of exacerbation
[x-axis: clinical periods; y-axis: IGFBP-3 levels (µg/mL)]
IGFBP-3: Insulin-like growth factor binding protein-3

After comparing IGF-1 and IGFBP-3 levels across the periods, the Spearman's correlation test revealed a significant correlation between IGF-1 and IGFBP-3 levels in all four periods (p<0.001).

The median, interquartile range, mean, and standard deviation of the FEV1 measurements, as shown in Table II, were calculated for the baseline, onset of exacerbation, and end of exacerbation, and Friedman analysis indicated statistically significant differences across these periods (p<0.001).

Significant differences were found in IGF-1, IGFBP-3, and FEV1 values across the periods. IGF-1 and IGFBP-3 levels measured alongside FEV1 were analyzed using Spearman's correlation test, which showed no significant correlation between IGF-1, IGFBP-3, and FEV1 values in any of the four periods.

Discussion

There is no consensus protocol for diagnosing CF-related PEx, and so its diagnosis is often made through clinical assessment. Despite treatment, exacerbations can lead to permanent losses in lung function. This suggests that the current diagnostic and treatment approaches may be insufficient. Therefore, there has been significant research into biomarkers (commonly tested in blood, sputum, or exhaled air) which could help predict, assess severity, evaluate treatment response, and anticipate those conditions which may develop during the post-exacerbation period (3,4,8).

In a review by Shoki et al. (9) it was stated that any biomarkers used in PEx should be clinically applicable, contribute to routine clinical assessments, and provide meaningful information to evaluate treatment efficacy. Additionally, biomarkers should be able to show the current exacerbation status and severity, be easily obtainable from patients, and be suitable to undergo practical laboratory analyses.

Shoki et al. (9), Scott and Toner (10), and Gray et al. (11), highlighted that no clinically applicable biomarker for PEx has been identified to date. Research on biomarkers such as C-reactive protein (CRP), interleukin (IL) 6, IL-8, IL-10, erythrocyte sedimentation rate, tumour necrosis factor alpha, calprotectin, IL-1ra, and lactoferrin reveal that serum CRP levels decrease after treatment, aiding in assessing treatment response. Additionally, serum calprotectin levels at treatment completion can predict the timing of the next exacerbation. A recent study has suggested that the short palate, lung, and nasal epithelium clone 1protein could be a potential biomarker for PEx (12).

In addition, studies have investigated the relationships between IGF-1 and IGFBP-3 with CF and PEx, indicating that CF patients exhibit lower serum levels of these markers, which may be related to growth impairment (5,6). Rogan et al. (13) found that both human and pig CF neonates had lower serum IGF-1 levels than normal. Consistent with this data, the patients included in our study had significantly lower IGF-1 and IGFBP-3 levels compared to the normal population (14).

The IGF-1 and IGFBP-3 levels of our patients were reviewed in relation to their PEx status. IGF-1 is linked to inflammatory and immune responses. Ashare et al. (15) found that reduced IGF-1 levels during sepsis impair bacterial clearance, highlighting its critical role in infection management. Andreassen et al. (16) found a significant correlation between IGF-1 and CRP, highlighting that inflammation suppresses IGF-1 production. Gifford et al. (7) studied IGF-1 changes during PEx in 12 CF patients aged 18 or over. They found that baseline IGF-1 deficiency worsened at PEx onset but improved after treatment. Higher IGF-1 levels were linked to better health in CF patients.

In our study, baseline serum IGF-1 and IGFBP-3 levels showed a statistically significant decrease at the onset of PEx, which is associated with high inflammation ($p<0.001$). IGF-1 levels, with a mean value of 128.28 ng/mL at baseline, decreased by 22.8% to 98.91 ng/mL at the onset of exacerbation. Similarly, IGFBP-3 levels, with a mean value of 3.49 µg/mL at baseline, decreased by 16% to 2.93 µg/mL at the onset of exacerbation.

When the values obtained on the day PEx treatment was completed were compared with the values at the onset of exacerbation, a statistically significant increase was found ($p<0.001$). The average IGF-1 level increased by 28.8%, reaching 139 ng/mL, compared to the values at the onset of exacerbation. Likewise, the average IGFBP-3 level increased by 24.8%, reaching 3.90 µg/mL compared to the onset of exacerbation.

No statistically significant difference was found between baseline and end of exacerbation levels for IGF-1 and IGFBP-3 ($p>0.05$). Although no significant difference was observed, the average and median values of both IGF-1 and IGFBP-3 exceeded the baseline values following treatment, which is noteworthy.

Our study confirmed that there is a decrease in IGF-1 and IGFBP-3 levels during PEx, and these levels rise again after treatment.

In the group of 16 patients from whom post-treatment check-up blood samples were obtained, the analysis showed that the IGF-1 and IGFBP-3 levels in the post-treatment follow-up period were statistically similar to the baseline and end of exacerbation levels ($p>0.05$). Although no significant difference was found, the highest IGF-1 and IGFBP-3 levels in this group were recorded at the end of exacerbation (141.80 ng/mL and 3.81 µg/mL, respectively). IGF-1 and IGFBP-3 levels, which peaked after treatment, showed a slight decrease during the one-month period following discharge; however, this decrease was not statistically significant.

When looking at the percentage changes in IGF-1 and IGFBP-3, it was observed that the change in IGF-1 was higher than that of IGFBP-3. However, it was also shown that IGF-1 and IGFBP-3 levels correlated with each other across the four different clinical periods.

Study Limitations

The FEV1 measurements in our patients showed a 24.3% decrease in their average value at the onset of exacerbation when compared to the baseline period. At the end of exacerbation, with treatment, the average value showed a 20% increase. These observed decreases and increases were statistically significant.

Although it was shown that IGF-1, IGFBP-3, and FEV1 decreased with the onset of exacerbation compared to the baseline and then increased with treatment, the correlation tests revealed that IGF-1 and IGFBP-3 did not show a correlation with FEV1.

Conclusion

Our findings suggest that serum IGF-1 and IGFBP-3 levels are valuable in diagnosing exacerbations and assessing treatment responses. These markers, requiring only small blood samples and being easier to handle in laboratories compared to many other biomarkers, show promise for use during PEx in CF patients. Further clinical studies are needed in order to explore this in greater depth.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the Marmara University Faculty of Medicine, Clinical Research Ethics Committee (date: 06/11/2015, approval no.: 09.2015.291).

Informed Consent: They were included in the study after obtaining informed consent from their legal guardians.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.F.E., Concept: A.F.E., E.E.E., Y.G., A.P.E., S.T., A.B., B.K., Design: A.F.E., E.E.E., Y.G., A.P.E., S.T., N.P.A., A.B., B.K., Data Collection or Processing: A.F.E., E.E.E., Y.G., A.P.E., A.B., B.K., Analysis or Interpretation: A.F.E., E.E.E., Y.G., A.P.E., S.T., N.P.A., A.B., B.K., Literature Search: A.F.E., B.K., Writing: A.F.E., B.K.

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