SERUM IGF-1 DURING CYSTIC FIBROSIS PULMONARY EXACERBATION: TRENDS AND BIOMARKER CORRELATIONS

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Background

Insulin-like growth factor-1 (IGF-1) is an anabolic hormone that reduces protein catabolism, restricts gluconeogenesis and ketogenesis, and stimulates tissue glucose utilization (1). Abundant clinical investigation, mostly in children, has shown that serum IGF-1 concentrations are abnormally low in cystic fibrosis (CF) and that low levels are associated with impaired growth (2). IGF-1 deficiency appears to be an innate feature of CF given that circulating levels are significantly reduced at birth (3). Bloodstream levels of IGF-1 and its binding protein, IGFBP-3, increase significantly after intravenous antibiotics and enteral nutritional support (3), raising the possibility that IGF-1 is a biomarker for pulmonary exacerbation onset and treatment response. Herein, we report trends in IGF-1 during this clinical context and associations with other biomarkers.

1) Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev* 1995; 16: 3-34.
2) Laursen EM *et al*. Diminished concentrations of insulin-like growth factor-1 in cystic fibrosis. *Arch Dis Child* 1995; 72: 494-97.
3) Rogan MP *et al*. Pigs and humans with cystic fibrosis have reduced insulin-like growth factor-1 (IGF-1) levels at birth. *PNAS* 2010; 107: 20571-75.
4) Lebl J et al. Insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 in cystic fibrosis: a positive effect of antibiotic therapy and hyperalimentation. *Acta Pædiatr* 2001; 90: 868-72.

Definitions and Methods

- Single-center study of 12 hospitalized adult CF patients
- CF pulmonary exacerbation (CFPE) was defined by an attending pulmonologist as new or acutely worsened sinopulmonary and/or constitutional signs and symptoms for a given patient – increased frequency of cough and/or sputum production, wheezing, shortness of breath, fevers, chills, sweating, anorexia, or weight loss.
- Phlebotomy occurred ≤24 hours after CFPE determination (early CFPE) and ≤24 hours before treatment completion (late CFPE). Serum was available from 8 patients during a period of clinical stability that preceded CFPE (baseline).
- 8 healthy control subjects provided serum for analysis.
- Serum IGF-1 was quantified by a commercially-available ELISA (R&D Systems, Minneapolis, MN).

Patient Characteristics

Number of Patients (*N*)	12
Age (years)	32 ± 11
Male / female (*N*)	9 / 3
FEV_1 (% predicted)	34 ± 14
Weight (kg)	54.3 ± 11.9

Table 1. Clinical attributes of 12 adult CF patients who were hospitalized for CFPE treatment. Data were obtained during early CFPE and are presented as mean ± standard deviation.

Serum IGF-1: Baseline CF vs. Controls

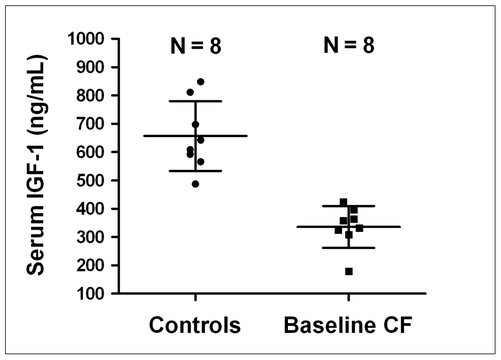

Figure 1. Comparison of serum IGF-1 concentrations between healthy controls and CF patients who subsequently experienced CFPE. The mean difference in [IGF-1] was 320.8 ± 50.7 ng/ml (95% CI of mean difference = 212.0 to 429.7). P-value for comparison by unpaired t-test <0.0001. Lines denote mean and SD.

Serum IGF-1: Baseline vs. Early CFPE

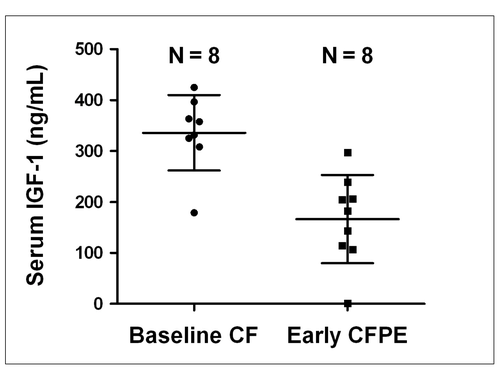

Figure 2. Comparison of serum IGF-1 concentrations between baseline health status and early CFPE. In 8 patients, the mean serum IGF-1 level fell by 174.4 ng/ml (95% CI of mean difference = 102.4 to 246.5). P-value for comparison by paired t-test = 0.0007. Lines denote mean and SD.

Serum IGF-1: Early vs. Late CFPE

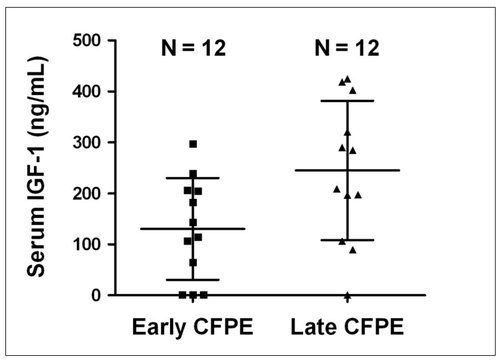

Figure 3. Comparison of serum IGF-1 concentrations between early and late CFPE. In 12 patients, the mean serum IGF-1 level increased by 114.7 ng/ml (95% CI of mean difference = 55.6 to 173.7). P-value for comparison by paired t-test = 0.001. Lines denote mean and SD.

Serum IGF-1: Correlations

Parameter	*N* = 12	Early CFPE	Late CFPE
FEV_1 (% predicted)	Spearman rho	0.67	0.78
	P-value	0.02	0.003
Serum iron (mcg/dl)	Spearman rho	0.82	0.84
	P-value	0.001	<0.001
Transferrin saturation (%)	Spearman rho	0.76	0.91
	P-value	0.004	<0.001
Hemoglobin (gm/dl)	Spearman rho	0.75	0.69
	P-value	0.005	0.013
A1AT (mg/dl)	Spearman rho	-0.66	-0.71
	P-value	0.02	0.009

Table 2. Spearman correlation coefficients (rho) describing the relationships among serum IGF-1 concentration and other variables at early and late CFPE. Negative values for rho signify indirect relationships. A1AT = alpha-1-antitrypsin

Conclusions

- Serum IGF-1 is distinctively low in adult CF patients.
- Reduction in serum IGF-1 is a feature of CFPE onset.
- Serum IGF-1 improves significantly after CFPE treatment.
- Serum IGF-1 and FEV_1% are directly related during CFPE.
- Throughout the exacerbation cycle, serum IGF-1 and iron-related hematologic biomarkers are directly related.
- Serum IGF-1 and A1AT levels are indirectly related in CF.