ASSESSMENT OF SERUM INSULIN LIKE GROWTH FACTOR -1 IN EGYPTIAN CYSTIC FIBROSIS PATIENTS

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ABSTRACT

Background: Cystic fibrosis is one of the most common autosomal recessive mutation in cystic fibrosis transmembrane conductance regulator (CFTR)gene. Like most chronic inflammatory diseases in childhood, CF is associated with impaired growth. The growth hormone insulin-like growth factor (GH-IGF) axis is the most important endocrine axis involved in linear growth in children and adolescents. **Aim:** To study serum IGF-1 level in cystic fibrosis patients in stable state and in exacerbation and to correlate its level with body mass index of the patients. **Methods:** This study was conducted on 60 CF patients and 30 healthy age and sex matched children as control group. Anthropometric measurements including height, weight and BMI were recorded, Serum IGF-1 level was performed by using Enzyme Linked Immuno Sorbent Assay (ELISA) technique, complete blood picture and C-reactive protein were done. **Results:** Our results showed that IGF-1 levels were statistically lower in cases compared to control (p value < 0.01), also IGF-1 levels were significantly lower in exacerbation compared to stable state (p value <0.01) but there was no correlation between IGF-1 and BMI, weight, height and age of the patients. **Conclusion:** Serum IGF-1 level was noted to be lower in CF cases and especially in CF cases in exacerbation and a significant relation was found between it and the haemoglobin and inflammatory status in CF patients.

Keywords: cystic fibrosis, insulin like growth factor -1, BMI.

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INTRODUCTION

Cystic fibrosis (CF) is an inherited multisystem disorder of children and adults; it is one of the most common autosomal recessive disorders **(Bradely and steven ,2016),** caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator Protein (CFTR) **(waters, 2012)**.

Dysfunction of the CFTR leads to a wide and variable array of presenting manifestations and complications. CF is responsible for most cases of exocrine pancreatic insufficiency in early life and is the major cause of severe chronic lung disease in children. It is also responsible for many cases of hyponatremic salt depletion, nasal polyposis, pansinusitis, rectal prolapse, pancreatitis, cholelithiasis and nonautoimmune insulin-dependent hyperglycemia. **(Kliegman et al., 2015)**.

Like most chronic inflammatory diseases in childhood, CF is associated with impaired growth. **(Cirillo F et al.,2017) (Bozzola E et al.,2012) (Pagani S et al.,2018).** The exact mechanisms of this effect are not known, although it is generally thought to be caused by concomitant severe disease complications due to the inflammation itself, as well as prolonged use of glucocorticoids and suboptimal nutrition. **(Wong SC et al., 2016).**

Poor nutrition is one of the important agents in CF patients that is accompanied with bad pulmonary condition and reduced long-term lung function and poor survival**. (Wong SC et al., 2016).**

Insulin-like growth factor I is an important circulating anabolic hormone promoting protein metabolism and inhibiting protein degradation (**Thissen et al., 1994).** It plays a critical role in myoblast proliferation and differentiation **(Singleton et al., 2001).**

In children with CF, growth impairment may be associated with abnormally low IGF-I concentrations. In fact, IGF-I signaling is mediated by CFTR, and consequently CFTR dysfunction may impact linear growth, adding to indirect effects due to malnutrition. **(Stalvey MS et al.,2017**) **(Gifford AH et al.,2014)**.Furthermore, IGF-I plays an important role in inflammation and, in turn, is related to lung function and nutritional status in CF.

PATIENTS AND METHODS

Patient population

This was a cross sectional study that included 60 cystic fibrosis cases (41 in stable state and 19 in exacerbation) diagnosed on basis of a known CF genotype and/or positive sweat chloride test >60 mmol/l. All patients were recruited from CF clinic of Specialized Children Hospital, Cairo University, along with 30 age and sex matched healthy control group, through the period starting from 1ST of November 2017 to 30th of May 2019.All patients

were enrolled after obtaining an informed consent from parent/ guardian.

Inclusion criteria were diagnosed CF cases during both stable and exacerbation state, from age of 2 months to 12 years. Exclusion criteria were patients suffering from any other systemic disease affecting growth.

Study Methods

Patients were evaluated clinico-laboratory by full history of age, sex, and consanguinity. respiratory system affection: chronic cough, recurrent pneumonia, hemoptysis and chronic wheezing. History of gastrointestinal system affection: steatorrhea and meconium ileus Family history of similar cases in the family. Anthropometric measurements: weight, height and body mass index (BMI). General examination of pallor, cyanosis and clubbing with special emphasis on respiratory system examination. Acute exacerbation was defined when there was increased cough or sputum production, dyspnea, fever, weight loss, decreased exercise tolerance, and absenteeism from school due to illness as well as new clinical findings, including tachypnea, retractions, wheezes and new crackles. All laboratory workups were done on the central lab of the Cairo university of children hospital: **CBC with differential** done on Sysmex Xs according to manufacture's instructions. **C-reactive protein (CRP)** done on Au 480 according to manufacture's instructions. **Insulin like growth factor-1 (IGF-1)** in the samples was detected by Enzyme Linked Immuno Sorbent Assay (ELISA) technique.

STATISTICAL ANALYSIS

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data was summarized using median, 1st quartile and 3rd quartile in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparing categorical data, Chi square (x2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlations between quantitative variables were done using Spearman correlation coefficient. ROC curve was constructed with area under curve analysis performed to detect best cut off value of IGF-1 for detection of cystic fibrosis. P-values less than 0.05 were considered as statistically significant.

RESULTS

In our study, the median age of the studied patients was 5.3 years ranged from 5 months to 12 years,56.7% of the studied patients were males while 43.3% were females.

The weight of patients ranged between 3.7 and 36 kg with median 15 kg, their height ranged between 52 and 133 cm with median 101 cm with BMI ranged between 10 to 24kg/m^2 with median 14.5kg/m^2. Thirty- six (60%) of the patients were < 3rd percentile for weight and height. Fifty-three (90%) of the patients had a low BMI (< 18.5 kg/m2) with statistically significant low weight and BMI in cases compared to control (P value < 0.001) while height showed no statistical difference between both.

51.7 % of patients were of positive consanguinity, and 23.3% had sibling affection in the family.

Regarding the clinical manifestations presented in our cases,95% of the CF patients had cough, 86% had wheezes, 16.7% had sinusitis, 20% of cases admitted in hospital in 2018, 93.3% of cases were failure to thrive (FTT), 28.3% had steatorrhea, 1.7% had meconium ileus, 91.7% had pallor and 56.7% had clubbing.

On comparing the laboratory data between cases and the control group, a statistically significant low IGF-1 and Hb level with increased TLC (leucocytosis) and raised staff : segmented ratio were found in CF cases than control group. Shown in table 1.

Table 1: Laboratory data of the studied groups

variable	Cases (n=60) Median (range)	Control (n=30) Median(range)	P value
IGF-1(ng\ml)	0.78 (0.24-2.83)	2.72 (0.80-3.44)	< 0.001
HB (g/dl) hemoglobin	10.5 (8-13)	12.55 (11-14.8)	<0.001
TLC (cmm) Total leucocytic count	9.55 (4-20)	6.53 (4.4-9)	<0.001
Shift staff: segmented	0.06 (0.00-0.05)	0.02 (0.00-0.08)	<0.001
PLT (cmm) platelet	314 (137-546)	278 (208-390)	0.373

p value <0.05 is considered significant

And we noted that serum IGF-1 level was signifcantly higher in stable cases than cases in exacerbation, while TLC, staff: segmented ratio and CRP were significantly raised in cases in exacerbation. Shown in table 2.

Table 2: Comparison of laboratory data between stable cases and cases in exacerbation (n=60)

CBC	Stable n=41	Exacerbation n=19	P value
Serum IGF-1(ng\ml) Median (range)	1.09 (0.44-2.83)	0.43 (0.24-0.76)	<0.001
HB (g/dl) Median (range)	10.6 (8-12.8)	10 (8.3-13)	0.225
TLC (cmm) Median (range)	8 (4-13)	16 (14-20)	<0.001
Staff: segmented ratio Median (range)	0.05 (0.00-0.19)	0.29 (0.03 -0.5)	<0.001
PLT (cmm) Median (range)	314 (137-546)	280 (180-531)	0.357
Positive CRP	0 (0%)	19 (100%)	<0.001

p value < 0.05 is considered significant.

Serum IGF-1level showed a significant negative correlation with TLC, and CRP while a significant positive correlation was noted with HB level. Shown in fig 1,2 and 3. While no correlation was detected between serum IGF-1level and weight, height, or BMI of CF cases. Shown in table 3.

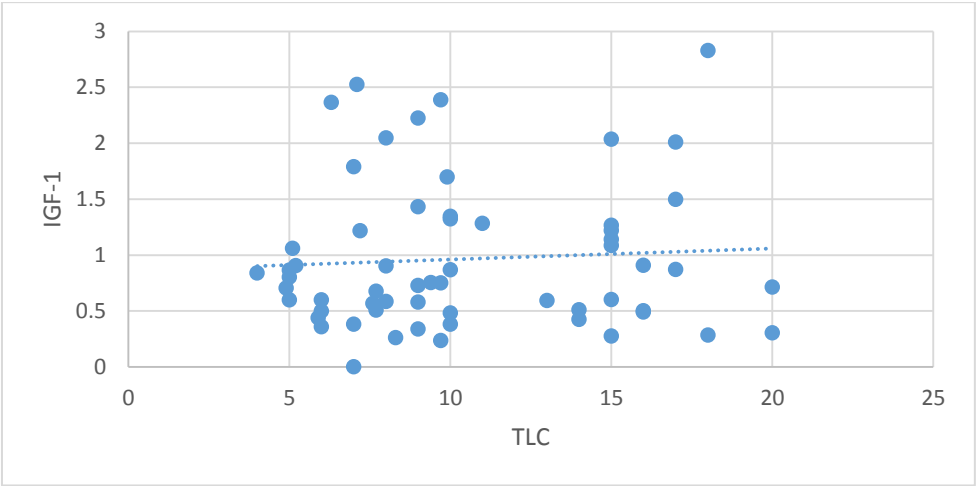

Figure 1: correlation of IGF-1 and TLC in CF patients

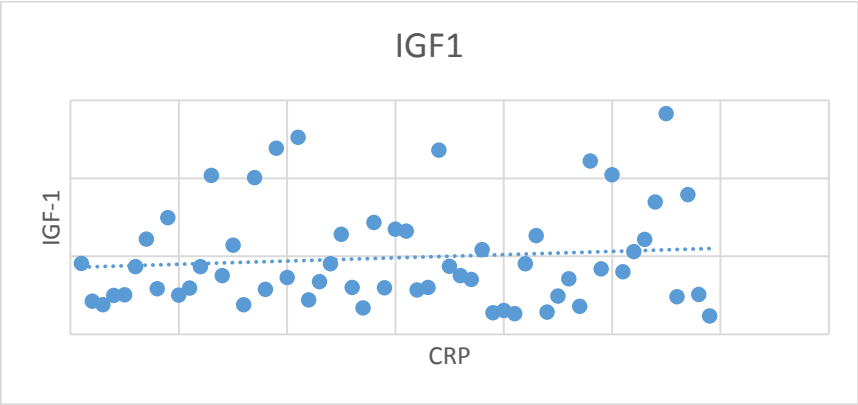

Figure 2: correlation between IGF-1 and CRP

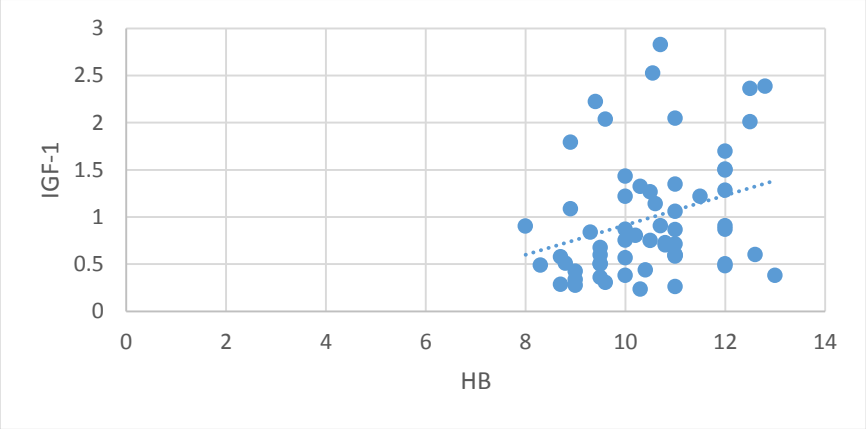

Figure 3: correlation of IGF-1 and HB in CF patients

Table 3: correlation between IGF-1 and other studied variables in cases:

Variable	P-value	R
Age	0.285	0.140
Weight	0.276	0.143
Height	0.613	0.067
BMI	0.480	0.093

r = correlation coefficient, p value≤ 0.05 is considered significant

DISCUSSION

Growth is a key indicator of health status in children with cystic fibrosis (CF) and is strongly linked with CF outcomes such as nutrition and pulmonary function **(Beker LT et al.,2001) (Yen EH et al.,2013).**

Poor Growth has been a main character in children with CF and this could be attributed to malabsorption, reduced caloric intake, increased resting energy expenditure, glucocorticoid exposure and systemic inflammation **(Le TN et al,2019).** In addition to indirect impact of CFTR genotype on nutritional status through the association with pancreatic exocrine function **(Kerem E et al,1990).** Whether there is a direct effect of CFTR on growth remains unknown.

Both altered GH metabolism and organ resistance to GH have been implicated as major contributors of growth retardation in CF subjects. **(Kyle UG et al,2015).**

In this study we aimed to detect the level of serum IGF-1 in CF cases either in stable or in exacerbation state and compare its level with healthy controls and to examine its relationship with nutritional status, BMI and hemoglobin level in CF patients.

Our study showed that 93.3% of our CF patients had failure to thrive, with 60% below 3rd percentile for weight and height and 90% had a low BMI (< 18.5 kg/m^2) compared to the control group.

Our findings of lower serum IGF-1level in CF cases than healthy controls, especially cases in exacerbation goes along with the assumption that CF is a state of IGF-1 insufficiency. **Rogan et al., 2010** discovered that mean IGF-1 level (~95 ng/ml) in 23 human newborns with CF was significantly lower than that (~110 ng/ml) of 41 healthy human newborns. **Pagani, et al., 2019** detected that at the second evaluation, significantly higher levels of IGF-I (*P*=0.003) were found in both the CF patients diagnosed through newborn screening (NBS) and late diagnosis (LD) groups compared to control group. In contrast to **Ozen et al., 2004** did not detect any difference in serum IGF-1 levels between 37 CF and 23 healthy pre-pubertal children.

Although no significant correlation was detected between serum IGF-1level and weight, height, or BMI of CF cases, but this could be attributed to different factors that affect growth in CF as malabsorption due to pancreatic insufficiency and severity of chest condition **Gifford et al., 2014** showed that although serum IGF-1 was significantly lower in CF cases than control, but it was not correlated with BMI at late CF pulmonary exacerbation. **Karami et al., 2019** evaluated 60 CF patients and detected that no correlation was observed between mean serum levels of GH, IGF1, and IGFBP3 with growth indices, such as weight, height, and BMI among CF children. In contrast to **Taylor et al., 1997**; and **Sermet et al., 2003** who reported a close correlation between the low level of serum IGF1and low BMI in patients with cystic fibrosis.

In this study serum IGF-1 level showed a significant correlation with other hematologic parameters having a direct correlation with low Hb level in cases. Using human fetal bone marrow, Hanley et al. 2005 found that IGF-1 has an anti-apoptotic effect on myeloid progenitor cells, implicating IGF-1 in the prevention of anemia.

Gifford, et al., 2014 found that serum IGF-1 values and parameters relevant to iron homeostasis, specifically, serum iron (p-value 0.006) and hemoglobin concentration (p-value 0.01) are significantly correlated.

This study also recorded an indirect correlation with increased TLC and raised acute phase reactant as CRP suggesting that inflammation suppresses IGF-1 production. In seventeen prepubertal CF patients **Street et al.,2009** concluded a relationship between inflammatory status and the IGF system and an effect of these interactions on longitudinal growth. **Andreassen et al., 2010** support the hypothesis of an inverse association between GH/IGF-I signaling and inflammation.

CONCLUSION

In Summary, serum IGF-1 level was noted to be lower in CF cases and especially in cases in exacerbation that supports that CF is a is a state of IGF-1 insufficiency. But we couldn't justify whether IGF-1 could be a biomarker of nutritional status and different growth indices like weight, height and BMI. At same time our data managed to find a relation between IGF-1level and hemoglobin and inflammatory status in CF patients.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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