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Growth factors in cystic fibrosis

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ABSTRACT

Introduction: Cystic fibrosis is one of the most common autosomal recessive diseases that affects sweat glands and mucosa. CF is a hereditary disease with annual incidence of about 2500 new cases in United Kingdom. Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 levels decrease in CF. The aim of this study was to assess the role of growth peptides in patients with CF.
Method: We searched PubMed, Google scholar, IranMedex, and Scientific Information Database (SID) in September 2012 to April 2014. We included clinical studies with available abstracts and full texts that were in English or Persian languages. Manual searching was conducted within the reference lists of articles. Two reviewers independently applied eligibility criteria, assessed quality, and extracted data.
Result: The earliest study was published in 1997 and the most recent one was in 2014. Study participants were adults in 3 studies (20%) and 12 studies (80%) were conducted in children. Patients with CF have lower levels of IGF-1 and there is a significant correlation between IGF-1 levels and growth index in patients with CF.
Conclusions: IGF-1 decreases in children with CF and might be the cause of poor growth and low body mass index in these children.

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Introduction

Cystic fibrosis (CF) is one of the most common autosomal recessive diseases that affects sweat glands and mucosa. It is a life-threatening condition which presents with malfunction of exocrine glands in various organs in childhood (1). Failure to thrive, meconium ileus, abdominal distention, intestinal obstruction, increased frequency of stool, jaundice, gastrointestinal bleeding, salty-tasting skin and delayed puberty are some signs and symptoms of CF (2). However, the main manifestation of the disease is chronic respiratory infections (3). Respiratory symptoms occur in about 90% of children survived after neonatal period. Respiratory failure is the main cause of children mortality.

CF is also known as mucoviscidosis that involves lungs, pancreas, liver, and intestine. Most patients are infertile (4).

CF occurs due to mutation in a protein called cystic fibrosis transmembrane conductance regulator (CFTR) gene. This protein acts as a chloride channel and its functional regulator is cyclic adenosine monophosphate (cAMP). CFTR mutations first were described in 1932 (4). Such mutations cause defect in chloride transport system in epithelial cells especially on mucosal surfaces. Reduction in chloride secretion leads to sodium and water reabsorption that decreases mucosal thickness and promotes bacterial overgrowth and invasion risk (5). High viscosity of pulmonary secretion results

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in difficulty clearing of small airway. Although the relation between CF and CFTR is clear, the cause of chronic inflammation and recurrent infection in this disease remains doubtful. Some studies revealed that alveolar macrophages could phagocytose bacteria, but enable to kill them in CF (2). Such impairment might be the cause of recurrent respiratory infections (6).

Insulin-like growth factor-1 (IGF-1) is a hormone with a similar structure to insulin and is produced by the liver. It has been considered that this peptide has a fundamental role in growth (7). IGF-1 has an antiapoptotic role. IGF-1 is associated with growth, development, and various metabolic actions. The body skeleton is the main target organ for IGF-1 deposition (8). IGF-1 is secreted by tissues and liver. The cortical bone size, bone growth, and bone mass are affected by IGF-1.

This hormone binds to one of six IGF-binding proteins. It is demonstrated that 80% of IGF-1 is attached to IGF binding protein-3 (IGFBP-3). Increasing the number and size of the alveolus is one of the probable effects of IGF-1 on lung growth. Studies showed that there was a relation between low level of IGF-1 and impaired macrophage function in CF patients. Other studies distinguished IGFBP-3 stimulation of fibroblasts to synthesize collagen and fibronectin (8-10). The aim of this study is to systematically review the articles about the relation between growth peptides and CF.

Methods

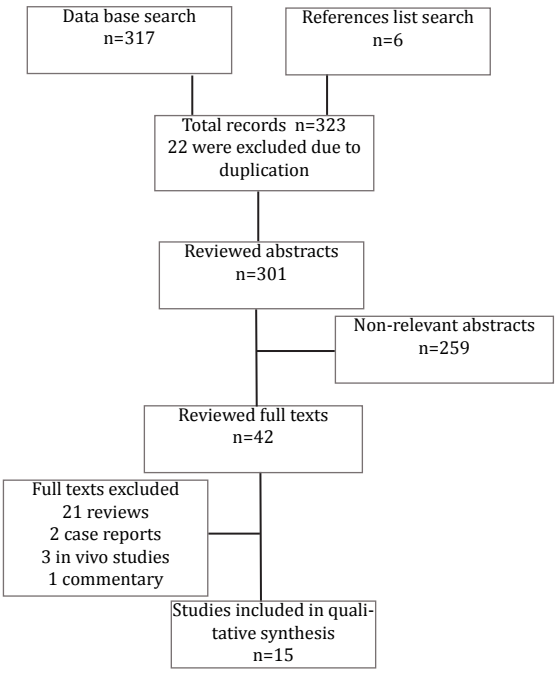
In this systematic review, we assessed all papers published in September 2012 to April 2014 about growth peptides and CF. Electronic databases were searched with a detailed search strategy to find relevant studies. We entered studies from PubMed, Google Scholar, IranMedex, and Scientific Information Database (SID) in 2012 to 2014. Search strategy was designed as follows: ("cystic fibrosis" OR CF) AND "growth factor" AND child. Retrieved articles were assessed to identify additional related articles from their reference lists. Possible duplicate publications were discussed and only the most recent studies were assessed. We included articles with available abstracts, full texts, and those in English or Persian languages. Exclusion criteria were in vivo or animal articles, article published in other languages (other than English and Persian), case reports, commentaries, and review articles. Finally, following CONSORT checklist (11), quality assessment was performed for each study.

Results

In the first step, abstracts were reviewed by two independent researchers. First search was started with 323 topics, 22 were withdrawn due to duplication, and 259 out of 301 reviewed abstracts were excluded due to no relevance to the topic. Full texts of remained articles were evaluated by the reviewers for more accurate selection if necessary.

We used a structural data extraction tool. However, meta-analysis was not performed due to heterogeneity in hormone and outcome measurements. Figure 1 shows the PRISMA flowchart of study selection.

Figure 1. Flowchart of selection of studies



The earliest study was published in 1997 and the most recent one was in 2014. Study participants were adults in 3 studies (%20) and 12 studies (%80) were conducted in childhood. Table 1 shows the general characteristics of the included studies. In terms of study sample size, two studies evaluated more than 100 patients and other studies (%86.6) assessed less than 100 patients. One study was a clinical trial and other were cohort studies.

IGF-1 enhances lean body mass in children and increases linear growth (7). Body mass index (BMI) was correlated with IGF-1 bioavailability (8). Serum concentration of IGF-1 decreases in children with CF and is associated with BMI (9). Combination of IGF-1 and BMI Z-scores may be useful for identifying children with CF who are at risk of impaired bone accretion (4). IGF-1 and IGFBP-3 are useful parameters in determination of growth retardation in children with CF. Some studies suggested that IGFBP-3 was more sensitive for growth monitoring (10). Others proposed that IGF-1 level could predict CF clinical outcome and respiratory function (11).

Table 1. Summary of the 15 studies included in the review

Author Reference	Year	Target population	Sample size Case/ control	Design	Final result
Taylor (1)	1999	Children	77	Cohort	[1]IGF-1 bioactivity was reduced and inversely related to [2]IGFBP-3
Schulze (4)	2006	Prepubertal children	18	Cohort	IGF-1 could identify children with CF at risk of bone growth disorders
Street (8)	2009	Prepubertal children	17	Retrospective cohort	Significant correlation between [3]BMI and IGF-1 bioavailability
Boguszewski (9)	2007	Children	26/33	Retrospective cohort	IGF-1 level decreased significantly in children with [4]CF
Ozen (10)	2004	Children	37/23	Cohort	Serum IGF-1 and IGFBP-3 levels can be considered as growth retardation index in CF
Gifford (12)	2014	Adult	123	Retrospective cohort	CF is associated with IGF-1 deficiency
Switzer (13)	2009	Children	27/25	Retrospective cohort	A significant correlation between IGF-1 levels and height
Schnabel (14)	2007	Children	42/21	Randomized clinical trial	Significant correlation between weight and height index and IGF-1 level
Gordon (15)	2006	Adult	32	Cohort	Significant correlation between IGF-1 and bone mineral content
Hardin (16)	2005	Prepubertal children	32	Cohort	IGF level decreased significantly in children with CF
Sermet-Gaudelus (17)	2003	Children	24	Cohort	Serum IGF-1 is associated with growth parameters and respiratory function in CF
Lebl (18)	2001	Children	92	Cohort	Significant correlation between IGF-1 levels and height
Laursen (19)	1999	Adult	20/20	Cohort	Reduction in IGF-I level indicating a relative GH resistance in CF patients
Dooghe (20)	1997	Children	23/13	Cohort	IGF-1 reduction correlated with the degree of growth failure
Taylor (21)	1997	Children	197	Cohort	Significant correlation between IGF-1 and IGFBP3 levels and body mass index in patients with CF

[1]IGF-1: Insulin-like growth factor-1; [2]IGFBP-3: Insulin-like growth factor binding protein-3; [3]BMI: Body mass index; [4]CF: Cystic fibrosis

It was revealed that insulin secretion abnormalities were presented in %65 of children with CF even if their glucose tolerance test was normal. Growth retardation is multifactorial in these children; impaired insulin secretion and impaired glucose tolerance are two passible causes of poor growth especially in puberty (12). Insulin insufficiency or resistance might be the cause of low IGF-1 level in CF, and a decrease in IGF1- bioactivity may result in poor growth in these children (1).

Growth hormone (GH) therapy might be useful in children with CF, have anabolic effect on total body protein, and bone accretion and can promote growth (13). IGF-1 treatment in a 6-month period showed no effect on linear growth, but an increased glucose/insulin ratio (insulin sensitivity) (14). Long-term studies are needed to identify GH and IGF-1 efficacy and side effects. Some studies showed that short-course antibiotic therapy, brief exercise, and hyperalimentation increase IGF1 and IGFBP-3 levels in CF patients and promote their clinical outcome (15,16). A study revealed isoenergetic exercise effects on IGF1- levels as an anabolic stimulus in patients who suffer from CF (17).

Discussion

CF is a hereditary disease with annual incidence of about 2500 new cases in United Kingdom (1). CF incidence is estimated about 1/2500 to 1/3900 in live births. CF heterozygote frequency in white population is higher (about 1 in 20). In family with 2 heterozygote parents, 25% of children develop CF. Disease is more severe in blacks than whites because of poor nutritional status and poor pulmonary function. Moreover, CF is more severe in females and they die at younger age in comparison with males (22).

Thirty to 80% of patients with CF have ΔF508 mutation in defective CFTR gene. Epidemiologic studies in Iran showed 16%-23% of patients with this mutation (23). CF could be confirmed by genetic testing, or sweat testing, and one of the following: chronic obstructive pulmonary disease, insufficiency of pancreas exocrine part, and positive family history (4).

Additional assessments in CF patients include radiologic studies (chest X-ray or computer tomography scan (CT), abdominal ultrasonography, and barium study), genotype, bronchoalveolar lavage, and pulmonary function tests (6,7).

Serum IGF-1 concentration decreases in patients suffered from CF with unclear cause. IGF-1 is an insulin-like molecule and has a crucial role in children growth and anabolic function in adults (24).

Serum concentration of insulin is in normal range in CF patients, while basal insulin level is higher in comparison with healthy people (25). Various studies have been performed to determine the correlation between growth peptides and CF. Impaired insulin secretion and glucose tolerance are common in cystic fibrosis (26). Although GH increases in many inflammatory conditions, IGF-1 and IGFBP-3 levels decrease in CF and lower levels correlate with poor prognosis. IGF-1 and GH are two therapeutic options which should be considered at puberty. On the other hand, exocrine pancreatic insufficiency (EPI) is reported in 90% of patients with CF that might lead to malabsorption and poor growth (27).

IGFs activate by local elements expressed in tissues and circulating IGFBP within body tissue. This circulating system is regulated by insulin, growth hormones, nutrition, and systemic disorders, such as cancer (28). Some recent evidences revealed that bone fractures and osteopenia are associated with decreased level of IGF-1 (29). This protein plays an important role in cellular homeostasis and repair. Moreover, IGF-1 is produced by fibroblasts and correlates with wound healing process and granulation tissue formation. Despite the low level of IGF-1 in normal skin, damaged skin has higher concentration of this peptide (30).

Many studies indicated that patients with CF suffer from growth defects; growth problems in CF patients are multifactorial (31). Chronic lung infections and malnutrition in childhood are the predisposing factors for growth retardation in childhood (32). Changes in GH regulation and release are the other probable causes of growth defects in CF.

Conclusion

We concluded that IGF-1 and related binding protein levels decrease in children with CF and might be the cause of poor growth and low BMI in these children.

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Conflict of Interest

The authors declare no conflict of interest.

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