Fibroblast growth factor-23 (FGF-23) in children with inflammatory bowel disease

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By

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CONTENTS

List of abbreviations

ADHR	Autosomal dominant hypophosphatemic rickets
ALP	Alkaline phosphatase
ARHP	Autosomal recessive hypophosphatemea
ASCA	Anti-Saccharomyces cerevisiae antibody
BMD	Bone mineral density
Ca	Calcium
CBC	Complete blood count
CRF	Chronic renal failure
CRP	C-reactive protein
DXA	Dual-energy x-ray absorptiometry
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FGF-23	Fibroblast growth factor 23
FGF-7	Fibroblast growth factor 7
HHRH	Hereditary hypophosphatemic rickets with hypercalciuria
HLA	Human leucocyte antigen
IFN-γ	Interferone gamma
IGF	Insuline growth factor
IL	Interleukin
OB	Osteoblast
OPG	osteoprotegerin
p-ANCA	perinuclear antineutrophil cytoplasmic antibodies
PHEX	Phosphate regulating gene with homologus to endopeptidase on the X-chromosome
Pi	Inorganic phosphorus
PTH	Parathyroid hormone
RANKL	receptor activator of nuclear factor-κ-B ligand
SD	Standard deviation
sFRP-4	Secreted frizzed-related protein 4
TC	Tumor calcinosis

TGF	Transforming growth factor
Th	helper T
TIO	Tumor induced osteomalacia
TNF-α	Tumor necrosis factor alpha
XLHR	X-linked hypophosphatemic rickets

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Aim of the work

The aim of this work is to measure FGF-23 in IBD pediatric patients and evaluate its relation to different clinical and laboratory variables causing this condition.

Introduction

Inflammatory bowel disease (IBD) is a generic term used was to describe 2 idiopathic disorders that are associated with gastrointestinal inflammation: Crohn disease (CD) and ulcerative colitis (UC), however, 8% to 13% of cases of IBD cannot be clearly categorized into CD or UC and are said to represent indeterminate colitis. It is an uncommon cause of chronic colitis in children but is becoming more frequent ***(Marion et al., 2000).***

IBD is a systemic disease associated with a number of extraintestinal manifestations that are encountered more commonly with CD (25-36%) than with UC (5-15%) ***(Lakatos et al., 2003).*** These manifestations may result from bacterial products or inflammatory mediators (eg, cytokines, prostaglandins, reactive oxygen metabolites) entering and subsequently being deposited in various tissues and organs and most frequently affecting the liver, bones, joints, skin, and eyes***(Danzi, 1988 & Su et al., 2002).***

Patients with IBD have an increased risk of developing osteoporosis, associated with fragility fractures and morbidity. The overall prevalence of osteoporosis in IBD is approximately 15% but is more prevalent with older age; the

overall relative risk of fractures is 40% greater when compared to the general population ***(Bernstein et al., 2000).*** Prevalence of osteopenia and osteoporosis in the pediatric population is estimated between 8 to 30% based on several smaller studies ***(Gokhale et al., 1998).***

A variety of studies have demonstrated both decreased bone mineral density (BMD) in patients with IBD (***Satsangi, 2003)***, and increased rate of bone loss when followed longitudinally in comparison to healthy controls ***(Roux et al., 1995)***. IBD commonly presents during adolescent and young adulthood when bone mass is being rapidly attained. IBD patients have inadequate intake or malabsorption of calcium and vitamin D. Also these patients are potentially prone to low bone mineral density secondary to corticosteroid use, low estrogen states in females, and effect of circulating proinflammatory cytokines ***(Hyams et al., 1997).*** A variety of cytokines and growth factors are probably pathologic mediators in systemic and regional bone loss. Interleukin (IL)1, IL-1, IL-6 and TNF-α among others have all been implicated ***(Mora and Barera, 2004).***

The term phosphatonin was introduced to describe a humoral factor or factors responsible for the inhibition of renal

phosphate reabsorption and therefore decreases serum phosphorus. Phosphatonin also decreases the activity of 1 α hydroxylase resulting in a decrease in 1,25 $(OH)_2D3$ ***(Greenbaum, 2007).***

The most important member of these phosphatonins is FGF-23 which is a secreted, circulating, 32-kDa protein that is predominantly expressed in osteocytes in the bone and in the endothelial cells that line the venous sinusoids of bone marrow and the thymus ***(Liu et al., 2006)***.

Abnormalities in FGF-23 has been found in a number of diseases characterized by phosphaturia, hypophosphatemia and rickets including XL hypophosphatemic rickets, AD hypophosphatemic rickets and tumor induced osteomalacia ***(Shimada et al., 2002 & Jonsson et al., 2003).***

CHAPTER I

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a disorder characterized by chronic inflammation of the gastrointestinal tract. There are two clinical subtypes, Crohn's disease (CD) and ulcerative colitis (UC). CD can affect any part of the intestine and is associated with discontinuous transmural lesions of the gut wall, whereas in UC lesions are continuous and superficial and inflammation is confined to the colon and rectum only. An etiologic model of IBD has been proposed, suggesting that individual expression of the disease could be influenced by complex interactions between environmental factors and promoting genes ***(Ahmed et al., 2006).***

Ulcerative colitis was first described in 1859 by Walks ***(Wilks, 1985).*** Crohn, Ginsberg and Oppenheimer described ileitis as a pathological and clinical entity different from intestinal tuberculosis in 1932 ***(Crohn et al., 1932).*** It was named Crohn's disease after the name of the first author. However, in 1913, Dalziel gave a remarkable accurate description of the disease ***(Dalziel, 1913).***

Epidemiology

About 20–30% of individuals with inflammatory bowel disease (IBD) have symptom onset before 20 years of age. Ten to 15% of all IBD patients have an established diagnosis under the age of 18 years. Young children (under 6 years of age) with IBD represent a unique cohort of patients that is recognized as a valuable group to investigate due to their relative lack of environmental exposures compared with older patients ***(Heyman and Gupta, 2008).***

Incidence of IBD:

Regarding the incidence of IBD in pediatrics, ***Watson et al., (2002)*** reported that the incidence of ulcerative colitis and Crohn's disease in Northeastern Scotland has risen from 0.7 in 100,000 and 2.2 in 100,000, respectively, in the years 1980 through 1989 to 1.5 in 100,000 and 4.4 in 100,000 in the period 1990 through 1999. The only pediatric study from North America reported the incidence of Crohn's disease in the state of Wisconsin to be 4.56 per 100,000 population, twice that of UC (2.14) ***(Kugathasan et al., 2003).***

Age of Diagnosis:

Pediatric IBD is generally diagnosed between 5-16 years. Approximately 4% of children are diagnosed with CD

when younger than 5 years While UC occurs less frequently in children younger than 5 years ***(Baldassano and Piccoli, 1999)***. The most common age of diagnosis among pediatric populations tends to favor young teens, possibly because older teens are lost to pediatric practices as they are referred to adult gastroenterologists. However, young children and infants are not infrequently diagnosed with IBD. Heyman et al. (2005) reported on 1739 IBD patients from a large mutlicenter registry, finding that 6.1% of the patients were diagnosed with IBD at age less than 3 years. Similarly, diagnosis was established in 211 (15.4%) prior to 6 years of age, 654 (47.7%) between 6 and 12 years, and 505 (36.9%) 13 to 17 years of age ***(Heyman et al., 2005).*** Kugathasan et al. reported that 20% of all pediatric cases were diagnosed before 10 years of age ***(Kugathasan et al., 2003).***

Gender and Pediatric IBD:

Although previous studies have not found gender to be a significant variable in the incidence, prevalence or outcome of IBD, recent epidemiological data suggest overall incidence and prevalence of CD among adult females slightly exceeds that of adult males ***(Logan, 1998)***. In sharp contrast, however, population based studies of pediatric onset CD in the US