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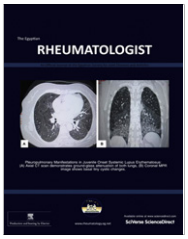

ORIGINAL ARTICLE

Early predictors of increased bone resorption in juvenile idiopathic arthritis: OPG/RANKL ratio, as a key regulator of bone metabolism

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KEYWORDS

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Abstract *Aim(s) of the work:* To explore early changes in the predictors of bone turnover in children with juvenile idiopathic arthritis (JIA). To identify osteoprotegerin/receptor activator of nuclear factor-κB ligand (OPG/RANKL) ratio in the serum of the same patients and its relation to the parameters of joint inflammation and joint destruction.

Patients and methods: Seventy children with JIA and 30 healthy children individually matched for age, sex, race, and county of residence were included in this study. Serum levels of calcium (Ca), phosphorus (Ph), alkaline phosphatase (ALP), osteocalcin (OC), RANKL and (OPG) were measured. Urinary concentration of deoxypyridinoline (DPD) was also done. All involved joints were assessed by plain radiography.

Results: Significant low serum concentrations of ALP and OPG was observed in JIA group, while there was a significant increase in serum level of RANKL and urine level of DPD compared to controls. OPG/RANKL ratio was significantly lower in JIA patients than in controls. OPG/

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RANKL ratio is correlated with most clinical characteristics, disease activity variables, JIA outcome measures and radiographic findings. DPD, RANKL and OPG/RANKL ratio, respectively, are considered as independent predictors of juxta-articular osteoporosis. OPG/RANKL ratio was the only predictor of bone erosion.

Conclusion: The OPG/RANKL ratio could be an early predictor of increased bone resorption and a valuable biomarker for joint inflammation and bone injury in JIA patients.

1. Introduction

In juvenile idiopathic arthritis (JIA), a decrease in bone mass has been described in a high percentage of children with increased risk of osteoporosis [1]. The decrease in bone mass is multifactorial in origin [2] and correlates with the duration of active disease and the number of affected joints [1]. Osteoporosis is characterized by loss of bone mass associated with increased fragility and risk of fractures [3]. It is diagnosed by measuring a real bone mineral density (BMD, g/cm^2) [4].

BMD in JIA is influenced by several factors as inflammation, medication, nutrition, and physical inactivity. It is important to detect the early changes of bone mass in JIA in order to identify patients at risk to develop reduced bone mass and osteoporotic fracture [5]. Dual energy X-ray absorptiometry (DEXA) is the preferred method for measuring bone mass in children [6].

Bone strength is compromised if bone remodeling favors resorption by osteoclasts over bone formation by osteoblasts [7]. Understanding the regulation of bone remodeling and detection of the early changes of bone predictors holds the key to the management of osteoporosis [8].

Biochemical markers of bone turnover are indirect indices of skeletal metabolism. A range of biochemical markers have been investigated for applicability to determine bone health in children with JIA [9]. However, good markers in children need more investigations [10]. Osteocalcin (OC) is the major non -collagenous protein of the bone matrix. OC is predominantly synthesized by mature osteoblasts and is mainly incorporated into the bone matrix. The circulating level of OC (10–25%) reflects the rate of bone formation [9]. Deoxypyridinoline (DPD) is one of two major cross-links in the collagen molecule. It is excreted in the urine and is considered a bone specific resorption marker [11].

Tumor necrosis factor (TNF) was identified as the main inflammatory pathogenic mediator for chronic arthritis [12]. Among the TNF family, the receptor activator of nuclear factor-κB (RANK), RANKL, and osteoprotegerin (OPG) are involved in many immunological and skeletal diseases characterized by bone resorption including inflammatory arthritis [13].

Recent data have indicated overlapping pathways between bone biology and biology of inflammation giving the impression that inflammation may have a role in pathology of osteoporosis [7]. RANKL is a type II homotrimeric transmembrane protein produced by osteoblastic lineage cells and T lymphocytes, and synoviocytes. It stimulates the receptor RANK present in dendritic cells and osteoclasts besides increasing survival and immune activation of dendritic cells. It promotes osteoclast formation, differentiation, activation, and survival leading to enhanced bone resorption [14].

Osteoprotegerin (OPG), a soluble protein synthesized by osteoblasts, acts as a soluble receptor that binds to RANKL and preventing its binding to RANK with a consequent decrease in osteoclast activation and function [15]. Therefore, RANKL and OPG act as key regulators of bone metabolism and osteoclast biology. OPG/RANKL ratio is an important determinant of bone mass and skeletal integrity [14].

The aim of this study was to explore the early changes in the predictors of bone turnover (osteocalcin, deoxypyridinoline, alkaline phosphatase, the receptor activator of nuclear factor-κB ligand and osteoprotegerin) in children with juvenile idiopathic arthritis (JIA), without clinical symptoms and/or radiological signs of osteoporotic fractures. To identify the expression of OPG/RANKL ratio in the serum of the same patients and comparing it to the parameters of joint inflammation and joint destruction.

2. Patients and methods

Seventy patients with JIA (32 boys and 38 girls) according to the International League of Associations for Rheumatology (ILAR) criteria [16] were consecutively selected from Rheumatology and Rehabilitation Department, Assiut University Hospital, for the study. Thirty apparently healthy children matched with the patients according to age, sex, ethnicity, average dietary intake, average sun exposure and geography were recruited as controls. The geographic match may reduce a bias caused by geographic differences in BMD and fracture rates related to environmental factors or genetic risk determinants [17]. Regarding patients' medication, patients were taking one of the following disease-modifying antirheumatic drugs: methotrexate, hydroqauine, sulfasalazine, azathioprine, leflonamide or combination therapy and 48 patients (68.6%) were receiving corticosteroids.

Children excluded from the study were those older than 16 years and younger than 4 years, Children with any clinical or radiological finding of osteoporosis, with secondary causes of low bone mass, such as a clinical history of rickets, hypoparathyroidism, hyperthyroidism or hypothyroidism, poor gastrointestinal absorption, and renal or hepatic insufficiency.

Informed consent was obtained from all children's parents or their relatives. The study protocol was approved by ethical committee of Faculty of Medicine, Assiut University.

2.1. Data collection

Demographic, clinical and anthropometric data for patients and controls were obtained through complete medical history, physical and articular examinations. All participants completed a translated Arabic form of self reported questionnaires [18] about fractures and leisure-time physical activities outside