

Biochemical markers of bone turnover, serum levels of interleukin-6/interleukin-6 soluble receptor and bisphosphonate treatment in Erdheim-Chester disease

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ABSTRACT

Erdheim-Chester disease (ECD) is a rare non-Langerhans form of histiocytosis characterized radiologically by symmetrical sclerosis of the metaphysis and the diaphysis of long tubular bones. Macrophages are potent interleukin-6 (IL-6) producers and elevated IL-6 serum levels have been described in pathological conditions characterized by increased bone resorption.

In a patient with ECD, during the acute phase of the disease we found high serum levels of IL-6 and IL-6 soluble receptor (sIL-6R) and high levels of bone turnover markers. After 5 years of combination therapy with oral prednisone and intravenous clodronate a significant reduction in the above mentioned biological parameters was seen. We suggest that the systemic disorders present in ECD could be related to the high serum levels of IL-6 and sIL-6R. We also propose the use of bisphosphonates in the clinical management of ECD.

Introduction

Erdheim-Chester disease (ECD) is a rare systemic histiocytosis syndrome of unknown aetiology that usually affects adults. Symmetrical long bone pain with associated pathognomonic morphological changes (sclerosis of the meta- and diaphysis of long tubular bones) suggest the diagnosis of ECD. About half of the patients have extra-skeletal manifestations, including involvement of the hypothalamus/posterior pituitary gland, retro-orbital tissue, central nervous system, retroperitoneum, skin, lung, pericardium and heart. Pulmonary involvement is an uncommon but important manifestation of ECD because it causes significant morbidity and mortality (1, 2).

The differential diagnosis of ECD includes fluoride intoxication, myeloid metaplasia, lymphoma, metastatic disease, toxic osteoarthropathy (polyvinylpyrrolidone storage disease), adult progressive diaphyseal dysplasia (Engelmann disease) and other histiocytic disorders such as Rosai-Dorfman disease, Langerhans's cell histiocytosis and Hand-Schüller-Christian disease (1, 2).

Recently, Chetrit and co-workers have suggested that ECD may be considered as the "macrophage" counterpart of Langerhans's cell histiocytosis in the histiocytosis spectrum (3). Nevertheless, it is still debated whether the histiocytic proliferation in ECD represents a monoclonal neoplastic population or is part of a polyclonal reactive process, as suggested by Al-Quran and co-workers (4). Macrophages are potent producers of interleukin-6 (IL-6); conversely IL-6 promotes the differentiation and activation of T cells and macrophages (5). IL-6 exerts its action through a cell surface receptor system that consists of two transmembrane subunits: the IL-6 binding gp 80 (named IL-6R) and the signal-transducing component gp 130, which is not ligand binding. The soluble form of IL-6R (sIL-6R) is a 55 kDa protein generated by proteolytic cleavage of the membrane-associated receptor (IL-6R) at the site adjacent to the transmembrane domain or by differential mRNA splicing. The sIL-6R binds IL-6 with an affinity similar to that of the membrane-bound receptor and enhances the biological effects of IL-6 in various cell types. The amplified effects of IL-6 due to its soluble receptor are relevant in several pathological conditions characterized by increased bone resorption and systemic inflammatory disorders (6).

In a patient affected by ECD we studied the variation in biochemical markers of bone metabolism and inflammation, IL-6 and its soluble receptor over a period of five years.

Case report

A 48-year-old man was admitted to the Department of Clinical and Experimental Medicine of the University of Naples "Federico II" in January 1997. Over the previous 6 months he had suffered asthenia, dyspnoea, cough and episodic bouts of fever and had lost about 10 kilograms in weight. He was a non-smoker and did not drink alcohol. Occupational exposure to asbestos or to polyvinylpyrrolidone was excluded. The patient denied any history of medication with beta-adrenoreceptor-blocking drugs, methysergide or ergotamine.



Fig. 1. Frontal (a) and lateral (b) roentgenogram of the left femur. Mixed osteolytic and sclerotic lesions are observed.

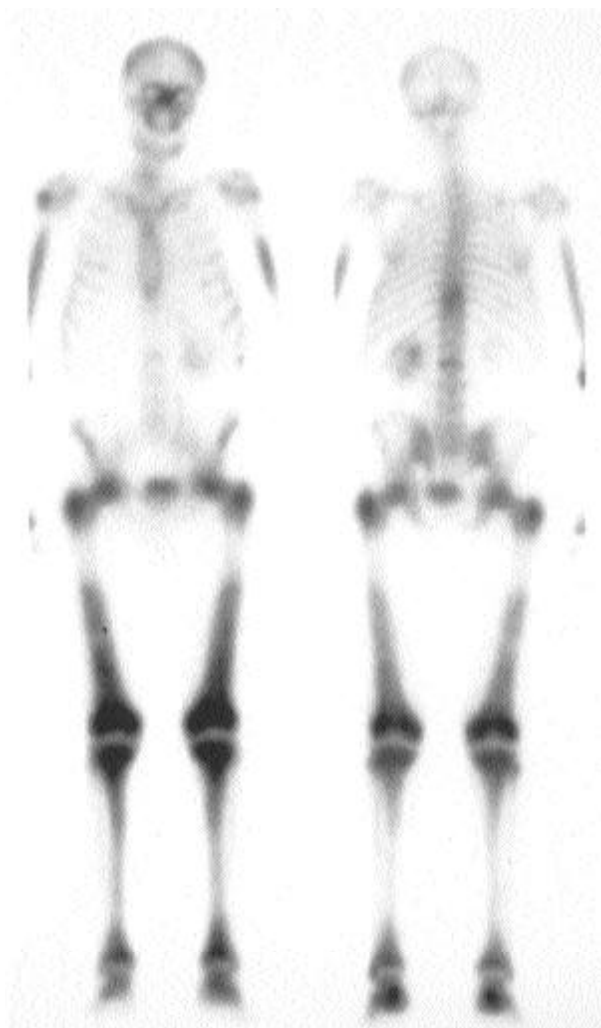


Fig. 2. ^{99m}Tc -MDP bone scan demonstrates symmetrically increased uptake in the femurs, tibias and humerus.

Physical examination showed paleness, muscle wasting, palpable enlargement of the bones of the thighs and arms, and diffuse skeletal tenderness on palpation. No other relevant physical signs were found.

A radiograph of both lower extremities and humerus showed diffuse sclerosis of the diaphysis and epiphysis of the femura, tibiae and humeri. An obliteration of the medullar space was observed in the femoral diaphysis (Fig. 1). A bone scan (^{99m}Tc -MDP) showed intensive symmetrical tracer uptake at the sites of radiographic abnormalities (Fig. 2). A magnetic resonance imaging (MRI) scan of the femoral lesions showed medullar osteolysis with focal sclerosis of the bones (Fig. 3). The patient rejected bone biopsy. Symmetrical long bone pain with associated radiographic, scintigraphic and MRI changes suggested the diagnosis of ECD (1, 2, 7).

Significant anemia (Hb 85 g/l) was present with low iron ($3.04 \mu\text{mol/l}$) and high ferritin ($856 \mu\text{g/l}$) serum levels. The erythrocyte sedimentation rate (ESR) was 130 mm/h and other inflammatory indexes, such as C reactive protein (106 mg/l), α_2 -microglobulin (5.120 ng/l), aptoglobin (6.94 g/l) and α_1 -antitrypsin (4.52 g/l) were increased. Serum levels of serotonin and urine excretion of serotonin metabolites were in the normal range. Antinuclear and anti smooth muscle antibody were undetectable.

Creatinine clearance, calcium, phosphate, alkaline phosphatase, calcitonin, 25 OH D_3 , $1,25 \text{ (OH)}_2 \text{ D}_3$ and intact parathormone levels were in the normal range, while total urinary hydroxyproline, cross-linked N-telopeptide of collagen type 1, free deoxypyridinoline crosslaps and serum osteocalcin were increased (Table I).

No clinical, biochemical or MRI evidence of hypothalamic-pituitary dysfunction were found. A CT scan of the thorax showed a pattern of diffuse interstitial pneumonia with the presence of effusion and fissural thickening of the pleurae (Fig. 4a). Pulmonary function tests demonstrated a restrictive defect with moderate hypoxemia. An abdomen MRI showed a reduction in

size of the left kidney with an ipsilateral obstruction of urinary flow and a bilateral thickening of the kidney capsule caused by the presence of sclerotic tissue around the kidneys and ureters (retroperitoneal fibrosis) (Fig. 4b). A bilateral stent was inserted into the ureters to restore normal urinary flow. The progression of the peritoneal lesion required surgical treatment (ureterolysis followed by application of a vascularized omental flap). The histologic appearance of the retroperitoneal tissue indicated xanthogranulomatous infiltration by spumous histiocytes surrounded by fibrosis (Fig. 5). The histiocytes stain negative for S-100 protein (negativity was determined by immunohistochemistry). These findings confirmed the diagnosis of ECD

Steroid therapy was started (prednisone 1 mg/kg/d). Taking into account the elevated serum and urinary levels of bone turnover markers and the presence of bone pain, clodronate (dichloromethylene bisphosphonic acid) treatment was started at a dose of 300 mg intravenously for 5 consecutive days (total dose 1500 mg) every 6 months, according to the criteria proposed by P.D. Delmas and P.J. Meunier for treatment of Paget's disease of bone (8). Both drugs were given in association. Since June 1997 we have gradually reduced the daily dose of steroid, given the considerable improvement in the patient's clinical condition and the partial remission of his systemic inflammatory parameters (Table I). At each visit, the patient was asked to fill out a pain assessment questionnaire in which he reported the presence or absence of bone pain, and its severity. It was at the patient's discretion to decide whether the pain was or was not related to ECD based on previous discussion with his physicians (GM, VN). After 20 days of combined clodronate/prednisone therapy, the patient reported the disappearance of skeletal tenderness. In addition, during the subsequent check up we found the disappearance of asthenia, cough and fever, and a progressive weight gain. Nevertheless no changes in the bone scan or in the radiographic appearance of the bone lesions were observed. At present the patient is

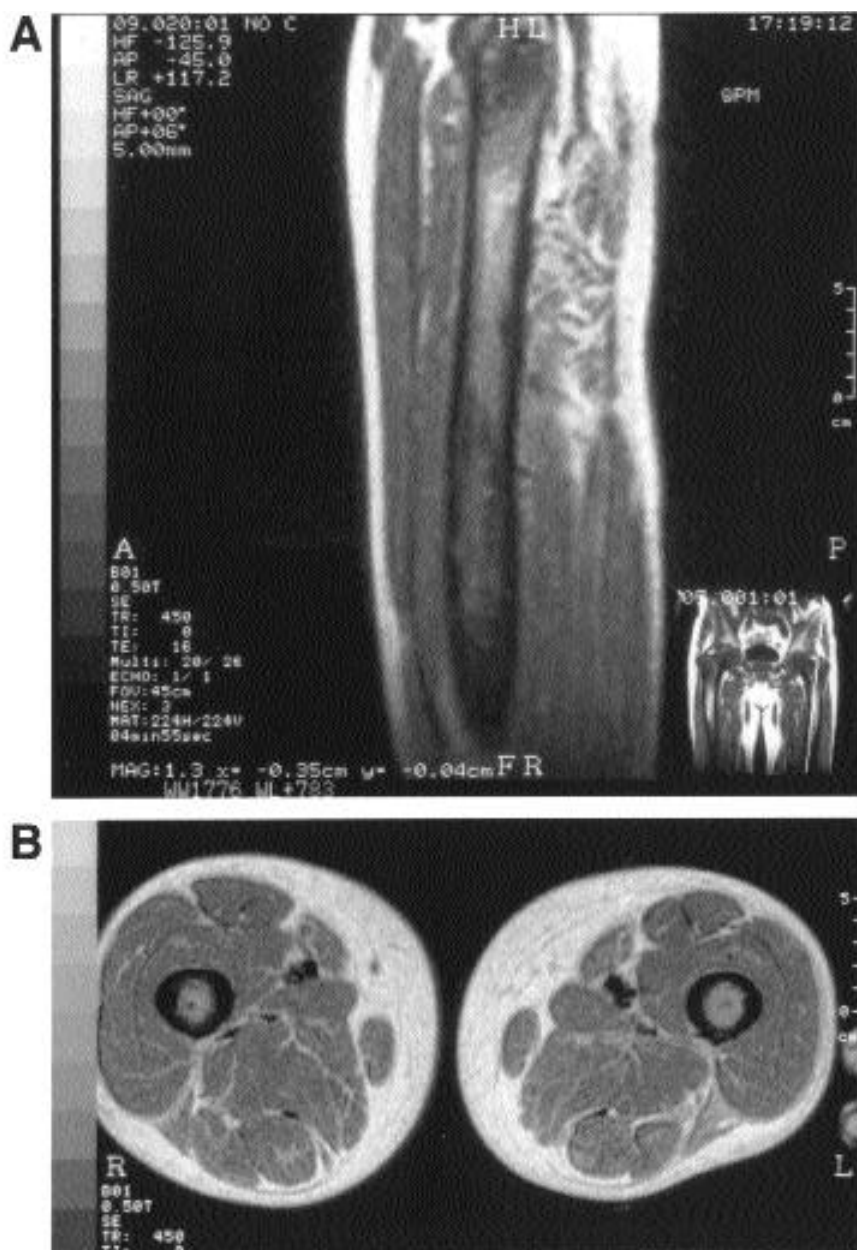


Fig. 3. Sagittal (a) and axial (b) T1-weighted MR images of the left femur show medullar osteolysis with focal sclerosis of the bone.

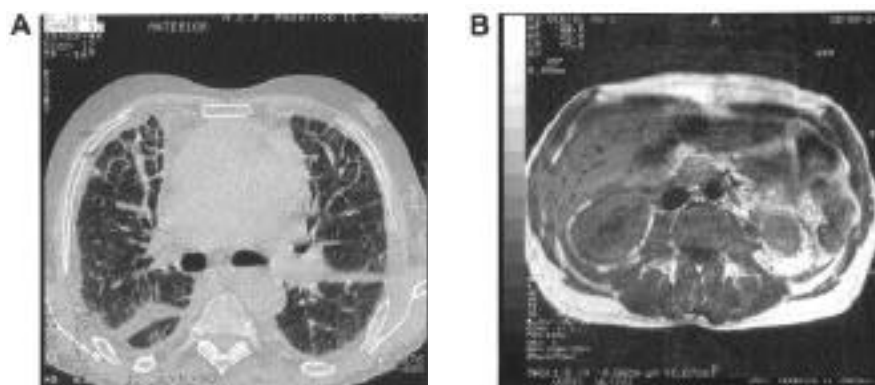


Fig. 4. (a) High-resolution chest CT scan shows diffuse interstitial pneumonia with the presence of effusion and fissural thickening of the pleurae. (b) Abdominal MRI shows sclerotic tissue around the kidneys and ureters (retroperitoneal fibrosis).

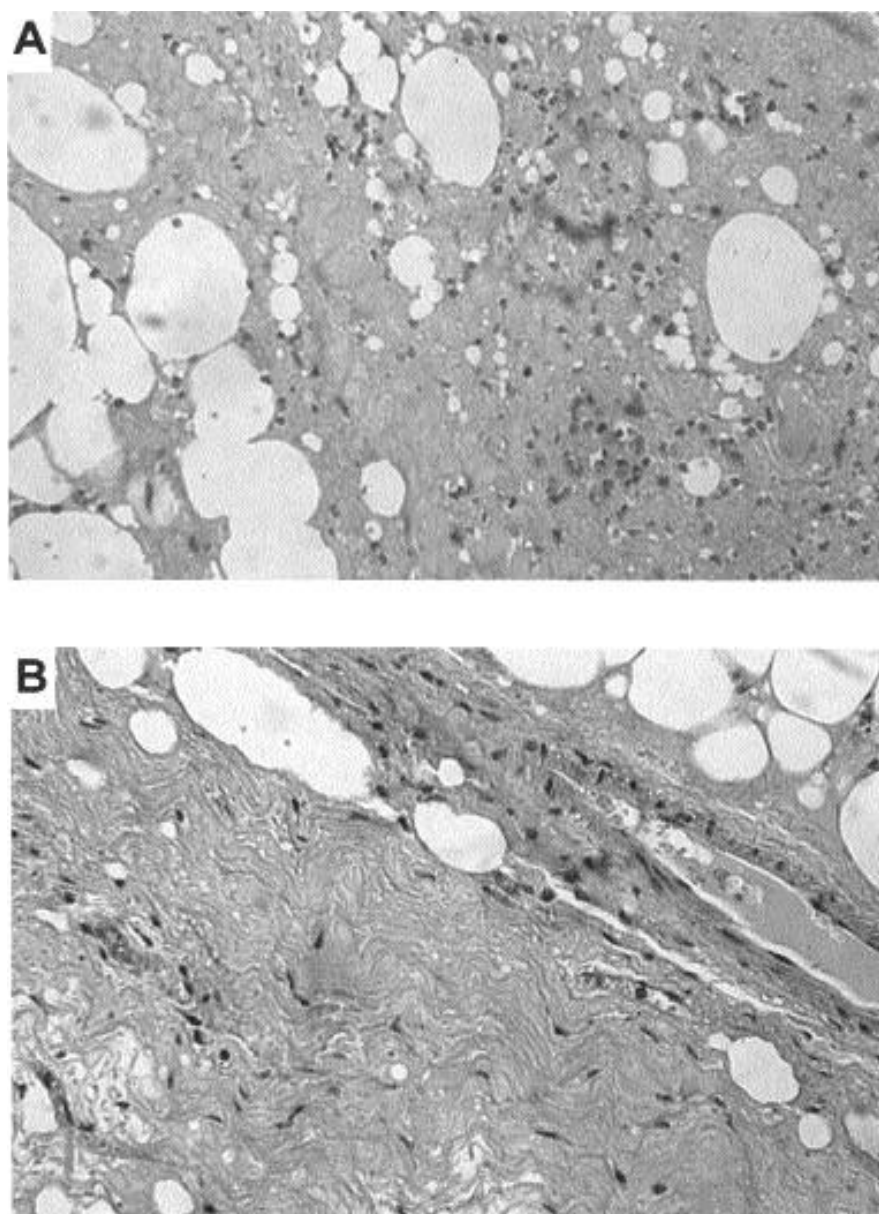


Fig. 5. Specimens from retroperitoneal tissue: (a) xanthogranulomatous infiltration by spumous histiocytes (hematoxylin-eosin stain, original magnification x25), (b) surrounded by fibrosis (hematoxylin-eosin stain; original magnification x40) can be observed.

receiving prednisone at the dose of 0.5 mg/kg/d (Table I).

We measured IL-6 and sIL-6R serum levels during the acute phase of disease and during the follow-up period. We found very high serum levels of IL-6 and of sIL-6R in the acute phase of the disease (27.4 pg/ml and 46.2 ng/ml for IL-6 and sIL-6R, respectively). On the other hand, we observed a progressive reduction in IL-6 and sIL-6R serum levels clearly related to the improvement in the patient's clinical condition and to the significant decrease in sys-

temic inflammatory parameters and bone turnover indices (Table I).

Discussion

In the present case, a patient affected by ECD showed abnormal values for the biochemical markers of bone turnover in the active phase of his disease. These biochemical parameters and their variation after therapy have not been analyzed in the literature. After steroid and bisphosphonate therapy over a period of 5 years, associated with the surgical correction of hydronephro-

sis, we observed a significant improvement in the patient's clinical condition. The values for the biochemical markers of bone metabolism decreased significantly, without any variations in the calciotropic hormones. In our opinion this effect is related to the pharmacological properties of the bisphosphonates (9).

We also found that the systemic disorders related to macrophage cell proliferation in ECD were associated with high serum levels of IL-6 and sIL-6R. IL-6, via its soluble receptor, induces osteoclast formation and bone resorption and has been implicated in the development of several metabolic bone diseases (6,10, 11). High levels of IL-6 and sIL-6R also contribute to the pathogenesis of pulmonary fibrosis associated with systemic sclerosis (6). Recently, Ammann and co-workers (12) have described elevated serum levels of IL-6 in a patient with ECD and echocardiographic evidence of a tumor in the right atrium. The improvement in clinical condition and the remission of systemic inflammatory parameters were related to the progressive reduction of IL-6 and sIL-6R serum levels. These findings could be attributable to combined steroid and bisphosphonate therapy.

New insights into the molecular mechanism of action of the bisphosphonates indicate that these compounds have several pharmacological properties (9). Indeed, the use of bisphosphonates to treat osteolytic and pulmonary Langerhans' cell histiocytosis has been suggested on the basis of their relative safety and their documented anti-macrophage activity (13,14). Our group also reported that intravenous clodronate infusion in patients with Paget's disease of bone reduces sIL-6R serum levels without significant variations in the serum levels of calciotropic hormones (15).

In conclusion, we suggest that the biochemical markers of bone turnover and serum levels of IL-6 and its soluble receptor should be used in the monitoring of ECD. We would also propose the use of bisphosphonates (clodronate or the more potent, nitrogen containing-bisphosphonates such as pamidronate,

Table I. Biochemical markers of bone turnover and serum levels of interleukin-6 and its soluble receptor in a patient affected by Erdheim-Chester disease, over a period of five years.

Data	Jan. 1997	June 1997	Jan. 1998	June 1998	Jan. 1999	June 1999	Jan. 2000	June 2000	Jan. 2001	June 2001	Jan. 2002	Reference values
Clodronate (total dose)	-	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500	
Prednisone (mg/Kg/24h)	-	1	1	1	0.7	0.7	0.7	0.7	0.5	0.5	0.5	
Serum parameters												
Ionized calcium (mmol/L)	1.13	1.14	1.12	1.13	1.15	1.14	1.13	1.15	1.14	1.13	1.12	1.12 ± 0.04
Phosphate (mmol/L)	0.12	0.11	0.10	0.12	0.12	0.11	0.13	0.12	0.11	0.12	0.12	0.12 ± 0.01
Magnesium (mmol/L)	0.9	0.8	1.0	1.1	0.8	1.0	0.9	1.0	1.1	1.1	1.0	1.0 ± 0.2
Alkaline Phosphatase (U/L)	245	195	201	235	192	204	210	237	202	208	214	198 ± 65
Intact PTH (pmol/L)	3.6	3.1	3.8	3.5	4.2	4.0	3.9	3.6	3.7	4.1	4.5	3.3 ± 1.6
25(OH)D ₃ (pmol/L)	72.68	72.92	71.85	75.21	72.38	76.28	72.41	73.18	74.01	75.07	72.89	71.94 ± 18.51
1,25 (OH) ₂ D ₃ (nmol/L)	85.44	98.68	89.86	95.14	100.73	89.77	87.79	31.26	95.71	92.22	89.75	90.98 ± 15.87
Calcitonin (ng/L)	5	7	8	10	4	6	2	9	10	7	9	7.5 ± 4.1
Interleukin-6 (pg/ml)	27.4	10.7	11.2	10.8	10.4	10.1	9.5	8.2	7.5	5.9	4.8	1.8 ± 0.9
sIL-6R (ng/ml)	46.2	37.8	38.1	38.4	38.5	38.0	37.9	36.6	36.7	36.0	35.9	30.5 ± 3.8
Osteocalcin (ng/ml)	60	44	40	38	38	36	32	31	30	28	28	19 ± 9
ESR (mm/h)	130	42	28	27	15	14	12	17	20	12	10	7 ± 5
Reactive C Protein (mg/l)	106	54	32	15	17	14	10	9	13	8	7	3 ± 2
Hemoglobin (g/l)	85	105	112	108	100	108	111	122	115	118	125	145 ± 15
Urinary parameters												
Calcium (mmol/24 h)	10.5	9.5	9.0	8.7	8.5	8.2	8.1	7.8	7.7	7.6	7.8	5.5 ± 2.1
Phosphate (mmol/24h)	25.28	24.39	23.47	25.01	26.36	24.98	24.16	24.10	24.14	24.02	24.01	24.61 ± 5.8
HYP/Cr (mmol/mmol)	0.14	0.08	0.07	0.06	0.05	0.05	0.04	0.03	0.02	0.01	0.01	0.011 ± 0.04
PRY (nmol/mmol)	93	77	79	68	63	62	52	50	47	41	37	29.1 ± 4.2
NTX (nMBECE/mmol)	254	161	127	109	108	95	88	74	59	45	37	33.1 ± 1.8
CL (µg/mmol)	421	307	267	222	201	184	178	161	147	142	139	119 ± 12

Clodronate was administered intravenously at a daily dose of 300 mg for 5 consecutive days.

sIL-6R: soluble interleukin-6 receptor; ESR: erythrocyte sedimentation rate; HYP/Cr: hydroxyproline/urinary creatinine ratio; PRY: pyridinoline expressed in relation to urinary creatinine; NTX: crosslinked N-telopeptides of type I collagen expressed as a ratio of urinary creatinine; CL: crosslaps expressed as a ratio of urinary creatinine. The reference values for the biochemical markers were obtained from 28 age- and sex-matched healthy adult subjects and are expressed as mean ± standard deviation.

alendronate or risedronate) in the long-term clinical management of ECD, given their pharmacological properties.

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