Strontium Ranelate and bone healing: report of two cases

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Introduction
There are several factors influencing the fracture healing process, the most important being age and bone quality. Cellular and molecular alterations that can be found in elderly patients make the healing process difficult, and may lead to complications such as pseudoarthrosis or delayed non-union. In the same way, in altered bone metabolism condition such as osteoporosis, physiological phases of fracture healing are impaired.
Due to the wide availability of anti-osteoporotic drugs whose primary end-points are to improve BMD and to reduce fracture risk, the secondary end-point of these drugs is now focused on their possible use on fracture healing deficiency conditions.

Case n° 1
Patient: B.G. Caucasian woman, age 57 years
Anthropometric parameters: h=166 cm; w=69 kg; BMI= 25
Physiological anamnesis:
former smoker, who has not smoked for 10 years (smoked 20 cigarettes/day for 10 years)
no reported use of alcohol
no regular physical activity
menopause at 44 years of age (physiological)
two full-term pregnancies
Dietary history:
varied and balanced diet
no specific food intolerances/allergies reported
Disease history:
no family history of osteoporosis reported
no reported cardiovascular or dysmetabolic disease
positive family history of cancer
previous surgery for cystopexy (2003)
no history of fractures
Diagnosis: fracture of the right distal radius and ulna (17-02-2009) (Figure 1)
Clinical history: the patient suffered an accidental fall from standing while leaving an ice rink; radiographic examination was performed and revealed a fracture of the *distal radial epiphysis,* which was treated by non-invasive reduction and immobilization in a brachiometacarpal plaster cast (17-02-2009) (Figure 2).
She came to our attention 21 days later for radiographic follow up which showed satisfactory reduction.

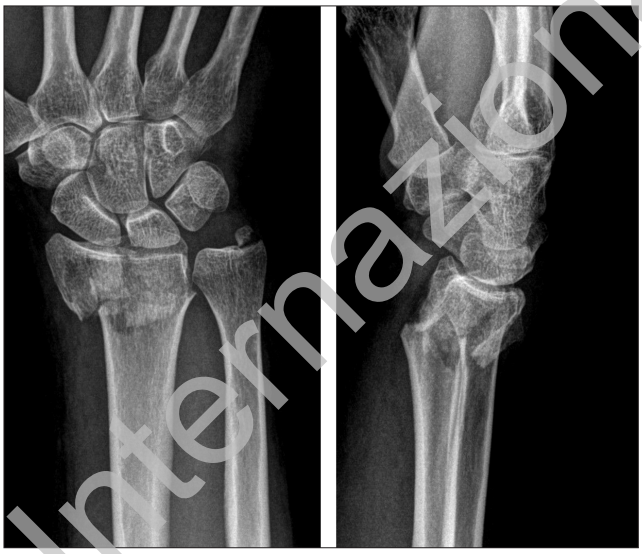

Figure 1 - Radiograph of the fracture of the distal epiphysis of the radius and right ulnar styloid process (AO 23-C1) (AP – LL).

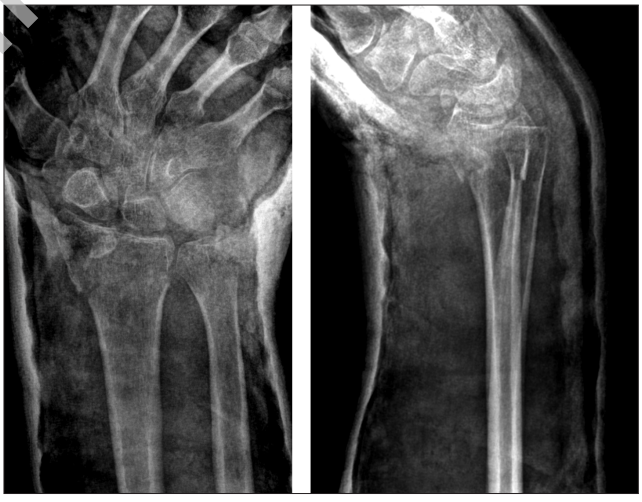

Figure 2 - Radiograph after non-invasive reduction (AP – LL).

Thirty days after sustaining the injury and following removal of the cast, the patient complained of severe wrist pain accompanied by almost complete absence of joint mobility; radiographic examination (Figure 3) revealed little bone callus formation. On the same day, the patient underwent a DEXA scan to measure bone density. This revealed osteopenia both at lumbar spine (L1-L4 = -2.0 DS; L4= -2.4 DS) and at femoral neck (-2.3 DS). Based on patient's clinical conditions and the instrumental findings an antebrachium metacarpus plaster cast was applied and the patient was prescribed calcium (1200 mg/day) + vitamin D (800 UI/day) supplement therapy, as well as pharmacological therapy with strontium ranelate (2 g/day).
After 30 days of treatment (60 days post fracture) radiographic examination revealed initial bone callus formation. Algodystrophic symptoms were completely absent and the patient had full and pain-

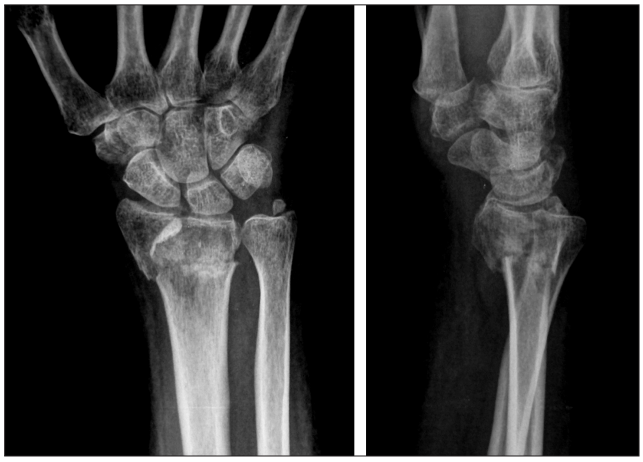

Figure 3 - Follow-up radiograph 30 days after the fracture (AP – LL), start of pharmacological therapy.

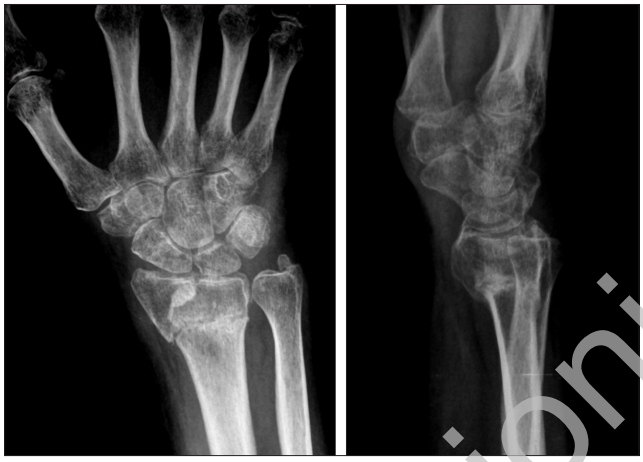

Figure 4 - Follow-up radiograph after 30 days of treatment (AP – LL).

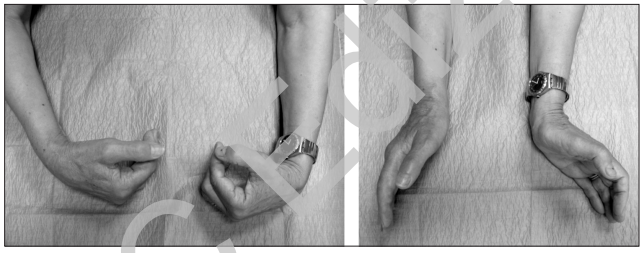

Figure 5 - Clinical follow up after 30 days of treatment.

less wrist function (Figures 4, 5).
After 60 days of treatment (90 days post fracture), the patient underwent a CT scan of the right wrist which showed advanced bone callus formation (Figure 6).
On radiographic follow up after 90 days of treatment the fracture rime had disappeared and there was evidence of an initial and structured process of bone remodelling at the level of the right distal radial metaepiphysis and healing, with union, of the ulnar styloid fracture (Figure 7).
The patient is still receiving anti-osteoporotic drug therapy.

Case n° 2
Patient: S.L. Caucasian woman, age 59 years
Anthropometric parameters: h=156 cm; w=50 kg; BMI= 21
Physiological anamnesis:
non-smoker

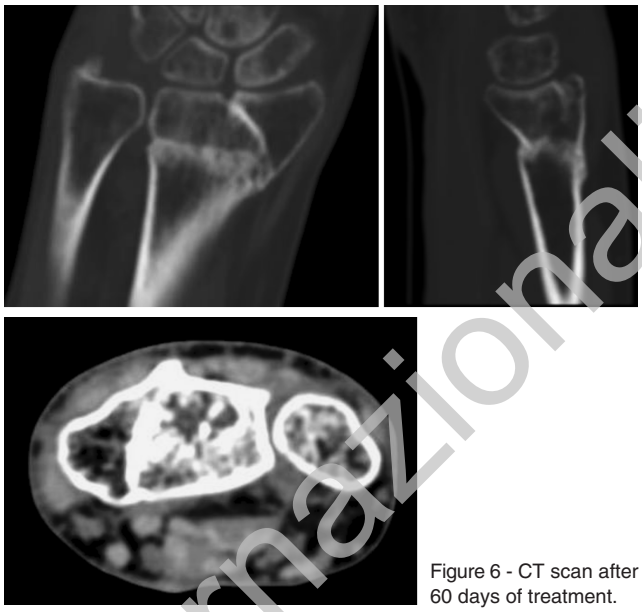

Figure 6 - CT scan after 60 days of treatment.

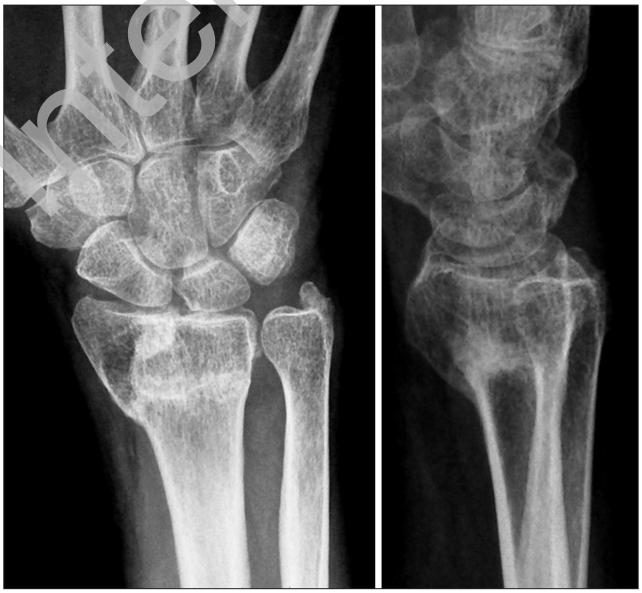

Figure 7 - Follow-up radiograph after 90 days of treatment.

occasional consumption of alcohol (1 glass of wine per day)
no regular physical activity
menopause at 54 years of age (physiological)
no pregnancies
Dietary history: varied and balanced diet
with plenty of calcium-rich foods
no specific food intolerances/allergies reported
Disease history:
family history of osteoporosis (the patient's mother with vertebral compression fracture, VCF)
no reported cardiovascular or dysmetabolic disease
no history of fractures
Diagnosis: fracture of the base of the fifth metatarsal in the left foot (29-06-2009).
Clinical history: the patient came to our attention complaining about localised pain in the anterolateral region of the left foot, following a mild trauma; radiographic examination revealed a fracture of the base of the fifth metatarsal (30-06-2009) (Figure 8).
The patient was treated non-invasively with immobilization in a boot cast.
Thirty days after the fracture the plaster cast was removed and a fol-

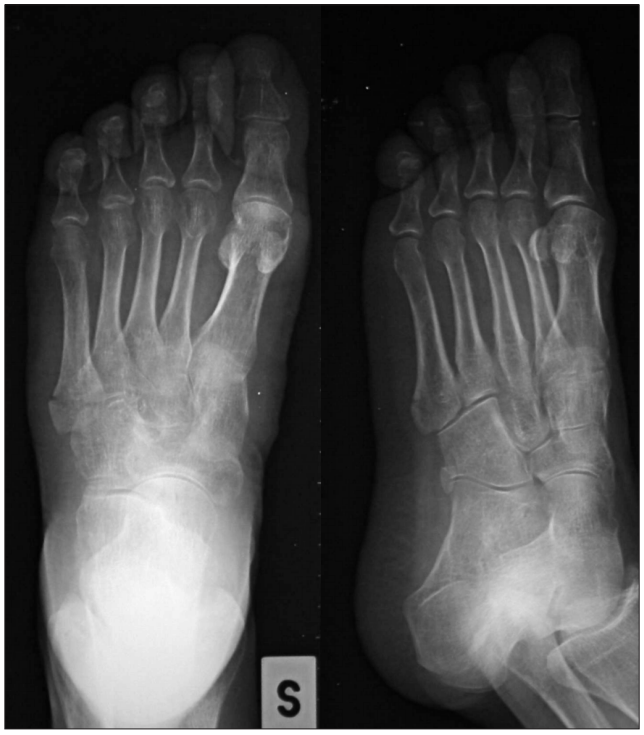

Figure 8 - Radiograph of the fracture (AP – LL).

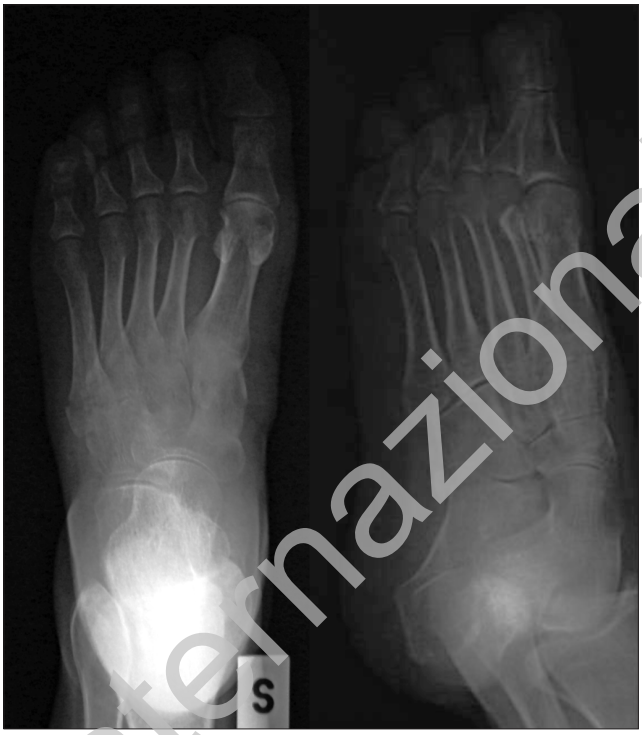

Figure 9 - Follow-up radiograph of the fracture at 30 days (AP – LL).

low-up radiographic examination was performed. This showed little bone callus formation and a clear fracture rime (Figure 9); in addition, the patient reported pain on prolonged standing and limp. On the same day, a DEXA scan of lumbar and femoral areas revealed the presence of osteoporosis at both sites (LUMBAR: L1 = -2.5 DS; FEMORAL: right femorar neck = -3.3 DS). The patient was prescribed pharmacological therapy with strontium ranelate (2 g/day), as well as calcium (1200 mg/day) + vitamin D (800 UI/day) supplementation; an insole in synthetic material to unload the fifth metatarsus was also prescribed.
On radiographic follow up after 40 days of treatment with strontium ranelate (70 days post-fracture), the fracture rime had disappeared (Figure 10), which was consistent with the clinical findings: regression of pain elicited by superficial and deep palpation and the presence of a complete and pain-free full step cycle with no limp.
The patient is still receiving anti-osteoporotic drug therapy.

Discussion and Conclusions

The frequency of osteoporosis is constantly increasing all over the world. This pathology generates several problems, mostly due to fragility fractures, the worst consequence of impaired bone quality. Osteoporotic fractures often cause disability and loss of independence, significant pain and deformity. If fracture union is not achieved, the patient may suffer from long-term disability (1).
Fracture healing consists in the replacement of the lost bone by a tissue that has the same biomechanical properties as those preceding the fracture. The repair process is triggered by the local response to the tissue injury which damaged the continuity of bone. The duration of each phase of the healing process can vary significantly, depending on the site and characteristics of the fracture, patient related factors and finally on the chosen treatment. The coupling between bone formation and resorption is a fundamental concept in skeletal metabolism, and it explains how a certain amount of removed tissue can be replaced by the same amount of new bone.
In skeletally-mature individuals it has been suggested that advancing age has a significant impact on skeletal repair (2). Studies of fracture healing in rats have shown that cartilage and bone formation and cartilage resorption, are delayed in elderly animals; there is evidence that callus mineralization is reduced in elderly animals (3-5).
The possibility of modulating anabolic and catabolic phenomena in the skeleton, both locally and systemically, opens a new horizon on enhancing bone healing, especially when bone tissue is qualitatively and/or quantitatively compromised.
The drug choice should also take into account long-term compliance of the patient and should be in accordance with national and international guidelines (6).

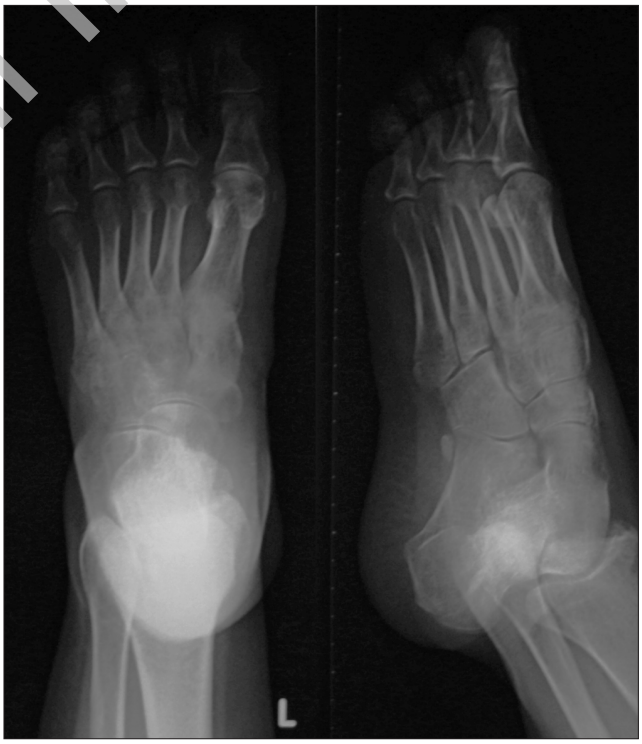

Figure 10 - Follow-up radiograph of the fracture 40 days after the start of pharmacological therapy (70 days post-fracture) (AP – LL).

Various drugs used to treat osteoporosis may also be used for orthopaedic conditions such as fracture healing; many animal studies have demonstrated that the drugs commonly used against osteoporosis can positively influence fracture repair and implant osseointegration. In experimental studies anti-catabolic agents, such as bisphosphonates, did not interfere with initial union and led to increased callus size; however, they affect both bone resorption and formation, hence the possibility of impairing subsequent callus remodeling (6).
In experimental studies in rats, results from radiological, histological, densitometric, micro-CT, and biomechanical evaluation indicated that systemic treatment with Strontium Ranelate (SR) could promote tibial fracture healing in ovariectomized rats. In these studies, SR treatment at the dose of 625 mg/kg/day significantly increased bone formation at 4 weeks post fracture, indicating the anabolic effect of SR on osteoblasts. At 8 weeks post fracture, when biomechanical strength had already been obtained, the remodelling process continued, accompanied by irregular woven bone resorption coupled with the formation of lamellar bone in the SR-treated rats. The SR dose of 625 mg/kg/day corresponded to 0,87-fold the median serum strontium concentrations observed in patients administered the therapeutic dose of 2 g/day and receiving 1500 mg calcium/day.
This result indicated that SR might not only increase bone formation but also promote endochondral ossification. This study suggests that systemic treatment with strontium ranelate could promote tibial fracture healing in OVX rats, increasing callus volume, BMD, and biomechanical strength and improving callus microstructural properties, without any negative effect on natural fracture healing progress compared with the non-treated OVX group (7).
It can be speculated that this drug could decrease the first phase of bone resorption while improving the second phase of bone formation by promoting the differentiation of bone marrow cells present at the callus site. Indeed, strontium ranelate was shown to promote stromal cell differentiation at the very first stage, but also during later stages and osteoblast differentiation (8, 9).
An experimental study was also conducted in order to evaluate fracture healing in OVX rats after treatment with pharmacological doses of strontium ranelate and PTH 1-34, compared with OVX and sham-treated control groups. Whereas both PTH 1-34 and strontium ranelate increased the volume of trabecular bone within the callus, only strontium ranelate improved the resistance to torsional testing. The superior results obtained with strontium ranelate compared to PTH could be the consequence of a better quality of the new bone formed within the callus (10).
In another study the objective was to investigate the efficacy of strontium ranelate (SR) on fracture healing in rat tibia. No significant difference was found in callus formation and bone union with respect to the control group. Histopathologically, it was seen that the fractures healed normally in both groups as weeks advanced. However the animals were given a dose of 450 mg/kg/day, which is lower than the dose of 625-900 mg/kg/day, commonly used in the other phase I and II studies to obtain a median serum strontium concentration similar to that observed in patients administered the therapeutic dose of 2 g/day (11).
Strontium ranelate has proven its efficacy in reducing the risk of vertebral, non vertebral, and hip fracture in women with postmenopausal osteoporosis (12, 13). This efficacy of strontium ranelate is independent of baseline risk factors (14) and is maintained for 5 (15) and even 8 years (16). However, large studies evaluating its possible role in promoting fracture healing are lacking.
In addition, the physiological condition of OVX rats was different from that of post-menopausal women, therefore, predicting the effects of SR on the quality of the healing process in humans on the basis of the results from SR-treated OVX rats should be cautious.
There are several solutions to facing problems related to fragility fractures, so surgeons should be more deeply involved in the patho-physiologic, clinical and biomechanical aspects of osteoporosis in order to properly apply available therapeutic measures. This is the only way to improve the quality of life in osteoporosis fracture patients (1).
Fracture-healing is a dynamic process and not a single event, but we must be cautious in comparing the outcomes between studies, as standardized assessment tools are lacking. The array of definitions for fracture union found in the literature reflects the lack of consensus in the orthopaedic community.
There is poor evidence about the reliability of commonly used radiographic measures and clinical assays for fracture union evaluation.
The most commonly used clinical criteria in defining fracture healing is the absence of pain during weight-bearing, while the most commonly used radiographic parameter is the bridging of fracture gap by bone callus or newly-formed bone tissue (17).
In our experience the use of SR to promote fracture healing brought great clinical improvement both due to pain relief and functional regain. It also caused radiographic evidence of fracture healing in patients who previously had shown fracture non-union or delayed union. Our results suggest a wider use of SR in promoting fracture-healing and encourage further scientific research in this field. Well structured clinical trials are needed, directed to patients with osteoporosis and/or wide bone gaps.
Future efforts will also need to address the assessment of fracture healing and to explore new quantifiable and reliable methods in order to improve research and clinical practice (17).

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