Bone mineral density is associated with pre-treatment pain levels of complex regional pain syndrome type 1 and predicts the response to N-containing bisphosphonates

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Abstract

Objective

Complex regional pain syndrome type 1 (CRPS type 1) is a debilitating pain disorder that often follows trauma or surgery. While bone involvement has been implicated in its pathogenesis, the relationship between systemic bone loss and disease severity or treatment response remains unclear. The aim of this study is to investigate the association between systemic bone loss and CRPS severity and response to treatment.

Methods

This prospective observational study enrolled patients with CRPS type 1 diagnosed per IASP criteria. Inclusion criteria were recent post-trauma CRPS (<4 weeks) and treatment initiation within 2 months. Patients received IV neridronate (100 mg/day for 4 days, total 400 mg). Pain was assessed using the Visual Analogue Scale (VAS) at baseline and 30 days post-treatment. Dual-energy x-ray absorptiometry (DXA) was used to measure one mineral density (BMD) at the lumbar spine, femoral neck and total hip. Stepwise linear regression and mixed-effects models assessed predictors of baseline pain and treatment response.

Results

Sixty-five CRPS type 1 patients were included in the study. Baseline VAS pain was 70.9±2.19, significantly decreasing to 24±3.8 post-treatment ($p<0.001$). Lower lumbar spine Z-score correlated with higher baseline pain and predicted greater pain reduction following neridronate ($\beta=-8.7$, SE 3.2, $p=0.008$) independently from age, sex, BMI and limb affected.

Conclusion

Lower BMD was associated with greater CRPS severity and better response to treatment. These findings support the role of bone in CRPS pathogenesis and suggest that DXA-derived Z-scores may help identify patients most likely to benefit from bisphosphonates.

Key words

complex regional pain syndrome type 1, neridronate, bone mineral density

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Received on March 13, 2025; accepted in revised form on May 12, 2025.

Competing interests: D. Gatti has received advisory board honoraria, consultancy fees and/or speaker fees from Accord Health Care, Abiogen, Amgen, Eli-Lilly, Mereo, Neopharmed-Gentili, UCB.
A. Fassio reports personal fees from Abiogen, Neopharmed-Gentili.
M. Rossini reports advisory board honoraria, consultancy fees and/or speaker fees from AbbVie, ItalFrarmaco, Neopharmed-Gentili, Eli-Lilly, Theramex, UCB, outside the submitted work.
O. Viapiana has received advisory board honoraria and speaker fees from Gilead, Fresenius Kabi, Biogen, Eli-Lilly, UCB, AbbVie, MSD, and BMS.
G. Adami has received advisory board honoraria, consultancy fees and/or speaker fees from Theramex, UCB, Lilly, Galapagos, Fresenius Kabi, Amgen, BMS, Abiogen and Pfizer.
The other authors have declared no competing interests.

Introduction

Complex regional pain syndrome type 1 (CRPS type 1) is characterised by disabling pain primarily affecting the limbs, which usually develops after a trauma or surgery. CRPS type 1 is traditionally defined by pain that is disproportionate in duration or intensity relative to the triggering event. Is it typically accompanied by abnormal sensory, sudomotor, and vasomotor disturbances (1, 2).

The pathogenetic mechanisms underlying CRPS type 1 are poorly understood. Several potential factors could be implicated in its development and progression such as neurogenic inflammation, disrupted microcirculation, aberrant expression of pro-inflammatory cytokines, and dysregulation of both the peripheral and central nervous systems (3). CRPS type 1 can be diagnosed using the IASP criteria, also known as the "Budapest Criteria," which encompass a defined set of clinical features. These criteria have been widely applied in the literature and are recognised for their strong sensitivity and specificity (4).

The involvement of bone tissue in the early pathophysiological stages of the disease seems to be a key factor, likely accounting for the effectiveness of bisphosphonates (BPs), as supported by existing evidence. Notably, imaging techniques such as X-rays, three-phase bone scans, and MRI are commonly used to assist in confirming or excluding a diagnosis of CRPS type 1, commonly demonstrating active local bone loss at the affected limb (2).

Yet, it is still unclear whether a definitive link exists between systemic bone loss and the onset, severity, and prognosis of CRPS type I.

Several pharmacological treatments (such as bisphosphonates, CSs, ketamine, scavengers/MgSO4, NSAIDs/selective inhibitors of cyclooxygenase-2, or anti-epileptics) have been proposed for CRPS type 1 in adults. In Italy, high dose IV neridronate, an amino bisphosphonates, has been approved for the treatment of CRPS type 1 based on the results of two randomised controlled trial and a metanalysis (5-7).

The objective of the present study was to investigate the potential association between systemic bone loss and the severity of CRPS and its response to IV bisphosphonate treatment.

Material and methods

We carried out a prospective observational study aimed at investigating the determinants of pain levels and response to treatment in patients with CRPS type 1. We enrolled patients diagnosed with CRPS type 1 with a recent diagnosis and satisfying IASP criteria.

Inclusion criteria were:

1. Diagnosis of CRPS type 1 according to IASP criteria.
2. Predisposing trauma or fracture within 4 weeks from symptoms onset.
3. Treatment initiation within 2 months within symptoms onset.

Exclusion criteria were:

1. Past treatment with oral or intravenous (IV) bisphosphonates, denosumab, teriparatide and romosozumab.
2. History of bone malignancy.
3. Severe liver or kidney disease (eGFR <30 ml/min or Child-Pugh grade B/C).
4. Uncontrolled endocrine disorders (*e.g.* hypocalcaemia, primary hyperparathyroidism).

All patients were treated with intravenous neridronate at a dose of 100 mg per day over four consecutive days, for a total cumulative dose of 400 mg. Treatment response was assessed 30 days after the last infusion. Baseline characteristics, including demographic, clinical, and densitometric variables, were summarised using descriptive statistics. The variables analysed included age, sex, height, weight, body mass index (BMI), site of CRPS (upper extremities or lower extremities), baseline pain as measured by the visual analog scale (VAS), and bone mineral density (BMD), T-score, and Z-score values at the lumbar spine, femoral neck, and total hip derived from dual-energy X-ray absorptiometry (DXA) using Lunar GE iDXA device. Baseline group comparisons were performed with Student's T-test or ANOVA post-hoc tests with p value adjusted with Holm method as appropriate. Categorical variables were compared with the $\chi 2$ test. All differences were considered significant when p value was inferior to 0.05. We

employed a stepwise linear regression model to identify potential associations between baseline VAS pain scores and clinical, DXA, and demographic variables. The variables included in the model were age, sex, BMI, site of CRPS, Z-score at the lumbar spine and femoral neck. To identify factors associated with the magnitude of pain improvement following treatment, a linear mixed-effects model for repeated measures (MMRM) was constructed. The model included the following fixed effects: age, time (baseline and 30 days), BMI, site of CRPS, Z-score at the lumbar spine, and Z-score at the femoral neck. Patients were included as a random effect. All statistical analyses were performed using SPSS version 26 (SPSS, Inc., Chicago, IL, USA), Orange (v. 3.37.0), GraphPad Prism version 9.5.1 (GraphPad Software, San Diego, CA, USA) and JASP (v. 0.19.0). This study was conducted according to the protocol REUMABANK, in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, and approved by the local Ethics Committee of the University of Verona (protocol registration: REUMABANK 1483CESC). All patients provided informed consent to participate in the study and retrospective collection of the data.

Table I. Baseline study population characteristic.

Characteristics	n=65
Sex, female (%)	53 (81)
Age, years (SD)	61.5 (13.6)
Height, cm (SD)	1.62 (0.01)
Weight, kg (SD)	69.8 (1.65)
BMI, (SD)	26.5 (0.59)
T-Score lumbar spine (SD)	-1.73 (0.18)
Z-Score lumbar spine (SD)	-0.26 (0.20)
T-Score femoral neck (SD)	-1.67 (0.13)
Z-Score femoral neck (SD)	-0.34 (0.12)
T-Score total hip (SD)	-1.32 (0.14)
Z-Score total hip (SD)	-0.27 (0.13)
VAS pain baseline, mm (SD)	70.9 (2.19)
Warm CRPS I, n (%)	65 (100)
Event	
None, n (%)	8 (12)
Fracture, n (%)	51 (78)
Sprain or trauma w/o fracture, n (%)	5 (8)
Orthopaedic surgery, n (%)	1 (2)
Site of CRPS I	
Foot/ankle, n (%)	10 (15)
Hand, n (%)	55 (85)
Smoking	
No	54 (83)
Past	3 (5)
<10 cigarettes/day	2 (3)
≥10 cigarettes/day	6 (9)
Alcohol	
No	55 (84)
<3 units/day	7 (11)
≥3 units/day	3 (5)
Comorbidities, n=22 (34%)	
Cardiovascular, n (%)	10 (45)
Metabolic/endocrinological, n (%)	8 (36)
Pulmonary disease, n (%)	5 (8)
Gastroenterological/liver, n (%)	2 (3)
Neurological, n (%)	2 (3)

Results

Sixty-five patients were included in the study, 53 females and 12 males, mean age 61.5±13.6 years. Table I shows the baseline characteristics of the study population. The baseline VAS pain of the study population was 70.9±2.19. The VAS score decreased significantly to 24±3.8 after treatment ($p<0.001$). Pain reduction was greater in males (VAS post treatment 12.7±4.3) than females (VAS post treatment 26.7±4.5, $p=0.03$). For patients with foot-ankle CRPS, post-treatment VAS was significantly lower than those with hand-wrist CRPS (VAS post treatment 18±4.12 *vs.* 34.7±6.03, $p=0.049$).

In the univariate analysis we found a significant association between lumbar spine Z-score and BMD levels and pre-treatment VAS pain levels. In the multivariable linear regression model the association remained significant after adjusting for age, sex, BMI, Z-score femoral neck, site of CRPS type 1 (Fig. 1).

We found that Z-score at the lumbar spine was a significant predictor of response to treatment with neridronate in terms of VAS pain reduction with an estimate of -8.7 (SE 3.2, $p=0.008$), which suggests that for each 0.1 decrease in baseline lumbar spine Z-score, the VAS pain is expected to decrease by 0.87 units, after adjusting for other factors in the model, including VAS pain at baseline (Table II).

Discussion

Herein, we found that lower BMD was associated with higher baseline pain scores in CRPS type 1 and that lumbar spine Z-score was a significant predictor of treatment response, with lower Z-scores correlating with greater pain reduction following neridronate therapy. Our findings provide further support for the "bone-first" hypothesis in the pathogenesis of CRPS type 1, highlighting the crucial role of bone tissue involvement in the early stages of the disease.

It has been previously shown that fractures, particularly complex fractures such as intra-articular or comminuted fractures, are more likely to lead to CRPS. Given that low BMD is a well-known risk factor for complex fractures, it is plausible that systemic bone fragility creates a fertile substrate for CRPS development. A more fragile bone is not only more prone to fracture upon impact but might also provide a microenvironment that is more likely to harbour inflammatory mediators, cytokines, and neuropeptides, which may self-sustain the chronic pain state characteristic of CRPS. This "niche" hypothesis is further supported by evidence from multiple myeloma and metastatic breast cancer, where osteoporo-

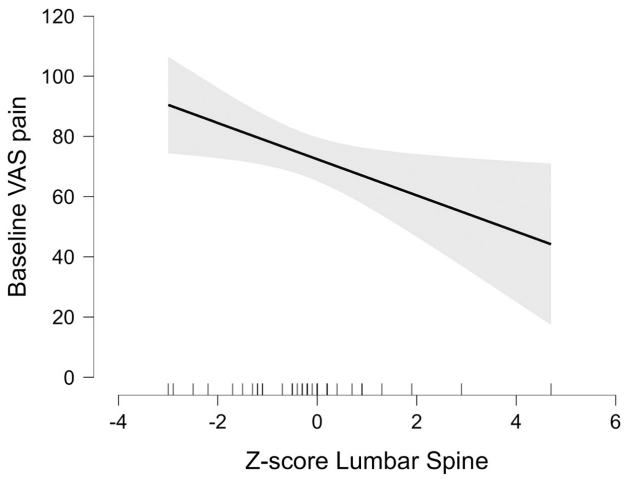

Fig. 1. Association between Z-score at lumbar spine and pre-treatment VAS pain levels in patients with CRPS type 1. r -0.693, p value 0.026 adjusted for: age, sex, BMI, Z-score femoral neck, site of CRPS type 1.

Table II. Predictors of response to neridronate treatment in CRPS type 1 patients.

Variable	Estimate	SE	*p*
Intercept	50.338	28.419	0.082
Age	0.014	0.267	0.959
Sex (F)	-1.801	4.901	0.212
BMI	0.088	0.773	0.909
Site of CRPS (lower extremity)	-2.205	5.461	0.688
Z-score lumbar spine	-8.743	3.159	**0.008**
Z-score femoral neck	8.832	4.893	0.077
VAS pain baseline	0.520	0.223	**0.024**

Linear mixed model for repeated measurements (MMRM).

sis creates a microenvironment that can harbour cancer cells and facilitate their progression (8, 9).

Our study suggests that the response to bisphosphonate therapy, specifically neridronate, is influenced by baseline bone density. The inverse relationship between lumbar spine Z-score and pain reduction following treatment suggests that patients with lower baseline BMD get greater benefit from bisphosphonate therapy. This may be due to again an increased presence of resorption lacunae in osteoporotic bone, which could act as niches for inflammatory mediators and nociceptive factors. A denser bone structure, on the other hand, may be less prone to harbouring such mediators, thereby limiting the self-perpetuating inflammatory cycle observed in CRPS. Neridronate, with its established anti-resorptive properties through osteoclast inhibition (10-13), can decrease the number and dimensions of osteoclastic lacunae and possibly halt the progression of CRPS. Nonetheless, neridronate appears to exert other immunomodulatory effects that contribute to its efficacy in CRPS type 1 (14, 15). Previous research suggests that gamma delta (γδ) T cells and other white blood cells play a crucial role in CRPS pathogenesis by perpetuating local inflammation and neurogenic sensitisation(14). By reducing the number and activity of γδ T cells and other inflammatory cells, amino bisphosphonates may help disrupt the pathological cycle of inflammation and pain (16-19).

An intriguing hypothesis further elaborates on this immunomodulatory mechanism: the administration of amino bisphosphonates, such as neridronate, induces an abrupt decrease in circulating γδ T cells, a phenomenon correlated with the intensity of the acute phase reaction (APR) (18-21). This rapid decline may result from the peripheral homing of γδ T cells to specific target sites, as demonstrated in mice studies showing migration to the ciliary body and enthesis, where these cells release IL-17 to stimulate local inflammation (22). This homing theory aligns with clinical observations of adverse events like uveitis and conjunctivitis following intravenous nitrogen-containing bisphosphonates, suggesting a targeted inflammatory response in susceptible tissues (23, 24). Additionally, in patients with CRPS, clinicians commonly see a mild exacerbation of symptoms within a few days post-infusion, potentially linked to γδ T cell homing into the affected limb. However, studies indicated that γδ T cell populations remain reduced even one year after the initial infusion, and subsequent infusions of amino bisphosphonates no longer trigger an APR (25). This could reflect a long-term depletion of γδ T cells in the bone marrow, which not only prevents further APR but may also underpin the broader anti-inflammatory properties of these drugs. Empirical evidence supports this, with reported reductions in cardiovascular events, pneumonia, and cancer incidence linked to amino bisphosphonate use (26-28). Notably, a *post-hoc* analysis of the HORIZON trial revealed that patients experiencing an APR at baseline derived greater anti-fracture benefits compared to those without APR, possibly due to enhanced anti-inflammatory effects mediated by this γδ T cell depletion (29).

A strength of our study is the prospective design, which allowed for systematic evaluation of clinical, densitometric, and therapeutic parameters. Additionally, the inclusion of a well-defined CRPS type 1 population with very early disease, homogeneous characteristics and rigorous diagnostic criteria ensures the reliability of our findings. The use of a standardised treatment protocol with neridronate also strengthens the validity of our conclusions.

However, our study has some limitations. First, although our sample size of 65 patients is relatively large for a CRPS cohort, it remains modest overall, which may limit the statistical power, particularly for subgroup analyses. Larger multicentre studies would be useful to validate our findings. Second, the follow-up period was limited to 30 days after treatment. While this time frame allows for the assessment of the early therapeutic effect of neridronate, it may not adequately capture long-term outcomes, recurrence rates, or the durability of pain relief, which are critical in

the context of chronic pain syndromes. Third, the lack of a placebo or standard-care control group limits our ability to draw firm causal inferences regarding treatment effects. Although implementing a placebo group in CRPS type 1 patients is ethically challenging due to the severity of the condition, the absence of a comparator group must be considered when interpreting the results. Finally, our cohort exhibited a gender imbalance, with a predominance of female patients. While this reflects the known epidemiology of CRPS type 1, the finding of greater pain reduction among male participants must be interpreted cautiously, as it may not be generalisable to the broader CRPS population. Finally, while our data suggests a mechanistic link between bone involvement and CRPS severity, the precise molecular and cellular interactions remain to be fully elucidated.

The predictive value of Z-score for treatment response highlights the potential of bone density assessments as a useful tool for identifying patients who may benefit most from bisphosphonate therapy. Further research is needed to elucidate the precise mechanisms by which bone interacts with the inflammatory and neurogenic components of CRPS, with the ultimate goal of developing more effective, personalised treatment approaches.

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