

## DESCRIPTIVE ASSESSMENT OF 54 CASES WITH COMPLEX REGIONAL PAIN SYNDROME IN LOWER LIMBS

DANIELA L. MANA<sup>1</sup>, ALBERTO MACKLIN VADELL<sup>2</sup>, RUBÉN ABDALA<sup>1,3</sup>, MARCELO SARLI<sup>1,3</sup>,  
ROSANA NAKUTNY<sup>1</sup>, MARÍA BELÉN ZANCHETTA<sup>1,3</sup>

<sup>1</sup>Instituto de Investigaciones Metabólicas (IDIM), <sup>2</sup>Sanatorio Finochietto,  
<sup>3</sup>Cátedra de Osteología y Metabolismo Mineral,  
Universidad del Salvador, Buenos Aires, Argentina

**Postal address:** Daniela Mana, Maza 578, 1220 Buenos Aires, Argentina

**E-mail:** daniela.mana@gmail.com

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### Abstract

**Introduction:** Complex regional pain syndrome (CRPS), also known as Sudeck syndrome, is a chronic painful condition usually affecting the limbs after trauma or surgery. Its presentation is heterogeneous and its pathophysiology, diagnosis and treatment remain controversial. The objective of this study was to analyze a group of patients with this rare syndrome, describing in detail the results of the dual energy X-ray absorptiometry (DXA) and the response to bisphosphonate treatment.

**Method:** We retrospectively analyzed 54 patients with CRPS, taking into account their demographic features, inciting events and diagnostic tests. As regards treatment, we analyzed the results and adverse events of the use of bisphosphonates

**Results:** We found a female predominance (74%), with 55 ± 13 years. The most common inciting event was trauma (59%), followed by surgery. The difference in bone mineral density between the affected limb and the healthy one was 12 to 15%. Forty-four patients were treated with bisphosphonates (pamidronate, ibandronate, zoledronic acid) and showed a clinical improvement, mainly in terms of pain intensity. Only six patients presented with adverse events, like pseudoflu syndrome and acute phase symptoms.

**Conclusion:** In our cohort, lower limbs CRPS predominantly affects middle aged women. DXA scans are tests used to quantify bone loss and the response to treatment. The use of bisphosphonates is an interest-

ing therapeutic option to improve clinical symptoms in most patients. Future prospective randomized studies will be needed to confirm our results.

**Key words:** Sudeck syndrome, chronic pain, bone mineral densitometry, bisphosphonates, lower limbs

### Resumen

**Evaluación descriptiva de 54 casos con síndrome doloroso regional complejo en miembros inferiores**

**Introducción:** El síndrome doloroso regional complejo (SDRC), también conocido como síndrome de Sudeck, es una enfermedad dolorosa crónica que generalmente afecta a las extremidades luego de un trauma o cirugía. Su presentación es heterogénea y existen controversias sobre su fisiopatología, adecuado diagnóstico y tratamiento. El objetivo de este trabajo es describir un grupo de pacientes con SDRC en miembros inferiores, describiendo los resultados de la densitometría mineral ósea (DMO) y la respuesta al tratamiento con bifosfonatos.

**Método:** Analizamos retrospectivamente 54 pacientes con SDRC, teniendo en cuenta características demográficas, factores desencadenantes y estudios diagnósticos. En relación al tratamiento, analizamos los resultados y efectos adversos del uso de bifosfonatos.

**Resultados:** Encontramos un predominio femenino (74%), con una edad de 55 ± 13 años. Los factores des-

encadenantes más comunes fueron los traumatismos (59%) y la cirugía. La diferencia de densidad mineral ósea entre el miembro comprometido y el sano fue 12 a 15%. En los 44 pacientes fueron tratados con bifosfonatos (pamidronato, ibandronato y ácido zoledrónico), su uso se asoció a mejoría clínica, especialmente del dolor. Seis pacientes tuvieron efectos adversos como síndrome pseudogripal y síntomas de fase aguda.

**Conclusión:** En nuestra población, el SDRC de miembros inferiores predomina en mujeres de edad media. La DMO es un método que permite cuantificar la pérdida ósea y la respuesta al tratamiento. Los bifosfonatos son una buena opción terapéutica para el control de síntomas. Son necesarios futuros estudios de naturaleza prospectiva y aleatorizada para confirmar nuestros resultados.

**Palabras clave:** síndrome de Sudeck, dolor crónico, densitometría mineral ósea, bifosfonatos

## KEY POINTS

- The chronic regional pain syndrome (CRPS) is a painful chronic disorder usually affecting the limbs after trauma or surgery. Its clinical presentation is heterogeneous. It is diagnosed by clinical criteria, while imaging tests help to identify the pathology and to differentiate it from other conditions. There is no treatment of choice, and the use of bisphosphonates has not been deeply studied but it has shown good results.
- This study revealed that DXA scans as a diagnostic tool for CRPS have sensitivity to detect and to objectivize the changes provoked by the syndrome in the affected limb and, also, post-treatment. The treatment with IV bisphosphonates (pamidronate, ibandronate and zoledronate) was efficient and with few adverse events.

Chronic regional pain syndrome (CRPS), also known as Sudeck syndrome, has been one of the most enigmatic medical pathologies since it was first described 150 years ago. Its name has undergone several changes over the years and more than 200 names, in different languages, have been identified for this syndrome<sup>1</sup>. The International Association for the Study of Pain (IASP) defines it as a chronic painful condition, characterized by spontaneous and evoked re-

gional pain, which usually starts in a distal limb and which is disproportionate in magnitude and duration to the typical course of pain after a similar tissue trauma<sup>2</sup>. In 1994, the IASP coined the name CRPS, with 2 subtypes, I and II, which share identical clinical features the only difference being the presence of a lesion in the peripheral nerve in type II. In a consensus meeting of the IASP which took place in Budapest in 2003, new clinical diagnostic criteria were proposed, which have been since known as “the Budapest Criteria”<sup>3</sup>. In 2007, due to a tendency towards overdiagnosis, the Budapest criteria were modified to include at least one symptom in 3 of the 4 categories, and the display of at least one sign found in the physical exploration in 2 or more of the considered categories<sup>4</sup> (Table. 1). By doing so, they retained a high sensitivity for CRPS (90%), but they improved its specificity enormously (69%). Imaging techniques such as Tc-99 bone scintigraphy and magnetic resonance imaging (MRI) are useful to make differential diagnosis with other pathologies and to confirm bone involvement<sup>5</sup>.

The condition presents itself with chronic pain usually affecting only one limb, together with a combination of distinctive signs and symptoms<sup>6</sup>. The main feature is pain, sometimes disabling, accompanied by a series of sensory, motor, autonomic, skin and/or bone disorders. The patient presents with different degrees of pain, allodynia, hyperalgesia, oedema and changes in skin color and temperature. Regional osteopenia, changes in hair and nail growth, and skin dystrophy can also be found<sup>1</sup>.

CRPS has a high impact on the person's life, and it represents a high economic burden for health systems. However, it still does not have a categorically effective treatment, probably because its physiopathology is not fully understood. Bisphosphonates (BP) are often used, but data on their efficiency and dosage are still scarce in the literature.

The objectives of this paper were to describe the features in a series of patients with diagnosis of CRPS in lower limbs followed up in our institution; to examine the inciting events; to evaluate the imaging methods used for their assessment, especially dual energy X-ray absorptiometry (DXA), and to analyze the results of treatment with BP.

**Tabla 1** | The International Association for the Study of Pain criteria for complex regional pain syndrome<sup>5</sup>

Continued pain that is disproportionate to any inciting event

Patient must report one symptom in three of the following four categories:

- Sensory: allodynia or hyperalgesia
- Vasomotor: temperature asymmetry, skin colour changes
- Sudomotor: oedema, changes in sweating
- Motor/trophic: decrease range of motion, motor dysfunction, changes in hair and nails growth

Must display one sign at the time of evaluation in at least two of the following categories:

- Sensory: evidence of allodynia or hyperalgesia
- Vasomotor: evidence of temperature asymmetry or skin colour changes
- Sudomotor: evidence of oedema or changes in sweating
- Motor: motor weakness/dysfunction

There is no other diagnosis that explains the patients sign or symptoms

CRPS 1 - Without evidence of major nerve damage

CRPS 2 - With evidence of major nerve damage

## Materials and methods

We carried out a retrospective, descriptive, observational cross-sectional study of 54 health records of ambulatory patients who had been evaluated in a bone clinic in Buenos Aires, Argentina.

We selected all the patients who had a diagnosis of “Sudeck” in their electronic health records between June 2013 and September 2017.

In a database, we recorded their demographic features (sex and age); inciting events; site of the lesion, results of imaging tests (radiographic images, Tc-99 bone scintigraphy, MRI and DXA), prescribed treatment (drugs and adverse events) and evolution (time of recovery and return to daily activities).

Bone mineral density (BMD) and bone mineral content (BMC) measurement:

BMD (g/cm<sup>2</sup>) and BMC (g) were measured by Lunar Prodigy DXA (GE Healthcare, Madison, WI, USA). We considered two regions of interest (ROIs) in the site of the lesion and two in the symmetric contralateral site (of equal surface area). We calculated the mean values of the BMD and the BMC of both the affected and the healthy limb ( $\pm$  standard deviation) and the difference between them. The results were expressed as mean  $\pm$  SD (standard deviation). The comparison between groups was made using the Student's t-test. A *p* value of  $<0.05$  was considered statistically significant.

## Results

The search for the term “Sudeck” as a diagnosis resulted in 77 patients, with a final cohort of

60 as 17 were excluded for lack of data and /or diagnostic mistakes. The diagnosis was primarily performed based on clinical findings with the support of imaging tests. Out of the 60 patients, 6 had upper limb involvement and were excluded.

### Demographic characteristics and inciting events

The average age was  $55 \pm 13$  years (range 24-85 years of age) and 74% were females.

Trauma was the most frequent inciting event ( $n = 32$ , 59% of the cases), especially when accompanied by fractures. Falls were the main cause of trauma, whereas strains, sprains and bumps followed in frequency. Other inciting events were programmed surgeries, mainly *hallux valgus*. Intense workout and immobilization were considered inciting events in a lesser proportion of patients, and no apparent cause was found in 5 cases.

The most common symptom was pain, which was present in 50 patients. Among the descriptive features, patients mentioned allodynia both while resting and walking, exacerbated when resting. Oedema was described in 35 patients. Seventeen patients presented with erythema, and 15 patients described an increase in skin temperature, whereas one patient showed just the opposite sign. One patient presented changes in sweating and another, less growth of nails and body hair.

Complementary tests: X-rays showed decalcification or loss of bone structure (characteristic findings of CRPS) in 87% of the patients. In 100%, Tc-99 bone scintigraphy was described as a hyper-capture pattern compatible with CRPS. MRI described oedema and bone involvement as the main findings in 87% of the cases.

Bone mineral densitometry tests were performed in 23 patients. All the averages (BMD of ROI 1 and 2, BMC ROI 1 and 2) of the affected side were lower (from 12% to 15%) than those of the healthy side, with statistically significant differences (Table 2). Individually, 21 of the cases showed 1 or the 2 ROIs with lower BMD and BMC in the affected side as compared with the healthy side. In 9 patients, we also performed a post-treatment control. The time elapsed between the two studies was  $10 \pm 5$  (range 4-18) months. The comparison of the affected limb before and after the treatment showed an improvement both in the BMD and in the BMC, although the differences were not statistically significant. The average increases ranged from 6 to 21% (Table 3).

### Treatment with bisphosphonates

A total of 44 patients received BPs. Ibandronate was the most widely used ( $n = 19$ ) both orally (monthly) and intravenously; in 7 patients it was used more than once (maximum 5 infusions). The second most used drug was zoledronic acid ( $n = 15$ ) and none of the patients repeated the treatment. Pamidronate was used in 10 patients, of which 5 had a particular regimen: 30–60–90 mg (once a week) and the rest received an irregular dosage, sometimes 30 or 60 mg. Only 2 patients were treated with 2 different BPs: one received pamidronate and another one ibandronate in the first instance and both received zoledronic acid later.

As regards BPs adverse events, 6 patients (14%) experienced pseudoflu syndrome and acute phase symptoms (3 had received zoledronic acid, 2 ibandronate and 1 pamidronate with the 30-60-90 mg regimen).

An improvement in symptoms, mainly pain intensity, was reported in 75% of patients. The individual analysis of each BP used showed that the best response, considering the percentage

**Table 2** | Bone mineral densitometry of both limbs ( $n = 23$ )

	Affected limb	Healthy limb	Difference % $\pm$ DS	p *
BMD ROI 1 (g/cm <sup>2</sup> )	0.65 $\pm$ 0.23	0.74 $\pm$ 0.26	-13 ( $\pm$ 10)	< 0.0001
BMD ROI 2 (g/cm <sup>2</sup> )	0.76 $\pm$ 0.40	0.88 $\pm$ 0.45	-13 ( $\pm$ 15)	< 0.005
BMC ROI 1 (g)	2.31 $\pm$ 0.81	2.62 $\pm$ 0.81	-12 ( $\pm$ 10)	< 0.0001
BMC ROI 2 (g)	2.16 $\pm$ 0.97	2.52 $\pm$ 1.05	-15 ( $\pm$ 17)	< 0.005

Data expressed as media  $\pm$  SD.

BMD: bone mineral density, BMC: bone mineral content, SD: standard deviation, ROI: region of interest

\*T-Student for paired data

**Table 3** | Comparison of affected limb before and after treatment ( $n = 9$ )

	Pre-treatment	Post-treatment	Increase % $\pm$ DS	p *
BMD ROI 1 (g/cm <sup>2</sup> )	0.73 $\pm$ 0.26	0.84 $\pm$ 0.39	13 ( $\pm$ 13)	0.07
BMD ROI 2 (g/cm <sup>2</sup> )	0.53 $\pm$ 0.27	0.58 $\pm$ 0.32	11 ( $\pm$ 26)	0.21
BMC ROI 1 (g)	2.28 $\pm$ 0.71	2.36 $\pm$ 0.56	6 ( $\pm$ 13)	0.42
BMC ROI 2 (g)	2.13 $\pm$ 0.58	2.49 $\pm$ 0.50	21 ( $\pm$ 26)	0.08

Data expressed as media  $\pm$  SD.

BMD: bone mineral density; BMC: bone mineral content; SD: standard deviation; ROI: region of interest

\*T-Student for paired data

of patients whose symptoms improved and returned to their daily activities, was obtained with ibandronate (16 out of 19 patients). All the patients who reported improvement did so within the first six months post treatment; two who received zoledronic acid and two who received intravenous ibandronate described improvement in their symptoms a week after treatment.

## Discussion

In this paper we describe the experience of the management of 54 patients with CRPS in lower limbs who were treated in an institution specialized in osteology. The epidemiological characteristics of our cohort, the female predominance and the average age (55 years) coincide with the data published in the literature<sup>7</sup>. Other authors found a male predominance, suggesting it might be due to men's higher disposition to trauma<sup>8</sup>. As regards age, some series described a higher prevalence of CRPS in older people, related to the higher rate of injuries and fractures associated with this age group<sup>7</sup>. A higher risk has also been described in post-menopausal women, suggesting that hormonal factors might be involved in the pathogenesis of CRPS<sup>9</sup>.

In our cohort, trauma was found to be the main inciting event for CRPS as described in many series<sup>7, 8, 10-12</sup>. Among trauma, fractures carry more risk of developing CRPS as the presence of fracture is usually related to more severe injuries, extensive destruction of tissue, the need for surgery in many cases, and a higher rate of medical complications<sup>11</sup>. There are some other conditions associated to fractures that might increase the risk, such as the need for reduction on a displaced fracture, the pressure of the cast used to immobilize it, the type of anesthesia used (local vs general), inappropriate physiotherapy<sup>10</sup> and intra-articular involvement of the fracture<sup>9</sup>. Despite discrepancies, most authors believe that the higher the severity, the greater the risk<sup>13</sup>.

Though it varies in different series, there is, in most cases, a predominant involvement of the upper limbs<sup>7, 8</sup>. However, in our initial cohort, 90% of the patients showed involvement of the lower limbs, which is probably due to an institutional bias as 85% of the referring physicians, are traumatologists who specialize in foot pathologies. In this context, which differs from what is

described in the literature; only those patients with lower limb involvement were analyzed and described in this study.

Programmed surgeries were the second cause of CRPS, in agreement with the literature data<sup>14</sup>, with a higher prevalence of Hallux Valgus<sup>15</sup>.

Complementary imaging tests are used to study CRPS and they are mainly useful to make a differential diagnosis with other chronic pain syndromes<sup>16</sup>. DXA scans of feet carried out in our center showed that in healthy patients there is no difference in BMD or BMC between both feet<sup>17</sup>. DXA results coincide with those described in the literature<sup>18</sup> where some authors report even greater differences between both limbs. Some of our patients showed a minimal difference between the affected and the healthy limb, sometimes only evident in a ROI, which might be explained by the patched and heterogeneous bone resorption pattern and is usually present in CRPS<sup>14</sup>. In the study of Bruscas Izu et al., this pattern was especially associated to hand/wrist and foot/ankle lesions<sup>8</sup>. Moreover, it has been reported that immobilization and lack of use lead to bone loss of both the affected limb and the contralateral one, which decreases the sensitivity of the method to detect changes. Kumar et al. studied patients suffering from post-stroke CRPS in which the BMD loss was correlated with duration of immobilization, severity of pain and autonomic involvement of the affected limb<sup>20</sup>.

DXA was also sensitive to the increase in bone content related to treatment. Arriagada et al. describe the post-treatment results of 8 patients treated with prednisone or calcitonin, identifying an increase of 20% in the DXA of the affected limbs<sup>18</sup>. Chapurlat et al., in a longitudinal study of CRPS patients, state that in those patients treated with pamidronate in an early stage, the DXA remained stable, preventing bone loss<sup>21</sup>. Our results reaffirm the assertion of the importance of DXA scans in the study of CRPS<sup>22</sup>. It is a simple, non-invasive method that involves minimum radiation and preparation that gives a quantitative measurement of the bone content and density.

Bisphosphonates have traditionally been the most studied drugs for the treatment of CRPS<sup>23</sup> and they should be considered the treatment of choice for patients with this diagnosis<sup>24</sup>. A

marked loss of bone (positive uptake on scintigraphy, demineralization on X-ray, bone oedema on MRI and loss of mineral density on DXA) along with the analgesic effect shown in several bone pathologies<sup>25</sup>, are the reasons that justify their use in CRPS type I<sup>26</sup>. However, the increase in osteoclast activity has never been well demonstrated in this pathology, which raises questions about the way bisphosphonates work in this syndrome<sup>27</sup>. A potential mechanism of pain in CRPS might be the activation of two main groups of acid-sensing nociceptors (TRPV1 and ASICs), due to local acidosis secondary to the hypoxemia produced by microvascular alterations. BPs might act on this pathway as they decrease the proton concentration in the bone microenvironment. They also inhibit the growth, migration and activity of the mononuclear cells derived from the bone marrow<sup>28</sup> with a reduced release of neuropeptides such as substance P and the calcitonin gene-related peptide<sup>26</sup>. Both *in vitro* and *in vivo*, they reduce the expression of TNF and of cytokines such as IL 1 and 6<sup>29</sup>, and their effect on other cells such as macrophages and microglia has been demonstrated, including those cells that release pro-pain substances such as nerve growth factor  $\beta$ . This mechanism via microglia, along with the inhibition of neurotransmitter release, might explain an additional analgesic effect of BPs at base level<sup>30, 31</sup>. In conclusion, the potential beneficial effects of BPs in the treatment of CRPS are not related to their traditional antiresorptive activity, but to a much more complex interaction<sup>32</sup>.

In the literature, only five randomized, placebo controlled and well-designed studies evaluated the results of the use of oral<sup>33</sup> and IV<sup>34</sup> alendronate, clodronate<sup>35</sup>, pamidronate<sup>36</sup> and neridronate<sup>27</sup> in CRPS. They all showed reduction of pain and improvement of functionality of the affected limb - especially with alendronate<sup>34,36</sup> - and of oedema<sup>35</sup>. Other benefits described were improvement of vitality, of mental state (feeling good) and of other indicators of quality of life<sup>27</sup>. The time elapsed before the improvement of symptoms was very variable, but an improvement in pain, oedema and mobility could be observed as early as two weeks after starting treatment with IV alendronate<sup>34</sup>. Evidence shows that the antinociceptive effect

of BPs on bone is dosage dependent<sup>37</sup>, therefore, some authors suggest using higher doses than those recommended for Paget disease and advise a regimen of 4 doses of 90 mg administered over 4 to 10 days<sup>27</sup>.

There are very few studies that analyze the efficiency of ibandronate and zoledronic acid. A study of 10 patients with CRPS<sup>38</sup>, used high doses of ibandronate (infusions of 6 mg /day for three consecutive days) and found a significant post-surgery improvement in the control of pain and in some features of neuropathic pain (sensitivity, depth, intensity) as well as in hyperalgesia and allodynia. The use of ibandronate 3 mg IV was also associated with improvement in pain and clinical signs<sup>39</sup>. As regards the use of zoledronic acid, Ahmad et al<sup>40</sup> described the case of a patient with CRPS who was treated with zoledronic acid, after the failure of NSAIDs, corticoids and physiotherapy. The patient received 2 doses of 4 mg IV, separated by one month, showing improvement in pain, oedema and in the DXA scan, with partial functional recovery. A recent study published by Walfish et al.<sup>41</sup> describes the case of 16 children and adolescents with CRPS treated with ibandronate and zoledronic acid who had recurrence or no response to conventional treatment. Nine of the 16 patients reported significant improvements in the score of the global impression of change (84% or more), 8 to 21 months after the last BP infusion. There was also a significant decrease in pain intensity and in the need for analgesics. The number of patients with minimum or no disability increased, and almost all the patients resumed their school activities.

As regards adverse events associated with treatment with BPs, we found 14% in our series, whereas large series showed percentages as low as 5% (with oral alendronate)<sup>33</sup> up to 50% (with IV pamidronate)<sup>36</sup>. In brief, the role of BPs in the treatment of CRPS is not very clear yet, and the published data are scarce. The proper dosages, along with the administration intervals have not been fully clarified, but our results are encouraging due both to the reported efficacy and the speed of response.

This study has several limitations: 1) the population was heterogeneous and its evaluation was carried out by different physicians, of varied specialties, therefore the study criteria,

diagnosis and treatment were different; 2) as it usually happens with retrospective studies, the data and the results are limited to the information available; and 3) the population under study comes from an institution that specializes in osteology, which, is probably associated with an attention and population bias and 4) the published results are those of patients with lower limb involvement. We do not know if they can be extrapolated to upper limbs or other variants of this syndrome.

On the other hand, it has several strengths: 1) its sample size, as we analyzed 54 patients suffering from a syndrome that is considered rare; 2) the interesting results obtained using DXA scans, which open the way to a promising field in the study of this pathology and 3) the important conclusions we could draw from the use of BPs for the treatment of this pathology, which turned out to be efficient and safe.

In conclusion, this research reflects the experience of a centre specialized in bone health regarding the study and treatment of this rare syndrome. Although our review has the above-mentioned limitations, it provides unpublished data that might open new lines of research in the future. The use of DXA in these cases offers a new perspective regarding bone involvement in this syndrome. Finally, the use of bisphosphonates for its treatment is very promising, and deserves to be evaluated in prospective studies involving a higher number of patients.

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