VITAMIN D
UpDates
2024;7(2):42-46
https://doi. org/10.30455/2611-2876-2024-3e

Vitamin D deficiency and Complex Regional Pain Syndrome

Massimo Varenna, Francesca Zucchi, Chiara Crotti, Raffaele Di Taranto, Francesco Orsini

Osteoporosis and Metabolic Bone Disease Unit, ASST Pini-CTO, Milan

To consider the possible relationships between vitamin D and algodystrophy syndrome, i.e. complex regional pain syndrome (CRPS), one must understand that bone tissue is a key player in the pathogenetic dynamics of the syndrome [1]. In addition to the results obtained by treatment with drugs whose mechanism of action involves bone tissue as their main target, there is also much evidence supporting the fundamental role that bone has in the onset and maintenance of the disease. Aside from findings arising from diagnostic testing (osteoporosis on standard radiology, hypercaptation on scintigraphy scans, bone oedema on magnetic resonance imaging), epidemiological studies have reported that fracture is the most frequent predisposing event. Consequently, all diseases that lead to an increase in bone fragility and therefore to the incidence of fractures (postmenopausal and senile osteoporosis, osteogenesis imperfecta) are often exacerbated by an increase in the incidence of algodystrophy. As further proof of this pathogenetic link, there are reports showing that osteoporosis is present in patients with CRPS at a significantly higher prevalence than in the general population [2]. Additionally, an animal model that closely reproduces human disease can been obtained by inducing a distal fracture of the tibia. Lastly, it is worth mentioning that an increase in osteoprotegerin (OPG), the molecule involved in the regulation of the RANK/RANKL system, has been implicated in the early stages of the disease.

As previously reported, in most cases, it has been ascertained that a traumatic fracture event is the most frequent predisposing factor for CRPS. In addition, the most reliable epidemiological findings [3] have shown that the peak incidence of distal radius fractures, i.e. the fracture event that is most often complicated by CRPS [4], among females and in the decade following menopause, is likely to be reflective of a similar trend within the general population. Data on the incidence following distal radius fractures in the literature vary widely (ranging from 1% to 37%). This variability can undoubtedly be attributed to the different diagnostic criteria used to document these events. The most recent studies using the diagnostic criteria adopted by the International Association for the Study of Pain (IASP), i.e. Budapest criteria, which have been recognised to be the best in terms of sensitivity and specificity, report that CRPS is present in 14% of patients who have suffered distal radius fractures [4].

It has been widely acknowledged that this type of fracture is the earliest clinical event related to osteoporosis, in that it occurs, on average, 15 years before proximal femur fractures, and that it is also a predictive event for other fragility fractures, namely vertebral fractures and proximal femur fractures [5]. Among the many clinical variables identified as being predictive of distal radius fractures is vitamin D deficiency [6]. Therefore, beginning from the premise that adequate vitamin D levels are essential for good bone health, researchers have investigated whether vitamin D deficiency might be why deficient subjects, who would clearly be more prone to fragility fractures, are more likely to be affected by CRPS.

Another aspect under investigation is whether vitamin D deficiency can, in the presence of a fracture event and independently of other variables, favour the onset of CRPS. Distal radius fracture (Colles' fracture) has been the most extensively investigated fracture event. In a retrospective orthopaedic study in 2020 of more than 100 postmenopausal women, those who experienced the onset of CRPS after a distal radius fracture had significantly lower levels of plasma vitamin D than those without CRPS (Fig. 1) [7]. It is compelling to point out that biochemical markers for bone turnover (i.e., osteocalcin and alkaline phosphatase), as well as bone density assessments carried out on both the lumbar

Correspondence
Massimo Varenna
Massimo.Varenna@asst-pini-cto.it

Conflict of interest
The Author declares no conflict of interest.

How to cite this article: Varenna M, Zucchi F, Crotti C, et al. Vitamin D deficiency and Complex Regional Pain Syndrome. Vitamin D – Updates 2024;7(2):42-46. https://doi.org/10.30455/2611-2876-2024-3e

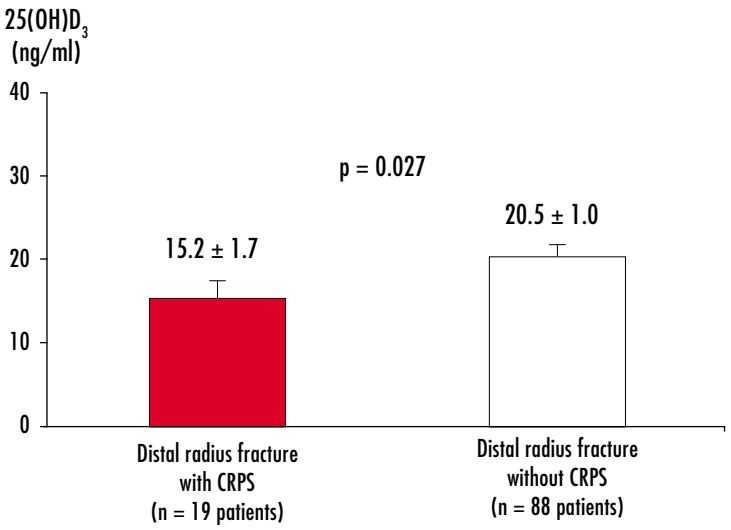

FIGURE 1.
Comparison of levels of $25(OH)D_3$ in 19 patients who developed CRPS after a distal radius fracture and 88 patients who did not develop CRPS.

spine and proximal femur, showed no significant differences between patients who developed CRPS and those who did not, even if they had the same fractures and the same surgical treatments.

From a theoretical standpoint, the results of the study have opened the door to a number of likely pathogenetic possibilities that link low levels of vitamin D to CRPS. First, bone density investigations showed no significant differences in the occurrence or non-occurrence of CRPS. This makes it possible to hypothesise that osteoporosis defined by bone density alone does not represent a risk factor for CRPS. On the other hand, the above epidemiological considerations are consistent with an indirect role of osteoporosis: the presence of low bone mass values might be considered the reason for which subjects with osteoporosis more frequently experience a predisposing event such as fracture of the distal radius. Similar considerations could also be made for metabolic biomarkers of bone. The fact that findings in subjects with CRPS and those without it are similar would tend to exclude that the levels of bone turnover represent a risk factor for the onset of the condition. Notwithstanding, other reports in the literature reveal a possible key to the interpretation of these results.

In a recent study of subjects who presented with distal radius fractures, it was shown that at the time of the fracture those with intra-articular fractures (with involvement of the distal cortical bone of the radius) had significantly lower serum levels of $25(OH)D_3$ than those with extra-articular metaphyseal fractures [8]. To further investigate this aspect, an observational study of approximately 600 patients with fracture explored predictive factors for CRPS [4]. It was found that those who developed CRPS more frequently had intra-articular and multifragmentary fractures than those who did not. Accordingly, vitamin D deficiency could play an indirect role and could be predictive of intra-articular fractures, which would in turn correlate with an increased likelihood of developing CRPS.

The same could easily apply to rheumatoid arthritis. Indeed, the high prevalence of vitamin D deficiency in patients with rheumatoid arthritis is well known [9], and its presence is a risk factor for development of CRPS following a fracture event [4]. Last, an additional causal link considering CRPS, fractures and vitamin D deficiency must include the propensity for falls among the elderly with inadequate vitamin D levels [10]. CRPS is characterised by intense pain, along with sensory and vasomotor changes, local oedema and functional deficits. Significant insights into the pathogenetic mechanisms of CRPS have been made in recent years (Fig. 2). A local increase in proinflammatory cytokines and the release of neuropeptide mediators by nociceptive afferents that interfere with the regulation of local microcirculation helps to trigger and maintain the condition. These events lead to hyperalgesia, i.e. a painful perception disproportionate to the intensity of the stimulus, together with and allodynia, i.e. a painful perception following a stimulus that is not normally capable of evoking pain. Subsequently, altered capillary permeability, interstitial oedema and hypoxia, as well as local acidosis, comprise the subsequent pathogenetic events that sustain the typical clinical manifestations, namely intense pain, oedema, alterations in palpable heat and local discolouration (Fig. 3) [11].

The use of highly sensitive biochemical methods and animal models have made it possible to identify neuroinflammatory events that are pathogenetically connected with the initial clinical manifestations of the condition. In mouse models of CRPS-1, high local concentrations of nerve growth factor, which is potentially implicated in the onset and transmission of pain and in inducing the production of local cytokines, has been observed. It is well-known that high local concentrations of proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6), are present during the early stages of the CRPS. Other studies have reported that high systemic concentrations of these cytokines are also present. Furthermore, there is evidence that the local release of certain proinflammatory cytokines is also mediated by the involvement of keratinocytes in skin, easily justifying the intense inflammation that is typical at the onset of CRPS.

To consolidate the epidemiological and clinical findings mentioned above, consideration must also be given to other pathogenetic factors correlating CRPS with vitamin D levels. One must also link the primary role of vitamin D in regulation of mineral metabolism with its deficiency and an increase in bone fragility and risk of fracture. The likelihood of developing neurological diseases characterised by inflammation/neuroinflammation also appears to be influenced by inadequate levels of vitamin D [12].

Further evidence of a pathogenetic role in the development of CRPS is the influence that vitamin D has on the endogenous production of proinflammatory cytokines. In an observational study published in 2014, which included 957 subjects over

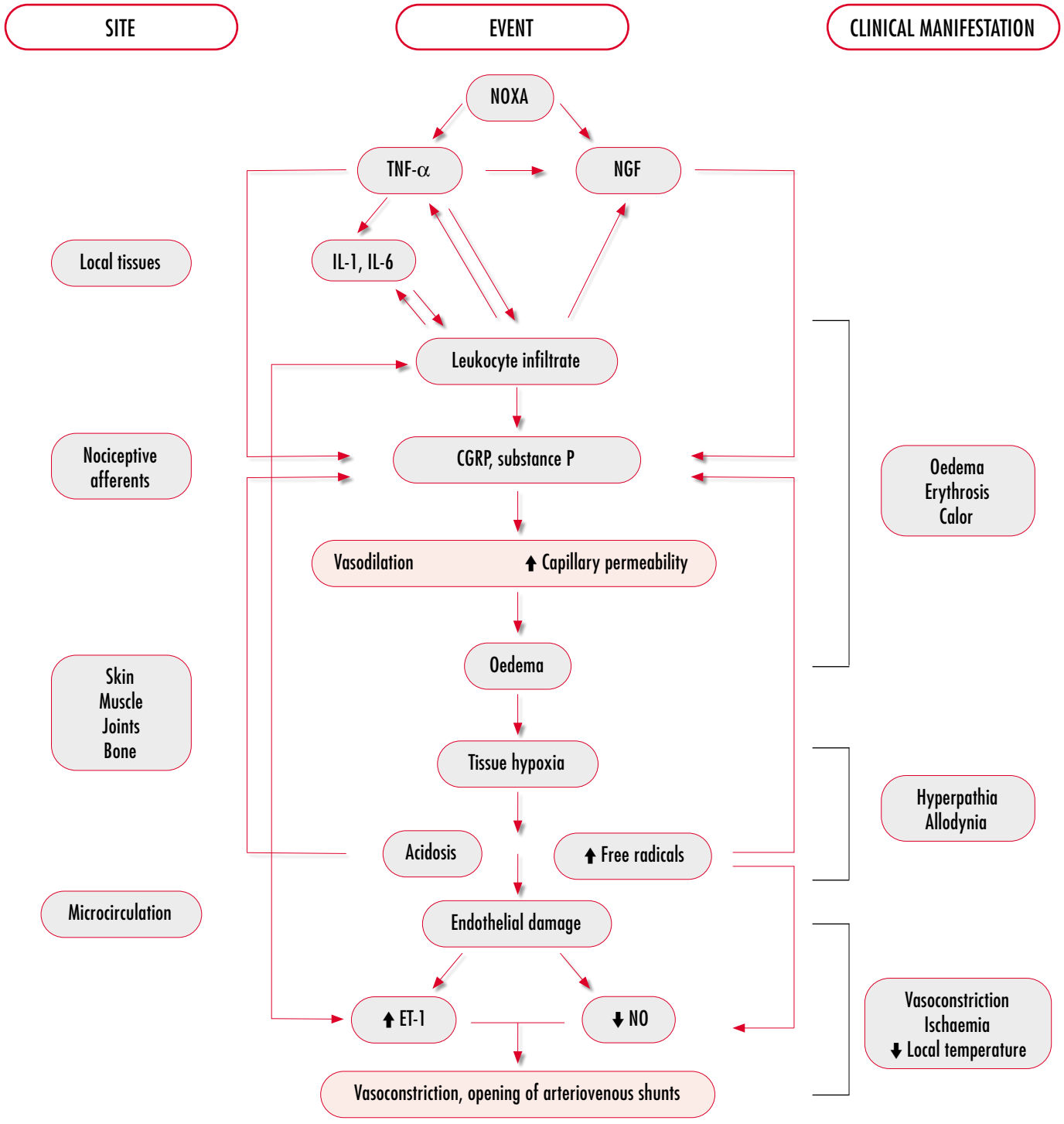

FIGURE 2.
Pathogenetic mechanisms involved in the onset, maintenance and clinical manifestations of CRPS-1.

the age of 60 years, plasma levels of selected cytokines were assessed along with $25(OH)D_3$ [13]. Plasma levels of IL-6 were found to be significantly higher in those with vitamin D levels < 25 nmol/L compared to those with normal values (> 75 nmol/L). It should be pointed out that IL-6 is among the cytokines whose levels are increased both locally and systemically during CRPS.

A similar finding was also observed for another proinflammatory cytokine involved in the pathogenesis of CRPS, namely TNF-α. In 69 healthy women between 25 and 82 years of age, the

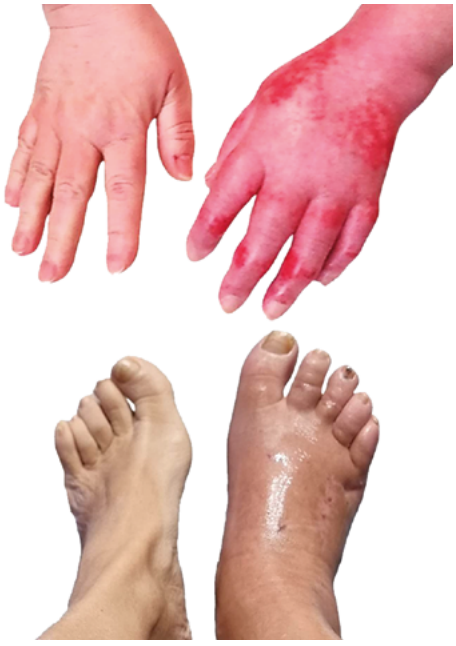

FIGURE 3.
Images of CRPS with involvement of the hand and the foot. The clearly intense inflammatory profile is evident in the early stages of the disease.

plasma levels of 25(OH)D_3 were inversely correlated with the levels of TNF-α [14]. As further corroboration of a plausible causal link between levels of vitamin D levels and proinflammatory cytokines, some studies have reported that vitamin D supplementation can reduce the plasma concentrations of TNF-α, IL-1 and IL-6 [15].

At present, there is no definitive evidence that vitamin D supplementation is a valid strategy to prevent CRPS. Nonetheless, it has been shown that vitamin D deficiency can promote algodystrophy, and the rationale for this correlation is based on the below considerations:

- Vitamin D deficiency leads to an increased risk of fracture events, which are the most typical predisposing event for CRPS;
- Low levels of vitamin D favour the occurrence of intra-articular fractures, which more frequently correlate with the development of CRPS;
- Vitamin D deficiency correlates with an increased risk of falls, thus favouring fractures, which are a trigger for the development of CRPS.

Since vitamin D deficiency promotes predisposition to CRPS following a fracture, the most likely pathogenetic pathway seems to be an immunological status characterised by increased serum levels of pro-inflammatory cytokines, which promote the inflammatory phase in CRPS. Accordingly, the rationale for vitamin D supplementation in those with deficiency is that normalisation of plasma 25(OH)D_3 levels should lead to reduced production of the inflammatory mediators of CRPS.
A point worthy of clinical investigation is the possible therapeutic role of vitamin D administration in patients with CRPS. In this respect, there are now therapeutic strategies that have profoundly improved patient outcomes. The efficacy of bisphosphonates should be considered a definitive finding, which has been shown in randomised placebo-controlled trials and meta-analyses, i.e. the tools with the highest levels of evidence. Among the different bisphosphonates, neridronate, which has been shown to have the highest efficacy, induces rapid remission of CRPS that is maintained in the long term [16,17]. In fact, neridronate is the only bisphosphonate approved by the Italian Medicines Agency (AIFA) for this indication.

Since the fundamental assumption is that high doses of the drug are required, which can only be obtained with intravenous administration, this implies treatment in a hospital setting, leading to logistic issues. From this consideration, attempts have been made to use older drugs via intramuscular administration, with the possibility of more manageable home-based treatments. Unfortunately, clodronate has not been demonstrated to be effective when administered intramuscularly, which is likely due to its pharmacokinetic and pharmacodynamic profile. However, some studies have recently reported that intravenous and intramuscular administration of neridronate have similar efficacy [17,18]. In this regard, AIFA has approved neridronate for treatment of CPRS when administered intramuscularly [19].
Lastly, another interesting aspect to investigate would be involve the potential benefits of vitamin D supplementation in combination with a bisphosphonate. However, it must be kept in mind that despite advances in therapy, early treatment, at a stage when the levels of proinflammatory cytokines trigger and maintain the condition, is essential.

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