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Commentary

Osteoprotegerin: Another piece in a complex (regional pain syndrome) puzzle

Much of the complex regional pain syndrome (CRPS) research has been performed to unravel the pathophysiological pathways underlying this multifaceted and multifactorial disease. Major pathophysiological mechanisms have been identified that, when combined, provide an explanation for the abundance of clinical features expressed by CRPS patients: aberrant inflammation, nociceptive sensitization, vasomotor dysfunction, and maladaptive neuroplasticity [12]. The study of mechanisms associated with impaired bone remodeling in CRPS has lost some attention, although spotty osteoporosis, shown by 7% to 52% of patients across different disease durations of CRPS [17], is still considered a key diagnostic feature by some. Krämer et al. evaluated the value of osteoprotegerin (OPG), an inhibitor of osteoclast formation, as a potential biomarker for CRPS. The work of Krämer et al. in a sense pays tribute to ideas of one of the founding fathers of CRPS, German surgeon Paul Sudeck (1866–1945), who first described bone reformation in cases of "acute inflammatory bone atrophy" [9,14]. However, it is interesting to see how well the findings of Krämer et al. fit in and contribute to current understandings of this disease.

The broader context

OPG, a decoy receptor belonging to the tumor necrosis factor (TNF) receptor superfamily, inhibits osteoclast formation, thereby decreasing bone resorption and protecting bone mineral density [1]. In a concise study, Krämer et al. found that OPG levels in CRPS patients were significantly increased compared with healthy control subjects and patients after uncomplicated fractures. Diagnostic accuracy of OPG was found (sensitivity of 0.74, specificity of 0.80) compared with a historical normative dataset. Furthermore, OPG values correlated with radiotracer uptake in a 3-phase bone scintigraphy analysis in phase III, which is indicative of bone turnover activity. There is, however, more to the story than just bone remodeling. OPG is closely involved in regulating NF-κB activation by inhibiting receptor activator of NF-κB (RANK) by binding to its ligand (RANKL) [1]. Increased NF-κB activity has been suggested in the pathogenesis of several chronic inflammatory disorders, including CRPS [5]. NF-κB is involved in general pathologic mechanisms that also have been proposed to play a role in CRPS, such as inflammation, oxidative stress, and sensitization. OPG can therefore be considered a more generalized marker of inflammation. What is also noteworthy is that in the work of Krämer et al., OPG levels are increased in the sample. OPG upregulation, as found by Krämer et al., therefore can be an expression of a counterbalance in the inflammatory cascade of CRPS, which in essence is what is supposed to happen. OPG protects the skeleton from excessive bone resorption. In that sense, a challenging thought would be to regard this as a good thing: biomarkers are always viewed in the context of existing pathology, whereas these elevated OPG levels also may be an expression of an adequate response of the body to address threats posed to the integrity of the organism. The problem may be further upstream or lie in the interlinking between different mechanisms. From a systems perspective, it has been proposed that the nervous-immune-endocrine ensemble works as an overarching system responding to tissue trauma, and dysregulation of this system may contribute significantly to chronic pain and multisymptom disorders [4]. It is therefore relevant to look at the balance. For instance, TNF-α and interleukin (IL) 1, both found in elevated levels in plasma and blister fluid in CRPS [8], acting in concert with RANKL are powerful promoters of osteoclast recruitment, as has been established in rheumatoid arthritis [13].

Is this a unique marker for CRPS?

The variety of symptoms observed in CRPS patients can be regarded as an expression of interindividual variability in the activation of pathophysiological pathways after trauma. Existence of distinct subtypes within the spectrum of CRPS has been shown based on K means cluster analysis [3], whereby indications were provided for a subgroup with vasomotor signs predominating, a subgroup with predominantly neuropathic pain/sensory abnormalities, and a more florid subtype showing the highest levels of motor/trophic signs and osteopenia on bone scan. OPG may be a puzzle piece providing a rationale for the mechanism leading up to this third subtype. However, in the grand scheme of things, OPG will have to compete with other biomarkers proposed for inflammation, sensitization, cortical reorganization, and vasomotor disturbances in CRPS, including (but not limited to) TNF-α, IL-1, IL-6 [8], glutamate, glycine [18], and endothelin-1 [7]. The combination of these and other parameters together with OPG, including both upregulating and downregulating mediators, should be assessed in the individual CRPS patient and correlated with the clinical presentation of the patient. Also the onset of the complaint should be taken into account; the sample of Krämer et al. consisted predominantly of patients with a significant limb trauma (fracture or surgery). It would be interesting to know whether these findings can be reproduced in a larger sample of CRPS patients with less substantial (i.e., sprains, minor lesion) or even spontaneous onsets.

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Furthermore, OPG elevation is by no means unique to CRPS. As mentioned by the authors, increased OPG is associated with osteoporosis, coronary heart failure, and irritable bowel syndrome. Elevated OPG levels are also associated with long-term renal dysfunction, and are suggested to predict the trajectory of renal decline in older women [10]. It is therefore likely that this also reflects a more common disease pathway occurring in many diseases.

Then there is the issue of biomarker quality. To be useful, a clinical marker needs to be easy to assess, and to have sufficient diagnostic capacity to distinguish a disease or mechanism from other diseases. The authors should be commended for including a post-fracture reference group in their study. The next step would be to assess the discriminative value of OPG levels compared with other differential diagnoses of CRPS, such as peripheral neuropathic complaints and inflammatory joint disorders. To be used in a clinical setting, it is suggested that sensitivity and specificity of a biomarker should be at least 90% [2] to be of diagnostic value, although what is acceptable may differ among illnesses.

Relevance for treatment

The interesting findings of Krämer et al. may lend some support to nonspecific modulators of the RANK/RANKL/OPG pathway already used for treatment of CRPS, such as free radical scavengers, corticosteroids [6], and bisphosphonates [11]. In animal studies of osteoporosis, bisphosphonates enhance OPG expression and inhibit the expression of RANKL [16]. It may also open a path to new treatment options. For instance, targeting the RANK/RANKL/OPG pathway with monoclonal antibodies against RANKL has been shown to be effective in reducing bone resorption in osteoporosis [15]. Although speculative, these findings also may be suggestive of the necessity of activation and exercise for CRPS patients to counter nonuse-associated dysregulation of this pathway. The authors should be commended for giving us these insights and providing data to further disentangle this complex phenomenon called CRPS.

Conflict of interest statement

The author has been involved in contract research for Grunenthal, and has received an unrestricted research grant and consultancy fees from Pfizer.

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