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Complex regional pain syndrome: A vitamin K dependent entity?

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Abstract

Complex regional pain syndrome (CRPS) is the complication of some injuries, such as a fracture, which affects the distal end of the injured extremity characterized by pain, allodynia, hyperalgesia, edema, abnormal vasomotor and sudomotor activity, movement disorders, joint stiffness, regional osteoporosis, and dystrophic changes in soft tissue. Exact pathogenic mechanism of CRPS is still unclear. Suggested pathogenic mechanisms of CRPS are evaluated in four major groups consist of classic inflammation, hypoxic changes and chronic ischemia, neurogenic inflammation and sympathetic dysregulation. All of these suggested pathogenic mechanisms produced by inflammatory cytokines mediated by nuclear factor kappaB. Vitamin K is a family of structurally similar, fat-soluble, 2-methyl-1,4-naphthoquinones. Vitamin K exerts a powerful influence on bone formation, especially in osteoporosis. Fat in bone stores some vitamin K. Gamma-carboxylation of the glutamic acid in osteocalcin is vitamin K dependent. Osteocalcin plays a role in calcium uptake and bone mineralization. Osteocalcin, the most abundant non-collagenous protein in bone, is produced by osteoblasts during bone matrix formation. Because osteocalcin is not carboxylated in case of vitamin K deficiency at the distal site of fracture or injury, it cannot bind to hydroxyapatite causing osteoporosis. Fracture starts a local inflammatory process in the fracture site and adjacent tissues as seen in CRPS. Vitamin K was shown to suppress the inflammatory cytokines and NF-kappaB and prevent oxidative, hypoxic, ischemic injury (which have key role in both initiation and progression of CRPS) to oligodendrocytes and neurons. We hypothesized that vitamin K has a key role and modulatory effect in CRPS pathogenesis. Vitamin K deficiency at the distal site of fracture occurs because of diminished and slowed circulation, local immobilization after extremity fracture or injury and use of vitamin K store at the distal site of the injured extremity and in the circulation for fracture healing and bone remodelling. In case of vitamin K deficiency at the distal site of fracture, classic inflammation starts with fracture at the distal tissues could not be restricted and classic inflammation, hypoxic changes, chronic ischemia, neurogenic inflammation, sympathetic dysregulation, which are the pathogenic mechanisms of CRPS, and patchy osteoporosis which occur due to high level of under-carboxylated osteocalcin could not be prevented. Briefly vitamin K level decreases in the distal site of the injured extremity consequently resulting in patchy osteoporosis due to high level of under-carboxylated osteocalcin and unrestricted inflammation which are the cause for both initiation and progression of CRPS.

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