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Letter to the Editor

Vitamin B12 (Cobalamin) Supplementation for the management of Autoimmune Rheumatic Diseases – potential indications and opportunity for future research

To

The Editor-in-Chief, Rheumatology International

We would like to bring to the attention of the Rheumatology International community the opportunity for research on vitamin B12 (cobalamin, VB12) supplementation in the pain management of autoimmune rheumatic diseases (ARD). As a large and heterogeneous group of systemic disorders characterized by inflammation and immune dysregulation, the ARD global prevalence is varied. In Taiwan, for example, ADRs are estimated to affect approximately 100 per 100,000 population [1]. Nonetheless, its prevalence appears to be much higher in other global regions. For example, the prevalence of adult rheumatoid arthritis ranges from 100 per 100,000 in South America, to 1,000 per 100,000 in North America [2].

VB12 deficiency is a relatively common disorder, mostly associated with its poor absorption due to losses of gastric intrinsic factor. VB12 deficiency can be manifested by non-specific clinical features and, in more severe cases, neurological and or haematological manifestations [3]. The roles of neurotropic B vitamins as modulators of inflammation and pain have been proposed in the literature [4-6]. In addition, antinociceptive, antiallodynic, and anti-hyperalgesic properties of B vitamins, and their synergistic effects when combined with commonly prescribed analgesics, have been proposed [5-7]. Understanding how B vitamins affect several nociceptive mechanisms can be of clinical significance when managing various pain conditions.

VB12 appears to have a role in ARDs, mainly those characterised by a prominent systemic inflammatory component and pain. Such speculation led us to perform a literature search in the Medline PubMed, SciELO, LILACS, Scopus, and Directory of Open Access Journals databases. No language restriction filters were applied, and the period searched covered 1965 to August 2023. The MeSH entry terms utilised were as follows: "cobalamin" OR "methylcobalamine" OR "vitamin B12" AND "rheumatic" OR "rheumatologic" OR "systemic lupus erythematosus" OR "lupus" OR "fibromyalgia" OR "rheumatoid arthritis" OR "spondyloarthritis" OR "Sjögren's syndrome" OR "myositis" OR "systemic sclerosis" OR "vasculitis" OR "Takayasu disease" OR "Wegener's disease" OR

"granulomatosis with polyangiitis" OR "Kawasaki's disease" OR "polyarteritis nodosa" OR "Livedoid vasculitis" OR "Churg-Strauss syndrome" OR "eosinophilic granulomatosis with polyangiitis" OR "osteoarthritis" OR "gout". The reference lists of the selected articles were also analysed, to identify potential studies gone undetected in the first search.

Unfortunately, very few clinical trial research articles were found, including [8-10]. The studies found involved a very small number of participants: 26 [8], 48 [9] and 130 [10], and presented varied supplementation protocols. Only [8] adopted a cross-over protocol.

In the study of Flynn and colleagues [8], 26 patients (in which 23 were females) suffering with hand osteoarthritis were assessed. The study participants were prospectively followed, supplemented with 6,400 mg folate, or 6,400 mg folate plus 20 mcg cobalamin, or a placebo, for 2 months. At the end of the supplementation period, handgrip strength readings were higher in the combined cobalamin/folate group than in the other groups. The former also showed readings similar to those of patients on non-steroidal anti-inflammatory drug (NSAIDs) therapy. Interestingly, the occurrence of tender joints was greater with the use of NSAIDs than with cobalamin/folate supplementation. No side effects were observed in the vitamin supplemented group.

The patients followed in the study of Magaña-Villa [9] were scheduled for knee arthroplasty and followed a clinical protocol with either a single intramuscular injection of sodium diclofenac (75 mg) alone or combined with thiamine 100 mg, pyridoxine 100 mg and cyanocobalamin 5 mg. The protocol of Kaur [10] included thiamine 10 mg, riboflavin 10 mg, nicotinamide 45 mg, pyridoxine 3 mg and cyanocobalamin 15 mcg, administered with or without 75 mg diclofenac orally to patients suffering with primary osteoarthritis of the knee. The results of Flynn, Magaña-Villa and Kaur were comparable overall, but the conditions investigated were dissimilar, and neither study investigated cobalamin in isolation.

The biochemical mode of action and roles of VB12 within the central and peripheral nervous system are complex, but in summary VB12 appears to participate in the synthesis of myelin by oligodendrocytes [11] and Schwann cells [12], and in remyelination processes associated with nerve regeneration [11, 12]. VB12 is involved in numerous metabolic pathways, including homocysteine metabolism, where the enzyme methionine synthase utilises methylcobalamin as cofactor to methylate homocysteine to methionine, an essential, proteinogenic amino acid needed for neurotransmitter synthesis [13].

The evidence currently available is extremely limited but does suggest a role for VB12, possibly combined with folate, in the management of hand autoimmune osteoarthritis. As a low-cost supplementation therapy, added to the non-observation of side effects, such approach only

encourages more research to test the efficacy of VB12 in ARD, mainly when pain is an important clinical feature.

Future randomized, double-blind, placebo-controlled, crossover studies with appropriate washout period and involving a combination of VB12 and NSAIDs in conjunction and separately will elucidate the efficacy of VB12, if any, for pain management in ARD. As most sources of VB12 are derived from animal products, careful consideration in the implementation of said studies would mean full dietary assessments prior to and during investigations. Veganism and vegetarianism are also factors to be considered in ADR research when VB12 deficiency is a potential culprit. In the interim, a sensible approach in clinical practice must be considered, as hypervitaminosis B12 has been described in the literature [14], but in most cases attributed to megadoses in prolonged supplementation regimens.

Conflict of interest: The authors declare no competing interests.

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