

Matrix metalloproteinase protein inhibitors: highlighting a new beginning for metalloproteinases in medicine

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Dear editor

The review by Mohan et al¹ is interesting because increased activity of various matrix metalloproteinases (MMPs), increasing the severity of tissue damage, is found in many different disease processes. To reduce tissue-damaging overactivity of these tissue remodeling enzymes, one can reduce MMP secretion, or increase the secretion of tissue inhibitors of MMPs (TIMPs); developing therapeutic agents, or boosting natural tissue MMP inhibitors, is therefore an important and worthwhile project. However, this review does not mention vitamin D which is essential for bone health and is known to regulate bone growth through MMP modulation,² and increasingly reported as suppressing the overactivity of certain MMPs, especially MMP-2 and MMP-9, in many pathological disorders (although vitamin A can also modulate some MMPs). This matters clinically, because MMP overactivity combined with the common problem of hypovitaminosis D will probably aggravate disease progression. Avoidance of hypovitaminosis D, currently reemerging within public health policy in many nations (eg, the UK),³ could provide potentially adjunctive benefits in the treatment of many disorders whose pathogenesis includes MMP overactivity. Furthermore, avoiding hypovitaminosis D at the population level is inexpensive.⁴

Examples of mechanistic evidence of suppression of overactivity of many MMPs by activated vitamin D include data from many specialties, for example, on rheumatoid arthritis,⁵ cardiovascular disorders (supported by vitamin D receptor-knockout mouse data), and where MMP overactivity is especially sinister,⁶⁻⁹ small airway disease,¹⁰⁻¹² skin and diabetic foot ulcers,^{13,14} some cancers,^{15,16} uterine fibroids,¹⁷ tuberculosis,^{18,19} periodontitis,²⁰ nasal polyps,²¹ and liver fibrosis.²² Circulating MMP-9 related inversely to vitamin D status [serum 25(OH)D] and was suppressed by 69% by modest vitamin D supplementation in “healthy” south Asians²³ and rose as 25(OH)D concentrations fell during healthy young submariners’ underwater tours of duty.²⁴ Overall, MMP-2/9 were commonly suppressed, MMP-1,2,3,7,10,12,13 were sometimes suppressed, and MMP-1,3,13,14 were rarely suppressed. Further investigation to determine what conditions with MMP overactivity may benefit from ensuring long-term vitamin D repletion could well prove to be of interest. Concurrent development of specific blocking agents especially for MMPs not suppressed by vitamin D and for situations

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where MMP suppression by vitamin D is inadequate, or may be found to lead to adverse effects, would provide a useful combined approach.

Why vitamin D was not discussed in this review is also of interest. Either the authors were unimpressed by the aforementioned reported work, or they were unaware of it as a consequence of the conditions under which much current medical research is necessarily carried out. These include the ever larger research groups, focusing on increasingly specific problems or methodology – this specialization necessarily spilling over into how research output is shared, as medical societies and medical journals have also become more specialized (vide this journal). Furthermore, literature searches are becoming increasingly focused as scientific search engines get more efficient. No one now trawls Index Medicus manually or meets other researchers regularly in interdisciplinary settings (eg, over meals and coffee breaks). Thus, opportunities for coming across other research of potential relevance to one's own area of interest may well be lost. Fortunately, the need for closer contact between researchers in disparate disciplines is becoming better appreciated, and reintegration of research is being promoted, for example, by reduction in the geographic separation of research specialties in new-built research facilities.²⁵ How else do researchers come across potentially relevant matters? For vitamin D and MMPs, for example, trawling PubMed (9 August 2016), for “MMP+Timp,” produced 8488 “hits,” a daunting number to search; trawling for “MMP+TIMP+circulating” produced 292 “hits” (one mentioning vitamin D); re-trawling MMP+TIMP plus “vitamin D” identified 16 papers, and for “MMP+vitamin D” there were 147 reports. Trawling earlier terms for MMPs (eg, stromlysin, gelatinase, and collagenase) +vitamin D identified 21, 83, and 171 “hits,” respectively.

Vitamin D, discovered once rickets was found to be due to lack of sunshine, and sunshine and cod-liver oil were identified as independent cures, is poorly provided by food (even when fortified), while modern lifestyles reduce outdoor activity and skin exposure to summer sunshine, even in tropical climates, causing virtually endemic hypovitaminosis D.²⁶ Putting the available data together suggests that increasing vitamin D intakes, as is being advised, together with moderate exposure to sunlight (but avoiding sunburn) might provide adjunctive benefits in the treatment of those disorders where various MMPs, most especially MMP-2/9, are overactive. This possibility could usefully be examined while awaiting further information on modulation of MMPs by vitamin D in vivo and on the role of more specialized MMP-suppressive agents.¹

Disclosure

The author reports no conflicts of interest in this communication.

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Authors' reply

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Dear editor

The authors thank BJ Boucher for their comments regarding their manuscript titled "Matrix metalloproteinase protein inhibitors: highlighting a new beginning for metalloproteinases in medicine" which we appreciate very much. Our effort in this review paper was to shed light on the role of dysregulated matrix metalloproteinase (MMP) activity in various disease scenarios and the available highly selective MMP inhibition strategies using small molecules, antibodies, antisense inhibitors, and engineered N-terminal tissue inhibitors.

Nevertheless, we agree with your suggestions that regulatory molecules such as vitamin D (but not only) should be investigated in-depth keeping in mind their clinical importance. Yet, the evidence presented in the literature so far suggests that the effect of vitamin D on many MMPs is not direct but is mediated through other regulatory molecules exhibiting wide range of activities. For example, Vitamin D₃ (cholecalciferol), 1,25D seems to elicit its function as a hormone through the vitamin D receptor (VDR) to regulate the transcription of many target genes and have been found to influence both tissue inhibitors of MMPs (1 and 2) and MMP (2 and 9) expression in oligonucleotide microarray studies of VDR knockout mice.¹ 24,25-(OH)₂D₃ vitamin D metabolite was shown to elicit plasma membrane protein kinase C-mediated phosphorylation of MMP-3.² Also, evidence of suppression of overactivity of many MMPs by activated vitamin D, for example, in rheumatoid arthritis synovial fibroblasts (RSFs) and human articular chondrocytes (HACs) showed that interleukin-1-activated RSFs and HACs respond differently to 1 α ,25D₃ exposure.³ JNK cascade was also shown to play an important role in both the upregulation

of MMP-9 by tumor necrosis factor α and its attenuation by calcitriol.⁴ MMP activation in diseased tissue has been thought to be a result of NF- κ B activation and regulation of transforming growth factor- β activity.⁵ In conclusion, vitamin D seems not to affect MMP expression directly and seems to involve complex signaling intermediates.

Vitamin D is hence an important risk factor associated with diseases that are characterized by MMP hyperactivity such as multiplesclerosis,⁶ inflammatory bowel disease,⁷ pulmonary tuberculosis,⁸ and so on, but its therapeutic potential is not yet clear. Vitamin D supplementation in unselected community-dwelling individuals (with or without calcium) was found to not reduce skeletal or nonskeletal outcomes⁹ or had a limited reduction in fracture risk.¹⁰ The latter study also showed that evidence was not sufficiently robust to draw conclusions regarding the effects of vitamin D supplementation for the prevention of cancer. As you rightly pointed out, further research is needed to elucidate the positive effect of vitamin D supplementation as an adjuvant to the more specialized MMP suppression modalities. We also agree that our communities should foster better communication and exchange of ideas between clinicians and basic researchers to promote holistic approaches for targeting dysregulated activities of MMPs in various diseases.

Disclosure

The authors report no conflicts of interest in this communication.

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