

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

Barbara J Boucher

The Blizzard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

## Dear editor

The review by Mohan et al<sup>1</sup> 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,<sup>2</sup> 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),<sup>3</sup> 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.<sup>4</sup>

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,<sup>5</sup> cardiovascular disorders (supported by vitamin D receptor-knockout mouse data), and where MMP overactivity is especially sinister,<sup>6-9</sup> small airway disease,<sup>10-12</sup> skin and diabetic foot ulcers,<sup>13,14</sup> some cancers,<sup>15,16</sup> uterine fibroids,<sup>17</sup> tuberculosis,<sup>18,19</sup> periodontitis,<sup>20</sup> nasal polyps,<sup>21</sup> and liver fibrosis.<sup>22</sup> 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 Asians<sup>23</sup> and rose as 25(OH)D concentrations fell during healthy young submariners’ underwater tours of duty.<sup>24</sup> 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

Correspondence: Barbara J Boucher  
The Blizzard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, 4 Newark Street, London E1 2AT, UK  
Tel +44 1243 881 230 / +44 7899846309  
Email [bboucher@doctors.org.uk](mailto:bboucher@doctors.org.uk)



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.<sup>25</sup> 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, stromelysin, 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.<sup>26</sup> 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.<sup>1</sup>

## Disclosure

The author reports no conflicts of interest in this communication.

## References

- Mohan V, Talmi-Frank D, Arkadash V, Papo N, Sagi I. Matrix metalloproteinase protein inhibitors: highlighting a new beginning for metalloproteinases in medicine. *Metalloproteinases Med.* 2016;3:31–47.
- Dean DD, Schwartz Z, Scmitz J et al. Vitamin D regulation of metalloproteinase activity in matrix vesicles. *Connect Tissue Res.* 1996;35(1–4):331–336.
- Public Health England. PHE publishes new advice on vitamin D. Available from: <https://www.gov.uk/government/news/phe-publishes-new-advice-on-vitamin-d>. Accessed July 21, 2016.
- Hypponen E, Boucher BJ. Avoidance of vitamin D deficiency in pregnancy in the United Kingdom: the case for a unified approach in National policy. *Br J Nutr.* 2010;104(3):309–314.
- Tetlow LC, Woolley DE. The effects of 1 alpha,25-dihydroxyvitamin D(3) on matrix metalloproteinase and prostaglandin E(2) production by cells of the rheumatoid lesion. *Arthritis Res.* 1999;1(1):63–70.
- Khalili H, Talasaz AH, Salarifar M. Serum vitamin D concentration status and its correlation with early biomarkers of remodelling following acute myocardial infarction. *Clin Res Cardiol.* 2012;101(5):321–327.
- Lee TW, Kao YH, Lee TI, Chang CJ, Lien GS, Chen YJ. Calcitriol modulates receptor for advanced glycation end products (RAGE) in diabetic hearts. *Int J Cardiol.* 2014;173(2):236–241.
- Newby A. Metalloproteinase production from macrophages – a perfect storm leading to atherosclerotic plaque rupture and myocardial infarction. *Exp Physiol.* In press 2016
- Rahman A, Hershey S, Ahmed S, Nibbelink K, Simpson RU. Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. *J Steroid Biochem Mol Biol.* 2007;103(3–5):416–419.
- Kim SH, Baek MS, Yoon DS, et al. Vitamin D inhibits expression and activity of matrix metalloproteinase in human lung fibroblasts (HFL-1) cells. *Tuberc Respir Dis (Seoul).* 2014;77(2):73–80.
- Song Y, Qi H, Wu C. Effect of 1,25-(OH)2D3 (a vitamin D analogue) on passively sensitized human airway smooth muscle cells. *Respirology.* 2007;12(4):486–494.
- Sundar IK, Hwang JW, Wu S, Sun J, Rahman I. Deletion of vitamin D receptor leads to premature emphysema/COPD by increased matrix metalloproteinases and lymphoid aggregates formation. *Biochem Biophys Res Commun.* 2011;406(1):127–133.
- Kobayashi H, Asano K, Kanai K, Suzuki H. Suppressive activity of vitamin D3 on matrix metalloproteinase production from cholesteatoma keratinocytes in vitro. *Mediators Inflamm.* 2005;2005(4):210–215.
- Lopez-Lopez N, Gonzalez-Curiel I, Cruz T-S, Rivas-Santiago B, Trujillo-Paez V, Enciso-Moreno JA, Serrano CJ. Expression and vitamin D-mediated regulation of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in healthy skin and in diabetic foot ulcers. *Arch Dermatol Res.* 2014;306(9):809–821.
- Koli K, Keski-Oja J. 1 Alpha,25-dihydroxyvitamin D3 and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells. *Cell Growth Differ.* 2000;11(4):221–229.
- Meephansan J, Komine M, Tsuda H, Ohtsukui M. Suppressive effect of calcipotriol on the induction of matrix metalloproteinase (MMP)-9 and MMP-13 in a human squamous cell carcinoma cell line. *Clin Exp Dermatol.* 2012;37(8):889–896.
- Halder SK, Osteen KG, Al-Hendy A. Vitamin D3 inhibits expression and activities of matrix metalloproteinase-2 and -9 in human uterine fibroid cells. *Hum Reprod.* 2013;28(9):2407–2416.
- Coussens A, Timms PM, Boucher BJ, et al. 1Alpha,25-dihydroxyvitamin D3 inhibits matrix metalloproteinases induced by Mycobacterium tuberculosis infection. *Immunology.* 2009;127(4):539–548.
- Anand SP, Selvaraj P. Effect of 1, 25 dihydroxyvitamin D(3) on matrix metalloproteinases MMP-7, MMP-9 and the inhibitor TIMP-1 in pulmonary tuberculosis. *Clin Immunol.* 2009;133(1):126–131.

20. Hosokawa Y, Hosokawa I, Shindo S, Ozaki K, Matsuo T. Calcitriol suppressed inflammatory reactions in IL-1beta-stimulated human periodontal ligament cells. *Inflammation*. 2015;38(6):2252–2258.
21. Wang LF, Tai C-F, Chien C-Y, Chiang FY, Chen JY. Vitamin D decreases the secretion of matrix metalloproteinase-2 and matrix metalloproteinase-9 in fibroblasts derived from Taiwanese patients with chronic rhinosinusitis with nasal polyposis. *Kaohsiung J Med Sci*. 2015;31(5):235–240.
22. Abramovitch S, Dahan-Bachar L, Sharvit E, Weisman Y, Ben Tov A, Brazowski E, Reif S. Vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats. *Gut*. 2011;60(12):1728–1737.
23. Timms PM, Mannan N, Hitman GA, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? *QJM*. 2002;95(12):787–796.
24. Baker A, Wood CL, Wood AM, Timms P, Allsopp AJ. Changes in vitamin D and matrix metalloproteinase-9 in submariners during a submerged patrol. *Occup Environ Med*. 2014;71(2):104–108.
25. Nurse P, Treisman R, Smith J. Building better institutions. *Science*. 2013; 341(6141):10.
26. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol*. 2014;144(Pt A): 138–145.

## Authors' reply

Vishnu Mohan<sup>1</sup>

Dalit Talmi-Frank<sup>1</sup>

Valeria Arkadash<sup>2</sup>

Niv Papo<sup>2</sup>

Irit Sagi<sup>1</sup>

<sup>1</sup>Department of Biological Regulation, Weizmann Institute of Science, Rehovot, <sup>2</sup>Department of Biotechnology Engineering, Faculty of Engineering Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Correspondence: Irit Sagi

Department of Biological Regulation, Weizmann Institute of Science, 234 Herzl St, Rehovot 76100, Israel

Tel +972 8 934 2130

Fax +972 8 934 4116

Email irit.sagi@weizmann.ac.il

## 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 D<sub>3</sub> (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.<sup>1</sup> 24,25-(OH)<sub>2</sub>D<sub>3</sub> vitamin D metabolite was shown to elicit plasma membrane protein kinase C-mediated phosphorylation of MMP-3.<sup>2</sup> 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 $\alpha$ ,25D<sub>3</sub> exposure.<sup>3</sup> JNK cascade was also shown to play an important role in both the upregulation

of MMP-9 by tumor necrosis factor  $\alpha$  and its attenuation by calcitriol.<sup>4</sup> MMP activation in diseased tissue has been thought to be a result of NF- $\kappa$ B activation and regulation of transforming growth factor- $\beta$  activity.<sup>5</sup> 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,<sup>6</sup> inflammatory bowel disease,<sup>7</sup> pulmonary tuberculosis,<sup>8</sup> 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 outcomes<sup>9</sup> or had a limited reduction in fracture risk.<sup>10</sup> 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.

## References

1. Rahman A, Hershey S, Ahmed S, Nibbelink K, Simpson RU. Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. *J Steroid Biochem Mol Biol*. 2007;103(3–5):416–419.
2. Schmitz JP, Schwartz Z, Sylvia VL, Dean DD, Calderon F, Boyan BD. Vitamin D<sub>3</sub> regulation of stromelysin-1 (MMP-3) in chondrocyte cultures is mediated by protein kinase C. *J Cell Physiol*. 1996;168(3):570–579.
3. Tetlow LC, Woolley DE. The effects of 1  $\alpha$ ,25-dihydroxyvitamin D(3) on matrix metalloproteinase and prostaglandin E(2) production by cells of the rheumatoid lesion. *Arthritis Res*. 1999;1(1):63–70.
4. Bahar-Shany K, Ravid A, Koren R. Upregulation of MMP-9 production by TNF $\alpha$  in keratinocytes and its attenuation by vitamin D. *J Cell Physiol*. 2010;222(3):729–737.
5. Sundar IK, Hwang JW, Wu S, Sun J, Rahman I. Deletion of vitamin D receptor leads to premature emphysema/COPD by increased matrix metalloproteinases and lymphoid aggregates formation. *Biochem Biophys Res Commun*. 2011;406(1):127–133.
6. Pierrot-Deseilligny C, Souberbielle JC. Is hypovitaminosis D one of the environmental risk factors for multiple sclerosis? *Brain*. 2010;133(Pt 7):1869–1888.
7. Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F. Association between inflammatory bowel disease and vitamin D deficiency: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2015;21(11):2708–2717.

8. Anand SP, Selvaraj P. Effect of 1, 25 dihydroxyvitamin D(3) on matrix metalloproteinases MMP-7, MMP-9 and the inhibitor TIMP-1 in pulmonary tuberculosis. *Clin Immunol.* 2009;133(1):126–131.
9. Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol.* 2014;2(4):307–320.
10. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2011;155(12):827–838.

Dove Medical Press encourages responsible, free and frank academic debate. The content of the Metalloproteinases In Medicine 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the Metalloproteinases In Medicine editors. While all reasonable steps have been taken to confirm the content of each letter, Dove Medical Press accepts no liability in respect of the content of any letter, nor is it responsible for the content and accuracy of any letter to the editor.

### Metalloproteinases In Medicine

#### Publish your work in this journal

Metalloproteinases In Medicine is an international, peer reviewed, open access journal that aims to provide a platform for the discussion and dissemination of knowledge about the role that metalloproteinases – such as matrix metalloproteinases (MMP), ADAMs, ADAMTSs, and astacins, as well as their inhibitors – play in diseases.

Submit your manuscript here: <https://www.dovepress.com/metalloproteinases-in-medicine-journal>

Dovepress

The manuscript management system is completely online and includes a very quick and fair peer review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.