Consequences of Vitamin K_2 Deficiency in Hemodialysis Patients

To the Editor:

We read the article by Westenfeld et al[1] with great interest because their results confirm the importance of vitamin K status to vascular health. We would like to mention that vitamin K intake can affect not only matrix Gla protein activity, which is relevant to cardiovascular calcification, but also osteocalcin (bone Gla protein) activity. The latter pathway, in a manner that is independent of bone mass, may protect against loss of bone mineral density and deterioration in the quality of bone structure. We wonder whether Westenfeld et al[1] have considered using vitamin K supplementation to prevent bone fractures, an important clinical outcome.[2] Data from the literature emphasize the potential risks: in a sample of 193 patients receiving hemodialysis, both severe vascular calcifications and vertebral fractures were associated with mortality (risk ratios of 3.2 and 4.8, respectively).[3] Interestingly, in a randomized controlled study of 334 early menopausal Norwegian women, half of whom were treated with vitamin K_2 (dose, 360 μg of menaquinone-7 [MenaQ7; NattoPharma, www.nattopharma.com]), at 12 months, there was no significant effect on bone loss, but there was a significant reduction in treated patients' levels of undercarboxylated osteocalcin, a marker of inadequate functional vitamin K activity.[4] Therefore, we suggest that adequate levels of circulating vitamin K could be important to maintain not only vascular health, but also bone health, in patients with chronic kidney disease and possibly in the general population.[5]

Maria Fusaro, MD
Institute of Neuroscience
Padua, Italy

Angela D'Angelo, MD
University of Padua
Padua, Italy

Maurizio Gallieni, MD
Ospedale San Carlo Borromeo
Milan, Italy

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Westenfeld et al declined to respond.

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Discounting the Efficacy of Sulodexide in Diabetic Nephropathy Is Premature

To the Editor:

I find the interpretation by House and Weir[1] in their editorial on the article by Lewis et al[2] that sulodexide is not effective for diabetic nephropathy to be simplistic. Lewis et al,[2] writing on behalf of the Collaborative Study Group (CSG), do not rule out the possibility that the preparation of sulodexide they used was pharmacologically inactive or not absorbed. Of note, the CSG trial used Sulonex (Keryx Biopharmaceuticals Inc, www.keryx.com), not Vessel 2F from Alfa Wassermann SpA (www.alfawassermann.it), the company that originally prepared sulodexide. As with other biosimilar-originator drug pairs, the bioequivalence of Sulonex and Vessel 2F has not been demonstrated. The drug used in the CSG trial was evaluated by testing only the heparin fraction without consideration for the dermatan sulfate constituent, which makes up 20% of the active ingredient portion of the drug. Furthermore, patients in the CSG trial had more severe diabetic nephropathy than those studied in previous trials of Vessel 2F. In DiNAS (Diabetic Nephropathy and Albuminuria Study),[3] most patients had stage 2 chronic kidney disease, whereas the CSG trial enrolled primarily individuals with stage 3 chronic kidney disease. Additionally, as recognized by Lewis et al,[2] because treatment with maximal doses of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker reduces albuminuria, the severity of kidney disease in CSG trial participants probably was underestimated. Thus, although sulodexide/Sulonex does not appear to add benefit to maximal-dose angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy in advanced diabetic nephropathy,[2,4] sulodexide/Vessel 2F has been shown to decrease albuminuria in patients with incipient diabetic nephropathy,[5] a finding that many would view as justification for continuing to develop this drug.

Giovanni Gambaro, MD, PhD
Catholic University
Rome, Italy

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Surrogate Versus Clinical End Points and Venture Capital Companies: The Doubts of a Clinician

To the Editor:

In their editorial about the trial by Lewis et al[1] of sulodexide for microalbuminuria in diabetic nephropathy, House and Weir[2] comment on the relationship between surrogate and clinical end points and suggest that a treatment may provide important benefits with respect to clinical end points while not affecting or perhaps even worsening surrogate end points. Importantly, concurrent with the sulodexide microalbuminuria trial published in the *American Journal of Kidney Diseases*[1] was a sulodexide phase 4 clinical end points trial for patients with macroalbuminuria[3]; this trial was terminated after the negative results of the microalbuminuria trial[1] became evident and an interim analysis for the Drug Safety and Monitoring Committee of the phase 4 trial that showed that sulodexide did not reduce proteinuria.[4] The termination therefore was based on a surrogate end point, proteinuria, and occurred even though the prespecified criterion for stopping the trial was the composite clinical end point of doubling of baseline serum creatinine level, development of end-stage renal disease, or creatinine level ≥6.0 mg/dL.[3,4] In addition, the venture capital company sponsoring the study stated in the press release announcing the termination of the sulodexide phase 4 trial that "our ability to successfully adjust our strategy and reduce our operating expenses in order to properly support the trials of our other drug candidates . . .",[4] which may reveal that there also were financial considerations in terminating the study.

Considering that no safety issues had occurred and all patients were continuing treatment with appropriate renin-angiotensin system blockade, the suspension of the sulodexide study is perplexing and leaves the question of the benefit of sulodexide on clinical end points unanswered, which is concerning for clinicians.

Antonio V. Gaddi, MD, PhD
Danilo Benedetto, MD
University of Bologna
Bologna, Italy

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In Reply to 'Discounting the Efficacy of Sulodexide in Diabetic Nephropathy Is Premature' *and* 'Surrogate Versus Clinical End Points and Venture Capital Companies: The Doubts of a Clinician'

We thank Dr Gambaro[1] and Drs Gaddi and Benedetto[2] for their comments regarding our editorial.[3] Their efforts in the development of sulodexide make their disappointment understandable.

We have no meaningful response to the argument that the sulodexide preparation used in the SUN-MICRO study of Lewis et al[4] was either unabsorbable or inactive. This cannot be investigated, so debate would be entirely speculative. However, the SUN-MICRO pilot study, which used the same agent and manufacturer, suggested some drug effect.[5]

The concerns raised about the characteristics of patients enrolled in SUN-MICRO warrant discussion. Although the mean estimated glomerular filtration rates reported in SUN-MICRO and the Diabetic Nephropathy and Albuminuria Study (DiNAS) differed (78 vs 85 mL/min/1.73 m^2, respectively), the difference was small.[4,6] More relevant is the similarity between study patients and those encountered in clinical practice. Considering the degree of decrease in kidney function and the underlying disease, both SUN-MICRO and DiNAS enrolled patients for whom adjuvant antiproteinuric therapy was reasonable. Because patients in SUN-MICRO received appropriate renin-angiotensin system blockade,[7,8] its results better generalize to clinical practice.

The discontinuation of the subsequent SUN-MACRO trial was disappointing, more so because termination was by the sponsor for a lack of surrogate outcome signal, not by the Data and Safety Monitoring Committee for safety or efficacy concerns.[9] This illustrates the tension between optimal science and shrewd business practice. Nonetheless, with more than 2,200 patients randomly assigned in SUN-MACRO and SUN-MICRO, the bar has been set high for investigators wishing to demonstrate the utility of sulodexide in diabetic nephropathy.

Matthew A. Weir, MD, FRCPC
Andrew A. House, MD, MSc, FRCPC
University of Western Ontario
London, Canada

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