

Correspondence

Reply

To the Editor:

The comments by Marlu et al¹ regarding our article on plasminogen activator inhibitor 2 (PAI-2) deficiency in patients with hereditary angioedema with normal C1 inhibitor (HAE-N) is timely and interesting. The very low levels observed in 22 of 23 untreated patients with HAE-N (with or without a factor XII mutation, 4.5 ± 5) were similar to the levels in 11 patients reported in their commentary, but the PAI-2 mean values in normal controls (54 ± 24) and patients with HAE type I (84 ± 52) were over 10 times higher. Hence, the strikingly positive statistical analysis we reported. With normal values so low (mean $\sim 3-4$), it would require very large numbers to document an abnormally low situation (5 are 0 for HAE-XII and 2 normal controls are 0 also).

We did pursue the idea of a possible mutation in PAI-2 as well as other fibrinolytic constituents in a patient with the T309R mutation with Dr Anna Feldweg and the genetics group at Harvard. Not surprisingly, none was found. However, HAE-U (HAE - unknown) is an HAE-N lacking a factor XII mutation whose clinical presentation is strikingly similar and we felt it to be worth trying. The defect in HAE-U remains unknown. We next studied a series of patients from Brazil with HAE-N (9 with HAE-XII and 13 with HAE-U) and found PAI-2 levels that were, in fact, normal (74 ± 70). Sample preparation and shipment were identical to the samples we originally reported, and when the 2 sets were assayed simultaneously, the difference remained (Fig 1). Fourteen Brazilian patients received progesterone and/or tranexamic acid, so we are pursuing a possible medication effect but 8 were off medication when samples were collected.

PAI-2 inhibits urokinase, and cytokine-stimulated endothelial cells secrete urokinase along with HSP-90, an activator of the prekallikrein-HK complex, linking kinin formation and fibrinolysis.² Given that plasmin activates the mutant factor XII in HAE-N,³ focus on fibrinolysis is an ongoing research endeavor. Our findings regarding PAI-2 levels thus far present as subpopulations because we have not seen a continuum of values that would suggest a normal distribution. In an additional 12 samples from Italy, all HAE-U (Fig 1) are low but compared with our normal controls, do not quite reach statistical significance ($P = .07$). If we were to pool all HAE-N samples tested ($n = 55$) and compare them with the sum of our normal controls ($n = 72$), the P value is .92. Given the variability reported for PAI-2 levels, regardless of explanation, it is not a biomarker for either form of HAE-N, and we agree that its determination is not recommended for routine clinical use.

Kusumam Joseph, PhD^a

Rosemeire N. Constantino-Silva, PhD^b

Anete S. Grumach, MD^b

Anna Feldweg, MD^c

Lakiea Wright, MD, MPH^c

Natasha Frank, MD, FACMG^c

Dana Vuzman, PhD^c

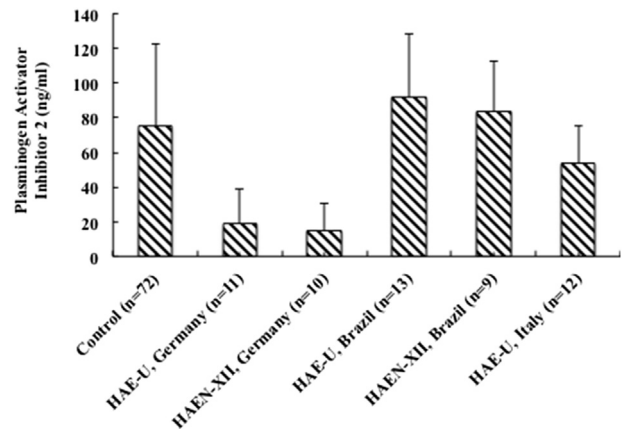


FIG 1. PAI-2 levels in plasma of patients with HAE-N and normal controls.

Rohit Sharma, MD^c

Chiara Suffritti, PhD^d

Marco Cicardi, MD^d

Lilian Varga, PhD^e

Henriette Farkas, MD, PhD, DSc^e

Konrad Bork, MD^f

Allen P. Kaplan, MD^g

From the Departments of ^aBiochemistry and Molecular Biology, and ^bMedicine, Medical University of South Carolina, Charleston, SC; ^cClinical Immunology, Faculty of Medicine ABC, Santo Andre, Sao Paulo, Brazil; ^dBrigham and Women's Hospital, Harvard Medical School, Boston, Mass; ^ethe Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy; ^fHungarian Angioedema Center, 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary; and ^gthe Department of Dermatology, Johannes Gutenberg University, Mainz, Germany. E-mail: josephk@musc.edu.

This study was supported by CSL Behring, King of Prussia, Pa.

Disclosure of potential conflict of interest: K. Joseph receives grant support from CSL Behring. A. S. Grumach serves as a board member for Shire, Baxalta, and CSL; serves as a consultant for Shire and Baxalta; receives payments for lectures from CSL, Shire, and Baxalta; and receives payment for educational presentations from CSL, Shire, and Baxalta. A. Feldweg receives grant support from Shire and receives royalties from UpToDate. L. Wright receives grant support from Shire and the National Institutes of Health. R. Sharma receives grant support from Shire. H. Farkas receives personal fees from CSL Behring, Shire, BioCryst, and SOBI. K. Bork receives payment for lectures from CSL Behring and Shire. A. P. Kaplan serves a consultant for Shire. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Marlu R, Deroux A, Du Thanh A, Boccon-Gibod I, Launay D, Bouillet L. Normal PAI-2 level in French FXII-HAE patients. *J Allergy Clin Immunol* 2017;139:XXX-XXX.
2. Joseph K, Tholanikunnel B, Kaplan AP. Cytokine and estrogen stimulation of endothelial cells augment activation of the prekallikrein-high molecular weight kininogen complex: implications for hereditary angioedema (HAE). *J Allergy Clin Immunol* 2016; <http://dx.doi.org/10.1016/j.jaci.2016.09.032>.
3. de Maat S, Björkqvist J, Suffritti C, Wiesenekker CP, Nagtegaal W, Koekman A, et al. Plasmin is a natural trigger for bradykinin production in patients with hereditary angioedema with factor XII mutations. *J Allergy Clin Immunol* 2016; 138:1414-23.

<http://dx.doi.org/10.1016/j.jaci.2016.12.983>