Comment to: Are fetuin-A levels beneficial for estimating timing of sepsis occurrence?

To the Editor

We read with great interest the recent study by Altinisik et al[1] reporting early (basal levels and at 24-hour) and late changes (at 72-hour) in serum fetuin-A levels in 40 adult septic patients admitted in the intensive care unit.[1] The authors concluded that serum fetuin-A levels may predict the time of occurrence and prognosis of sepsis. There are some important points in their study that merit further discussion. First, the authors did not present any data regarding the association of fetuin-A with sepsis severity. Second, no data regarding sepsis outcome (mainly mortality) in the studied patient cohort were presented in their paper. Thus, any conclusions regarding the prognostic value of fetuin-A cannot emanate from the presented data and study. Third, fetuin-A values were reported in ng/mL. Serum fetuin-A level represents a good indicator of liver function and ranges from 400-600 μg/mL in healthy individuals.[2,3] Altinisik et al[1] presented mean basal fetuin-A levels as 58.5±29.2 ng/mL for the study group. This means that this study provided approximately 10,000-fold lower mean serum fetuin-A value, which cannot be acceptable. Most likely, we presume that values for fetuin-A levels present a serious post-analytical error as the authors applied for fetuin-A values those calculated from the standard curve without multiplying them by their respective dilution factor. Most commercially available diagnostic enzyme-linked immunosorbent assay (ELISA) kits for determinations of human fetuin-A define this multiplication step in their insert.[2,3] Nonetheless, as methodology of determination of fetuin-A is not standardized yet, there is an urgent need for international consensus and standards on biomedical methods for fetuin-A measurement; but this fact has nothing to do with any post-analytical errors derived from this multiplication step.

Contrary to what is stated by the authors, there is one previous large prospective clinical study of fetuin-A in 102 critically ill septic patients (102 age and gender matched healthy controls) coming from our group,[4] not mentioned in their study. In this study, we have shown that serum fetuin-A levels decrease early in sepsis and significantly increase one week later only in patients with sepsis compared to patients with septic shock as well as in survivors compared to nonsurvivors at 28 days from sepsis onset. We further showed that lower fetuin-A levels at enrolment and one week after sepsis onset, as well as lower percentage change during the first week, were independently associated with 28-day mortality. Finally, we found significant negative correlations of fetuin-A with baseline C-reactive protein, procalcitonin, IL-6, IL-10 and lactate, and a positive one with albumin.[4]

The finding of Altinisik et al, regarding the decrease in serum fetuin-A early in sepsis is in agreement with our findings as well as with experimental models of sepsis.[5] However, their study failed to reveal any significant changes in serum fetuin-A between 24 and 72 hours after sepsis onset. Due to our study design which extends monitoring of fetuin-A levels to one week after sepsis onset, we have shown a significant increase in fetuin-A levels one week later. Due to the small sample size and low statistical power, Altinisik et al could not explore the independent association of serum fetuin-A and its kinetics with sepsis prognosis taking into account other important confounding variables, such as Acute Physiology Age and Chronic Health Evaluation score; Sequential Organ Failure Assessment score; or laboratory variables.

As fetuin-A is considered a major hepatokine and adipokine playing an important role in metabolism and insulin resistance, we have also investigated adiponectin, the most abundant adipokine in blood, and showed that, contrary to fetuin-A, adiponectin increased early in sepsis and further increased one week after. Similarly to fetuin-A, our study showed that adiponectin is associated with sepsis severity and lower adiponectin kinetics is independently associated with sepsis mortality.[4] By combining these novel biomarkers (measured in μg/mL) into a new one, namely fetuin-A to adiponectin ratio (F/A ratio, without units), we have shown that the F/A ratio is decreased in septic patients and has a better diagnostic value than fetuin-A or adiponectin alone, being significantly and independently associated with sepsis severity and 28-day mortality.[6]

Hepatic expression of fetuin-A is double-faced and varies according to stimuli. Therefore, fetuin-A increases in ischemic injury and chronic inflammation, including obesity and metabolic syndrome, while it decreases in acute inflammation. Proinflammatory cytokines such as IL-1 and IL-6, tumor necrosis factor and interferon γ inhibit fetuin-A expression, while High Mobility Group Box 1, a late inflammatory mediator, promotes fetuin-A expression.[7] Our finding regarding recovery of fetuin-A levels in less severely affected patients and in survivors one week after sepsis onset are in line with experimental

data supporting a protective role of fetuin-A in sepsis.[5] It is true, however, that large clinical studies on fetuin-A in sepsis are lacking. It would be more interesting if Altinisik et al could explore the independent association of fetuin-A with sepsis severity scores and mortality in a larger patient cohort. Further longitudinal studies are warranted to elucidate fetuin's role in sepsis.

In conclusion, we believe that the explanation of the above concerns will certainly offer the clearest information for the readers.

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Reply from the Author

Firstly, thank you for your interest about our publication.

We planned this study in 2014. As mentioned in the material-method section, we performed our analyses and collected our results in 2015. At that time, there were few studies on the role of fetuin-A in sepsis. Most of these studies were experimental. We formed our study plan in light of this information. Therefore, we did not have the opportunity to discuss your article in 2017 in our article.

In our study, we showed that fetuin-A is an important biomarker in septic patients. In accordance with literature information, we evaluated fetuin-A levels in the first 72 hours. We believe that, "evaluation of the first 7 days" are valuable in your study. In our study, fetuin-A levels decreased in acute phase and increase in the following days like yours. If we've planned it for longer, maybe we will have obtained similar results with yours.

We determined fetuin-A levels using commercially available ELISA kits from MyBiosource, Inc.(San Diego, CA 92195-3308, USA) (Catalog Number: MBS725791). According to the manufacturer's manual of fetuin-A kit, the unit used was ng/mL. We did not dilute all samples. However, we obtained suitable optical densities from samples, we have no extreme absorbance value was observed. Then,the concentrations of Fetuin A can be calculated without using dilution factor. Thus, it is impossible for us to make a post analytical error. Absorbance values of the assay (standards and samples), will be available upon request. In addition, several scientists use 'ng/mL' for fetuin-A unit in their studies.[8-12]

We emphasized that further studies with a larger number of patients are needed to draw more definitive conclusions. Further study regarding fetuin-A and sepsis are still to be considered. We believe that your study contributes to the literature.

We also looked at your study. Thank you for your comments.

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