Letter to the Editor

Matrix metalloproteinases do not properly work as peripheral blood biomarkers without taking into account the preanalytical impact of blood sampling

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I read with great interest the article by Aharinejad et al. [1]. The authors measured matrix metalloproteinases (MMP) 1, 8, and 9 and tissue inhibitor of metalloproteases 1 (TIMP-1) in the serum of heart transplant recipients during the first year after cardiac transplantation at different time intervals. The changed serum concentrations of these analytes following cardiac transplantation were interpreted as possible consequences of allograft damage due to ischemia—reperfusion injury or acute and chronic rejections, respectively. However, the aim of this Letter to the Editor is to address the attention of the reader on a basic pitfall that was obviously overlooked by Aharinejad et al. [1] when they designed and performed their study.

My concerns refer to the well-known impact of blood sampling procedure that has been repeatedly demonstrated as important preanalytical interfering factor in measuring the true concentrations of circulating MMPs and TIMPs in peripheral blood [2,3]. Serum collected either with or without clot activator generally show higher concentrations of MMP-1, MMP-8, MMP-9, and TIMP-1 compared with concentrations of corresponding analytes measured in plasma samples collected with citrate or heparin as anticoagulants. That effect is additionally influenced by the time interval between blood collection and centrifugation of the blood specimen [2]. Aharinejad et al. [1] used serum instead of plasma for their measurements. Moreover, they did not give any details of the serum sampling procedure, neither the type of serum collected with or without clot activation nor the time intervals between venipuncture and centrifugation of samples were explained.

Citrated plasma has been recommended as sample of choice to measure true circulating MMPs in blood [3,4]. Considering the concentrations in citrate plasma as reference, the concentrations of the above-mentioned MMPs were shown in our own experiments 20–30-fold higher in serum collected with clot activator as generally applied in clinical practice. Platelets and leukocytes contain abundant amounts of these components [3]. It explains that there are high background levels in serum due to the release of these analytes from platelets and leukocytes depending on the blood sample preparation with and without clot activator. Thus, serum concentrations do not certainly correspond to the true concentrations of circulating components in peripheral blood. The misinterpretation of MMP measurements in serum compared with determinations in plasma samples was recently proven [5]. It can be assumed that the failure to take into account the effect of sample preparation on the measurement of MMPs during the follow-up study as done by Aharinejad et al. [1] could not be avoided by a consistent use of serum samples.

In conclusion, the study of Aharinejad et al. [1] clearly exemplified the basic principle that reliable preanalytical conditions for the measurement of biomarkers have to be ascertained before the diagnostic validity of the markers should be explored in clinical trials. From this point of view, it would be advisable to re-evaluate the data of Aharinejad et al. [1].

References


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