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COMMENTARY

The Potential Importance of Paraoxonase-1 in Surgical Patients

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In recent years, the understanding of surgical stress has been expanded due to increased research interest, mainly driven by the introduction of novel biomarkers and innovative surgical techniques. Surgery itself is a pro-oxidative and pro-inflammatory stimulus [1]. Moreover, changes of circulating oxidative stress and inflammatory biomarkers in postoperative period have prognostic potential regarding patient's recovery and survival. In this context, it has been demonstrated that surgical patients with sepsis have reduced serum paraoxonase-1 (PON1) activity, associated with disease severity and adverse outcome [2]. PON1 is high-density lipoprotein (HDL)-associated enzyme with anti-oxidative and anti-inflammatory properties [3]. The enzyme has wide substrate-specificity and possesses lactonase, paraoxonase and arylesterase activities, with the latter two being the most commonly assessed. The enzymatic activity of PON1 is affected by numerous polymorphisms in *PON1* gene, but the most widely studied are PON1Q192R and L55M polymorphisms [3]. In spite of substantial interest in PON1 status in cardiovascular diseases [4–6], importance of PON1 determination in surgical patients has been less explored.

In this issue of *Journal of Investigative Surgery* an interesting paper "Influence of surgical procedures on serum paraoxonase-1-related variables and markers of inflammation in hospitalized patients" expanded currently available data on the factors that modulate PON1 status in surgical patients. The authors measured paraoxonase and lactonase PON1 activities and PON1 concentration, along with the PON1Q192R polymorphism analysis in 128 healthy controls and 258 hospitalized patients, of whom 115 patients underwent surgery. A panel of inflammatory markers (CRP, CCL2 and procalcitonin) and HDL-cholesterol level were also determined [7]. The authors showed that hospitalized patients had lower PON1 activities, but higher levels of all examined inflammatory markers than controls. These findings are consistent with the differences in PON1 activity observed in other case-control studies [4–6]. Despite similar PON1 concentrations, both groups of patients had reduced specific PON1 activities, suggesting an inhibition of enzymatic activity rather than down-regulation of PON1 synthesis. The authors raised the possibility that overproduction of reactive oxygen species in hospitalized patients was the main reason for PON1 enzymatic activity exhaustion, although the role of inflammation should not be neglected. Indeed, PON1 protects against lipid peroxidation, but it may be inactivated under oxidative stress conditions [6]. Furthermore, the acute-phase protein serum amyloid A (SAA), produced by the liver in response to pro-inflammatory stimuli, is able to replace PON1 within HDL, leading to decreased serum PON1 activity [8]. The study also demonstrated that patients who underwent surgical procedures had significantly higher paraoxonase and lactonase PON1 activities in the postoperative period than the patients who did not undergo surgery. Previously published studies have yielded inconsistent results on PON1 activity in the postoperative period. The discrepancy between the data could be attributable to different populations of patients and surgical techniques. For instance, serial measurement of PON1 activity and lipid hydroperoxides (LOOH) before and following double coronary artery bypass grafting revealed significant fall in PON1/LOOH ratio after surgery, which was more prominent in the patients who underwent surgery with

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cardiopulmonary bypass [9]. Another possible reason could be the time elapsed between the surgery and the analysis of PON1, which varies among the studies. In line with previous, the authors reported significant differences in PON1 activities and CRP levels with respect to duration and invasiveness of surgical procedure and the type of anesthesia [7], indicating that these factors may additionally modulate PON1 activity under stress conditions, such is surgical procedure itself. Finally, the data presented in this paper suggest that the carriers of the R allele of the PON1Q192R polymorphism could be more sensitive to surgery-mediated oxidative stress and inflammation, which should be confirmed in future studies with larger study groups. Nevertheless, these data resemble the results of earlier studies which demonstrated that R isoform of PON1 was less efficient at retarding the oxidation of low-density lipoprotein (LDL) particles, and therefore might be associated with higher cardiovascular disease risk [3, 4].

The physiological functions of PON1 and HDL are mutually related [8]. In particular, HDL facilitates PON1 secretion and offers a hydrophobic environment, necessary for the PON1 enzymatic activity. On the other side, PON1 prevents oxidation of HDL particles and mediates cholesterol efflux from the cells to HDL. Interestingly, in the presented study PON1 activity was not associated with HDL-cholesterol level [7]. The cholesterol content in HDL particles traditionally serves as a surrogate measure of circulating HDL particles concentration. Yet, circulating HDL particles are highly heterogeneous with respect to density, size and composition [8]. In addition, various factors, including oxidative stress and inflammation, are able to modify the content and the distribution of plasma HDL particles, and such adverse changes in HDL composition further affect its functionality [10]. The reduction of HDL-cholesterol level in hospitalized patients observed in this study was in line with the well-described effects of acute inflammation on lipid status parameters. However, the effects of surgical stress on HDL particles distribution and functionality are largely unknown. Another missing piece in the puzzle regarding PON1-related variables is the impact of surgery on PON1 activity distribution within HDL subclasses. Investigation of this issue could be relevant for future studies in order to improve our understanding of PON1 status in surgical patients.

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DECLARATION OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

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