

## COMMENTARY

# Apolipoprotein M - a new biomarker in sepsis

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See related research by Kumaraswamy et al., <http://ccforum.com/content/16/2/R60>

### Abstract

Sepsis is one of the leading causes of mortality in non-cardiac intensive care units, and the need for markers of progression and severity are high. Also, treatment of sepsis is highly debated and potential new targets of treatment are of great interest. In the previous issue of *Critical Care* Kumaraswamy and colleagues have investigated whether plasma apolipoprotein M (apoM) is affected during different grades of sepsis, septic shock and systemic inflammatory response syndrome. Interestingly, plasma apoM was significantly decreased in all groups of patients with a relationship to severity of disease. This identifies apoM as a potential new biomarker in sepsis. It also underscores the possibility that altered high-density lipoprotein in sepsis patients can affect the course of disease. Thus, since apoM is the carrier of Sphingosine-1-P (S1P), a molecule with great influence on vascular barrier function, the study presented raises the interest and relevance for further studies of apoM and S1P in relation to sepsis and inflammation.

In the previous issue of *Critical Care*, Kumaraswamy and colleagues [1] show that plasma apolipoprotein M (apoM) is reduced in patients with sepsis and systemic inflammatory response syndrome (SIRS). Patients with severe sepsis and SIRS had the most pronounced drop compared to the control group. This suggests that apoM is a negative acute phase reactant. This is the first report of such a dramatic decrease in plasma apoM in a group of patients without genetic diseases affecting high-density lipoprotein metabolism but solely based on clinical scores for sepsis. This indicates the potential importance of the present study [1]. Interestingly, plasma apoM is decreased by 9% in patients with type II diabetes

compared to controls [2]. Type II diabetes is also associated with low grade inflammation, and therefore this could support the idea of apoM being a new marker of inflammatory diseases.

ApoM is an apolipoprotein mainly bound to high-density lipoprotein (HDL) particles [3]; however, plasma apoM is not only associated with HDL cholesterol but also with low-density lipoprotein cholesterol in normal individuals [4]. Sepsis decreases HDL cholesterol and several HDL apolipoproteins, which may affect the clinical course in sepsis. For instance, both apoCI and apoAI are low in sepsis patients and are able to bind and initiate elimination of lipopolysaccharide (LPS) from plasma [5,6]. Binding of LPS to the HDL particles is thought to be part of the innate immune response. Sepsis also increases apoE-enriched HDL particles; however, apoE has both been shown to protect against LPS-induced sepsis by binding LPS [7], but also to accelerate cytokine production and increase mortality in animal models [8]. ApoL, another apolipoprotein on HDL particles having anti-trypanolytic effects, also plays an important role in the innate immune system [9]. The present study by Kumaraswamy and colleagues [1] adds apoM to the list of apolipoproteins on HDL particles that are affected by sepsis. As such, apoM might have potential as a marker of severe disease, but recent knowledge on apoM biology could also indicate a possible effect on the clinical course of sepsis.

Leaking vessels are a feature of severe sepsis and SIRS, causing increased distribution volume and shock. Sphingosine-1-P (S1P) preserves endothelial function, induces formation of tight junctions, and prevents vascular leak. S1P is a small bioactive lipid, carried by apoM in the HDL particle, and studies of apoM-deficient mice suggest that the apoM-S1P complex is crucial for maintaining normal endothelial function and vascular permeability [10]. Plasma apoM and S1P correlate positively, suggesting that sepsis patients could have decreased plasma levels of S1P as a consequence of low apoM levels; however, no reports on plasma levels of S1P in sepsis patients have so far been published. Genetically modified mice with low plasma S1P levels are more prone to LPS infections and develop more severe lung symptoms than wild-type mice [11,12]. The drug FTY720

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is an analog of S1P that interacts with the S1P1 receptor, and reduces attack frequency in patients with multiple sclerosis [13]. FTY720 and new S1P agonists might have beneficial effects in diseases involving, for example, leaky endothelial barrier and enhanced migration of inflammatory cells, such as sepsis. Indeed, when mice or rabbits are treated with LPS, the vascular leak and inflammatory response can be dampened by treatment with FTY720 or S1P [14,15]. Also, mice infected with H1N1 influenza die due to a 'cytokine storm', but treatment of mice with an S1P1 receptor agonist prevents this lethal effect, implying that S1P and its receptors have important functions in cytokine amplification [16]. A future possibility could therefore be to explore the protective role of both plasma apoM and plasma S1P and further investigate the use of S1P analogs to improve vascular barrier function in sepsis patients and as modulators of the inflammatory response.

#### Abbreviations

Apo, apolipoprotein; HDL, high-density lipoprotein; LPS, lipopolysaccharide; S1P, sphingosine-1-phosphate; SIRS, sepsis and systemic inflammatory response syndrome.

#### Competing interests

The authors declare that they have no competing interests.

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