CRITICAL CARE

COMMENTARY

Apolipoprotein M - a new biomarker in sepsis

Christina Christoffersen[1]* and Lars Bo Nielsen[1,2]

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

*Correspondence: christina.christoffersen@rh.regionh.dk
[1]Department of Clinical Biochemistry, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
Full list of author information is available at the end of the article

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.

Author details

[1]Department of Clinical Biochemistry, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. [2]Department of Biomedical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark.

Published: 17 May 2012

References

1. Kumaraswamy SB, Linder A, Åkesson P, Dahlback B: **Decreased plasma concentrations of apolipoprotein M in sepsis and systemic inflammatory response syndromes.** *Crit Care* 2012, **16:**R60.
2. Plomgaard P, Dullaart RP, de VR, Groen AK, Dahlback B, Nielsen LB: **Apolipoprotein M predicts pre-beta-HDL formation: studies in type 2 diabetic and nondiabetic subjects.** *J Intern Med* 2009, **266:**258-267.
3. Christoffersen C, Nielsen LB, Axler O, Andersson A, Johnsen AH, Dahlback B: **Isolation and characterization of human apolipoprotein M-containing lipoproteins.** *J Lipid Res* 2006, **47:**1833-1843.
4. Axler O, Ahnstrom J, Dahlback B: **An ELISA for apolipoprotein M reveals a strong correlation to total cholesterol in human plasma.** *J Lipid Res* 2007, **48:**1772-1780.
5. Berbee JF, van der Hoogt CC, Kleemann R, Schippers EF, Kitchens RL, van Dissel JT, Bakker-Woudenberg IA, Havekes LM, Rensen PC: **Apolipoprotein CI stimulates the response to lipopolysaccharide and reduces mortality in gram-negative sepsis.** *FASEB J* 2006, **20:**2162-2164.
6. Gupta H, Dai L, Datta G, Garber DW, Grenett H, Li Y, Mishra V, Palgunachari MN, Handattu S, Gianturco SH, Bradley WA, Anantharamaiah GM, White CR: **Inhibition of lipopolysaccharide-induced inflammatory responses by an apolipoprotein AI mimetic peptide.** *Circ Res* 2005, **97:**236-243.
7. van OM, Rensen PC, van Amersfoort ES, Van EM, Van Dam AM, Breve JJ, Vogel T, Panet A, van Berkel TJ, Kuiper J: **Apolipoprotein E protects against bacterial lipopolysaccharide-induced lethality. A new therapeutic approach to treat gram-negative sepsis.** *J Biol Chem* 2001, **276:**8820-8824.
8. Kattan OM, Kasravi FB, Elford EL, Schell MT, Harris HW: **Apolipoprotein E-mediated immune regulation in sepsis.** *J Immunol* 2008, **181:**1399-1408.
9. Vanhamme L, Paturiaux-Hanocq F, Poelvoorde P, Nolan DP, Lins L, Van Den Abbeele J, Pays A, Tebabi P, Van Xong H, Jacquet A, Moguilevsky N, Dieu M, Kane JP, De Baetselier P, Brasseur R, Pays E: **Apolipoprotein L-I is the trypanosome lytic factor of human serum.** *Nature* 2003, **422:**83-87.
10. Christoffersen C, Obinata H, Kumaraswamy SB, Galvani S, Ahnström J, Sevvana M, Egerer-Sieber C, Muller YA, Hla T, Nielsen LB, Dahlbäck B: **Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M.** *Proc Natl Acad Sci U S A* 2011, **108:**9613-9618.
11. Bachmaier K, Guzman E, Kawamura T, Gao X, Malik AB: **Sphingosine kinase 1 mediation of expression of the anaphylatoxin receptor C5L2 dampens the inflammatory response to endotoxin.** *PLoS One* 2012, **7:**e30742.
12. Zhao Y, Gorshkova IA, Berdyshev E, He D, Fu P, Ma W, Su Y, Usatyuk PV, Pendyala S, Oskouian B, Saba JD, Garcia JG, Natarajan V: **Protection of LPS-induced murine acute lung injury by sphingosine-1-phosphate lyase suppression.** *Am J Respir Cell Mol Biol* 2011, **45:**426-435.
13. Chun J, Brinkmann V: **A mechanistically novel, first oral therapy for multiple sclerosis: the development of fingolimod (FTY720, Gilenya).** *Discov Med* 2011, **12:**213-228.
14. Szczepaniak WS, Zhang Y, Hagerty S, Crow MT, Kesari P, Garcia JG, Choi AM, Simon BA, McVerry BJ: **Sphingosine 1-phosphate rescues canine LPS-induced acute lung injury and alters systemic inflammatory cytokine production in vivo.** *Transl Res* 2008, **152:**213-224.
15. Peng X, Hassoun PM, Sammani S, McVerry BJ, Burne MJ, Rabb H, Pearse D, Tuder RM, Garcia JG: **Protective effects of sphingosine 1-phosphate in murine endotoxin-induced inflammatory lung injury.** *Am J Respir Crit Care Med* 2004, **169:**1245-1251.
16. Teijaro JR, Walsh KB, Cahalan S, Fremgen DM, Roberts E, Scott F, Martinborough E, Peach R, Oldstone MB, Rosen H: **Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection.** *Cell* 2011, **146:**980-991.

doi:10.1186/cc11320
Cite this article as: Christoffersen C, Nielsen LB: **Apolipoprotein M - a new biomarker in sepsis.** *Critical Care* 2012, **16:**126.