An evolutionary look at cholesterol

Tietge, Uwe J. F.

Published in:
Current Opinion in Lipidology

DOI:
10.1097/MOL.0000000000000563

Publication date:
2019

An evolutionary look at cholesterol

Uwe J.F. Tietge

Cholesterol, contained in lipoproteins and cellular membranes of animals, is a fascinating molecule first identified in 1769 by Poulletier de la Salle [1], that is commonly employed in cardiovascular risk prediction. However, using advanced mass spectrometry techniques, a recent astonishing phylogenetic study determined that 558 million year old fossils of the previously unclassified Dickinsonia from the Ediacaran period consisted to at least 99.7% of cholesteroids [2▪▪]. This result allowed distinguishing it from other eukaryotes such as fungi or plants and to establish Dickinsonia as one of the earliest animals populating earth.

The first lipoprotein, HDL, was isolated in 1929 by Michel Macheboeuf from horse serum [1]. HDL are now widely recognized as being protective against the development of atherosclerotic cardiovascular disease, evidence derived from large epidemiological studies [3▪]. However, there is no selection pressure on cardiovascular disease in evolution, as it occurs past the reproductive age. Thus, the teleological role of HDL in the dangerous lifestyle of our ancestors with high physical activity and scarceness of food is unclear. Conceivably HDL could function in wound healing/coagulation to recover from accidents or after childbirth, reproduction (in fact, HDL are the main cholesterol-carrying components in follicular fluid surrounding the developing oocyte in the ovaries) or warding off infections, suggested by the HDL protein cargo (e.g. presence of lipopolysaccharide-binding protein) and by HDL remodeling occurring in response to inflammation [4].

A recent study explored the prospective association of HDL cholesterol (HDL-C) levels with the risk of hospitalization for an infectious disease in a large, well characterized general population cohort [5▪▪]. Of the 97 166 participants in the Copenhagen General Population Study, 9% were admitted for infectious disease during a median follow-up of 6 years. Significantly, both low and very high levels of HDL-C resulted in an increased risk of overall and bacterial infections, whereas only low HDL-C associated with increased susceptibility to viral infections. The strongest relationships were seen with gastroenteritis and bacterial pneumonia. Although multifactorial adjustment attenuated the observed associations, still sensitivity analyses indicated independence of the conclusions from several perceived confounders such as diabetes, smoking, triglyceride levels or alcohol consumption. Importantly, the association of low HDL-C with increased hospitalization risk for infections could be replicated in an independent smaller scale cohort with a longer follow-up, the Copenhagen City Heart Study (9387 participants, 20 years follow-up, 31% events).

In addition, another study in patients with bacterial sepsis concluded that genetically reduced HDL-C associated with poor outcomes, and specifically cholesteryl ester transfer protein (CETP) was shown to critically modulate this association [6▪]. This brings the ILLUMINATE trial to mind, in which CETP inhibitor-treated participants suffered significantly more infection-related deaths than controls [7]. Such results suggest that CETP is either directly involved in innate immunity, indicated by its structural similarity to lipopolysaccharide binding protein, and/or contributes to generating dysfunctional HDL. Although causation cannot be derived from these studies, further research into antiinfectious properties of HDL seems warranted and bears the potential to also discover novel protective mechanisms against atherosclerosis, a postreproductive age disease with a large inflammatory component.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Department of Pediatrics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Correspondence to Dr Uwe J.F. Tietge, Department of Pediatrics, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. Tel: +31 50 3636762; fax: +31 50 3611746; e-mail: u_tietge@yahoo.com

Curr Opin Lipidol 2019, 30:48–49

DOI:10.1097/MOL.0000000000000563

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Olson RE. Discovery of the lipoproteins, their role in fat transport and their significance as risk factors. J Nutr 1998; 128(2 Suppl):439S–443S.
2. ■■ Bobrovskiy I, Hope JM, Ivantsov A, *et al.* Ancient steroids establish the Ediacaran fossil Dickinsonia as one of the earliest animals. Science 2018; 361:1246–1249.

Although not related to cardiovascular disease *per se*, this article describes a fascinating technical achievement in the field of cholesterol research, which could have translation potential to study human evolution fossils.

3. ■ Cuchel M, Rohatgi A, Sacks FM, Guyton JR. JCL roundtable: high-density lipoprotein function and reverse cholesterol transport. J Clin Lipidol 2018; 12:1086–1094.

Up-to-date review summarizing knowledge on HDL metabolism and function.

4. Triolo M, Annema W, Dullaart RP, Tietge UJ. Assessing the functional properties of high-density lipoproteins: an emerging concept in cardiovascular research. Biomark Med 2018; 7:457–472.
5. ■■ Madsen CM, Varbo A, Tybjærg-Hansen A, *et al.* U-shaped relationship of HDL and risk of infectious disease: two prospective population-based cohort studies. Eur Heart J 2018; 39:1181–1190.

Large prospective study carried out in a well characterized general population cohort to explore the association of the biomarker HDL cholesterol with the risk of hospitalization for infectious disease.

6. ■ Trinder M, Genga KR, Kong HJ, *et al.* Cholesteryl ester transfer protein influences high-density lipoprotein levels and survival in sepsis. Am J Respir Crit Care Med 2018; doi:10.1164/rccm.201806-1157OC. [Epub ahead of print]

Interesting approach indicating that a genetic reduction in HDL cholesterol levels is a risk factor for reduced sepsis survival.

7. Barter PJ, Caulfield M, Eriksson M, *et al.* Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007; 357:2109–2122.

FURTHER RECOMMENDED READING

Marín-Palma D, Castro GA, Cardona-Arias JA, *et al.* Lower high-density lipoproteins levels during human immunodeficiency virus type 1 infection are associated with increased inflammatory markers and disease progression. Front Immunol 2018; 9:1350. ■

Further indication that HDL cholesterol (HDL-C) is associated with the clinical course of viral infection.

Kaysen GA, Ye X, Raimann JG, *et al.* Lipid levels are inversely associated with infectious and all-cause mortality: international MONDO study results. J Lipid Res 2018; 59:1519–1528. ■

Large cohort study in dialysis patients indicating that higher HDL-C, among other lipid biomarkers, is related to a lower risk of death from infectious disease.