Response to "High-density lipoprotein: a double-edged sword in cardiovascular physiology and pathophysiology"

Marta Lewandowska[1]^, Kate E. Shipman[1,2]^

[1]Department of Clinical Chemistry, University Hospitals Sussex NHS Foundation Trust, Worthing, UK; [2]Department of Undergraduate Studies, Brighton and Sussex Medical School, Brighton, UK

Correspondence to: Marta Lewandowska. University Hospitals Sussex, Royal Sussex County Hospital, Eastern Rd, Brighton BN2 5BE, UK.
Email: marta.lewandowska@nhs.net.

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We have recently read and enjoyed the excellent review article entitled "High-density lipoprotein: a double-edged sword in cardiovascular physiology and pathophysiology" by Gjin Ndrepepa published in the *Journal of Laboratory and Precision Medicine* (1). We would like to thank the author for their remarkably comprehensive and informative review and wanted to input from a clinical laboratory aspect.

We recognise that congenital high-density lipoprotein (HDL) abnormalities are outside the scope of the review, and that there are good reviews available elsewhere (2). However, from a clinician's perspective, we thought it would be worth signposting non-experts to a practical approach to interpreting abnormal HDL results, including when to consider referring to a specialist or requesting genetic studies.

HDL concentration is considered normal when it is above 1.0 mmol/L for men and 1.2 mmol/L for women (or 38.61 and 46.33 mg/dL respectively), although this may be too low with some recommending >1.4 mmol/L (54.05 mg/dL) (3). Although there is no official upper reference limit, we recommend that the upper limit of normal for a healthy range should be 2.5 mmol/L (96.53 mg/dL) (1,4). Above this concentration, the risk of all cause mortality increases.

In day-to-day practice, how should clinicians approach abnormal HDL levels?

Abnormally low HDL concentrations may be secondary to several causes: biochemical (very high triglyceride concentrations), underlying disease (obesity, infection, malignancy, type 2 diabetes mellitus), medications (anabolic steroids), as well as genetic abnormalities (familial hypoalphalipoproteinaemia, Tangier disease, lecithin acyltransferase deficiency) (2).

A phenotype of moderately high triglycerides with HDL below normal range is indicative of atherogenic lipoprotein phenotype. In these cases, health care professionals should exclude secondary causes as mentioned above. With no obvious underlying pathology, lifestyle interventions should be promoted such as weight loss and exercise and limited alcohol consumption. This will improve HDL and triglyceride concentrations with good effect through a number of physiological pathways, including reducing insulin resistance (5). However, abnormally low HDL (0.5 mmol/L or 20.00 mg/dL) present alongside severe hypertriglyceridaemia (>20.0 mmol/L or 1,771.50 mg/dL) may be indicative of an extremely rare genetic disorder, familial chylomicronaemia syndrome (6).

Should HDL be abnormally low (<0.5 mmol/L or 20 mg/dL) with normal triglyceride concentrations, other rare genetic disorders may be considered as a cause of HDL deficiency; for example in a paediatric population presenting with corneal opacifications (6). However, monogenic disorders lowering HDL affect less than 1% of the population (7). With low HDL, measuring apolipoprotein-A is a useful investigation and, should the

^ ORCID: Marta Lewandowska, 0000-0002-4172-9717; Kate E. Shipman, 0000-0002-6043-3532.

result be abnormal (<0.5 g/L), with a clinical presentation suggestive of causes other than obesity and lifestyle choices, a referral to relevant services is warranted (6).

Likewise, increased HDL concentration can also be multifactorial. It can be caused by lifestyle factors (alcohol consumption, smoking, obesity, excessive exercise), underlying disease (primary biliary cirrhosis, emphysema), medications (exogenous oestrogen) and genetic conditions (cholesterol ester transfer protein deficiency, hepatic lipase deficiency, hyperalphalipoproteinaemia) (2).

As mentioned in the review, smoking cessation and limiting alcohol intake are lifestyle interventions that will have a beneficial effect on raised HDL (1). Again, the importance of a thorough medical history and examination must be emphasised; secondary causes of elevated HDL should be managed accordingly.

It has been shown in the literature that there is a correlation between raised lipoprotein (a) and raised HDL, for example in African American women and overweight children (8,9). Therefore, checking lipoprotein (a) concentration when an isolated high HDL is detected may be considered, particularly if there is a family or personal history of premature cardiovascular disease and, if high, managed accordingly.

HDL at 1.8 mmol/L (70 mg/dL) is considered moderately elevated, and levels above 2.6 mmol/L (100 mg/dL) are markedly elevated (6). Apolipoprotein A concentration can be tested to support the diagnosis; specific thresholds may be method-specific but concentrations equal to and greater than 1.6 g/L are unusual and supportive of a possible underlying genetic abnormality (10). In cases of such concentrations without secondary causes, genetic testing could be considered, therefore a referral to a relevant specialist may be advisable.

In summary, there are a variety of potential causes contributing to both high and low HDL concentrations. In most cases, the abnormality is due to a secondary cause rather than a genetic condition. Therefore, the whole clinical picture should be considered when deciding on the most likely diagnosis and formulating a management plan. The importance of thorough assessment, including past medical, drug, lifestyle and family history with a physical examination is, as with all pathologies, paramount. Further investigations may be of benefit and, if abnormal, specialist advice should be sought. As Ndrepepa explained, neither too high nor too low HDL is desirable in clinical practice (1).

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Footnote

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