Pathology (February 2019) **51(2)**, pp. 129–130

EDITORIAL

Lipids and cardiovascular disease

JOHN R. BURNETT[1,2], AMANDA J. HOOPER[1,2], ROBERT A. HEGELE[3]

[1]*Department of Clinical Biochemistry, Royal Perth Hospital and Fiona Stanley Hospital Network, PathWest Laboratory Medicine, Perth, WA, Australia;* [2]*School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, WA, Australia;* [3]*Departments of Medicine and Biochemistry, Schulich School of Medicine and Robarts Research Institute, Western University, London, Ontario, Canada*

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality worldwide. Lipoproteins, particularly low density lipoprotein (LDL) and other apolipoprotein (apo) B-containing lipoproteins including very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and lipoprotein (a) [Lp(a)] play a fundamental role in the initiation and evolution of atherosclerosis. During atherogenesis, the cholesterol-rich, apoB-containing lipoproteins are retained and accumulate within vascular intima of the arterial wall and together with reactive immune and inflammatory mechanisms result in plaque formation and progression. In this special theme issue of *Pathology* dedicated to lipids and cardiovascular disease we have assembled 12 articles authored by internationally recognised experts who share their insights into the current state of lipids, lipoproteins and their relationship with cardiovascular disease.

Lipid testing has long played a major role in cardiovascular risk assessment. Historically, it has been recommended that blood samples for lipid testing should be obtained after a 10–12 hour fast. However, more recently, many countries have revised their guidelines to advocate measuring a lipid profile in the non-fasting rather than the fasting state to simplify blood sampling for patients, laboratories and clinicians. Langsted and Nordestgaard review the evidence for and advantages of a non-fasting over a fasting lipid profile for cardiovascular risk prediction.[1]

Depressed levels of high density lipoprotein (HDL) are a strong and independent risk factor for ASCVD, but recent human genetic and pharmacological intervention studies challenge the causality of this relationship. HDL plays a central role in reverse cholesterol transport and recent evidence has shed light on the complex nature of HDL metabolism and function. Nicholls and Nelson review the current state of HDL in protection from ASCVD.[2]

Non-HDL-cholesterol (a measure of the cholesterol content in the atherogenic lipoproteins) and apoB (a measure of the number of atherogenic lipoproteins) are more accurate measures than LDL-cholesterol in hypertriglyceridaemic individuals, non-fasting samples, and in those with markedly-low LDL-cholesterol concentrations. Accumulating evidence suggests that non-HDL-cholesterol and apoB are superior to LDL-cholesterol in predicting ASCVD risk, and both have been designated as secondary targets in some treatment guidelines. Carr *et al.* review the measurement, utility and current status of non-HDL-cholesterol and apoB when compared with LDL-cholesterol in cardiovascular risk assessment.[3]

Lp(a) consists of a complex, cholesterol-rich, LDL-like particle covalently bound to apo(a), a large glycoprotein sharing homology with plasminogen. Recently published epidemiological and genetic studies strongly suggest that genetically determined elevated Lp(a) levels are an independent, and causal, risk factor for atherothrombotic diseases including coronary heart disease. McCormick and Schneider review the current status of knowledge about receptor-mediated pathways of Lp(a) catabolism.[4]

ApoE is a glycoprotein primarily synthesised in the liver that associates with triglyceride-rich lipoproteins to mediate remnant lipoprotein clearance. There are three common *APOE* variants or isoforms (i.e., E3, E4 and E2), with E2 being the most favourable and E4 the least favourable with respect to cardiovascular and neurological health. However, under metabolic stress, homozygosity for E2 may result in dysbetalipoproteinaemia in adults owing to impaired remnant clearance. The E4 allele is a strong risk factor for the development of Alzheimer's disease. Marais reviews the role of apoE in lipoprotein metabolism, health and cardiovascular disease.[5]

Proprotein convertase subtilisin-kexin type 9 (PCSK9) is secreted by the liver and can associate with LDL particles in the circulation. When these PCSK9-associated particles bind to the LDL receptor, the complex is internalised and the receptor is targeted for degradation rather than recycling back to the cell surface. Reducing the level or activity of PCSK9 enables greater numbers of LDL receptors to return to the cell surface, thereby increasing the clearance of LDL particles from the circulation and reducing LDL-cholesterol levels. Clinical trials have shown that in addition to effectively lowering LDL-cholesterol, PCSK9 inhibition using monoclonal antibodies can improve cardiovascular outcomes. Blanchard *et al.* review the important studies that helped establish the mode of action of PCSK9 and led to the development of PCSK9 inhibitors for clinical use.[6]

With advances in gene sequencing technology genetic testing is becoming more cost effective and more widely available. Next-generation sequencing also has the advantage of allowing panel-based analysis of genes, the detection of copy number variants, and the generation of polygenic risk scores for lipid traits. Berberich and Hegele review the state of genetic testing for dyslipidaemia, including the methods

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: https://doi.org/10.1016/j.pathol.2018.12.001

available, potential benefits and drawbacks, and the indications for testing.[7]

With the exception of familial hypercholesterolaemia (FH), inherited lipid disorders are classified as rare, affecting fewer than 1 in 2000 individuals. These disorders can lead to severe multisystem complications if left untreated. Genetic lipid disorders can be caused by mutations in apolipoproteins, receptors, enzymes, cofactors or transporters, leading to characteristic changes in lipoproteins which are reflected in the lipid profile. Ng *et al.* provide an overview of the rare genetic lipid disorders, including diagnostic strategies and treatment and management options.[8]

Lipodystrophies are a family of heterogeneous rare disorders characterised by varying degrees of body fat loss and predisposition to insulin resistance and its metabolic complications. They are sub-classified as congenital generalised lipodystrophy, familial partial lipodystrophy, acquired generalised lipodystrophy and acquired partial lipodystrophy. The metabolic abnormalities associated with lipodystrophy include insulin resistance with diabetes, hypertriglyceridaemia, and hepatic steatosis. Management focuses on preventing and treating metabolic complications. Hussain *et al.* review the prevalence of dyslipidaemias and ASCVD in patients with lipodystrophies.[9]

FH is the most common genetic disorder causing premature ASCVD and death. Most people with FH are undiagnosed, which represents both a public health concern and opportunity, because early treatment of FH with statin therapy together with lifestyle measures can normalise life expectancy. Multiple screening strategies to detect index cases of FH have been proposed including the application of electronic screening tools to general practice databases, universal screening of children at the time of immunisation as well as targeted screening of patients with premature cardiovascular disease. Lan *et al.* outline the recent advances and emerging strategies for FH detection.[10]

Health effects of dietary fats have been extensively studied for decades. However, the cardiovascular effects of various types of fatty acids are controversial, especially for saturated fatty acids. A significant reduction in ASCVD risk can be achieved if saturated fatty acids are replaced by unsaturated fats, especially polyunsaturated fatty acids. Both n-6 and n-3 polyunsaturated fatty acids are associated with lower cardiovascular disease risk although the effects of fish oil supplementation remain inconsistent. Clifton reviews the effect of diet, exercise and weight loss on dyslipidaemia and cardiovascular disease.[11]

Despite the use of currently available lipid-lowering therapies, a significant proportion of patients with severe hypercholesterolaemia do not reach treatment goals as defined by guidelines and consequently remain at increased risk for ASCVD. Lifestyle modification and currently available drugs either fail to effectively lower plasma Lp(a) levels or do not result in clinical benefit. In both of these patient groups, lipoprotein apheresis effectively lowers LDL and Lp(a) levels. Waldmann and Parhofer review the role of lipoprotein apheresis as a therapeutic option for some patients with severe hypercholesterolaemia and elevated Lp(a).[12]

Over the past decade there have been numerous tangible advances in the field of lipids, lipoproteins and cardiovascular disease. The topics for this special theme issue of *Pathology* were selected with the aim of informing pathologists, medical scientists and physicians of some of the more important developments that will likely impact on their clinical practice. We sincerely wish to thank each of the contributors for their time and effort in this endeavour.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

Address for correspondence: Dr John R. Burnett, Department of Clinical Biochemistry, PathWest Laboratory Medicine, Royal Perth Hospital, GPO Box X2213, Perth, WA, 6847, Australia. E-mail: john.burnett@health.wa.gov.au

References

1. Langsted A, Nordestgaard BG. Nonfasting versus fasting lipid profile for cardiovascular risk prediction. *Pathology* 2019; 51: 131–41.
2. Nicholls SJ, Nelson AJ. HDL and cardiovascular disease. *Pathology* 2019; 51: 142–7.
3. Carr SS, Hooper AJ, Sullivan DR, Burnett JR. Non-HDL-cholesterol and apolipoprotein B compared with LDL-cholesterol in atherosclerotic cardiovascular disease risk assessment. *Pathology* 2019; 51: 148–54.
4. McCormick SPA, Schneider WJ. Lipoprotein(a) catabolism: a case of multiple receptors. *Pathology* 2019; 51: 155–64.
5. Marais AD. Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. *Pathology* 2019; 51: 165–76.
6. Blanchard V, Khantalin I, Ramin-Mangata S, Chémello K, Nativel B, Lambert G. PCSK9: from biology to clinical applications. *Pathology* 2019; 51: 177–83.
7. Berberich AJ, Hegele RA. The role of genetic testing in dyslipidaemia. *Pathology* 2019; 51: 184–92.
8. Ng DM, Burnett JR, Bell DA, Hegele RA, Hooper AJ. Update on the diagnosis, treatment and management of rare genetic lipid disorders. *Pathology* 2019; 51: 193–201.
9. Hussain I, Patni N, Garg A. Lipodystrophies, dyslipidaemias and atherosclerotic cardiovascular disease. *Pathology* 2019; 51: 202–12.
10. Lan NSR, Martin AC, Brett T, Watts GF, Bell DA. Improving the detection of familial hypercholesterolaemia. *Pathology* 2019; 51: 213–21.
11. Clifton PM. Diet, exercise and weight loss and dyslipidaemia. *Pathology* 2019; 51: 222–6.
12. Waldmann E, Parhofer KG. Apheresis for severe hypercholesterolaemia and elevated lipoprotein(a). *Pathology* 2019; 51: 227–32.