Lipids and Cardiovascular Risk with CKD

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Multiple clinical and epidemiologic studies link lipoprotein abnormalities to atherosclerotic cardiovascular disease. A key process in the pathogenesis of atherosclerosis is the accumulation of cholesterol-laden macrophages in the artery wall. This process is greatly enhanced by atherogenic lipoproteins such as LDL cholesterol, which delivers cholesterol to macrophages in the artery wall. In contrast, studies have demonstrated a strong inverse relationship between HDL-cholesterol levels and risk for cardiovascular disease. HDL cholesterol retrieves cholesterol from macrophages in atherosclerotic lesions for elimination in the liver, a process known as reverse cholesterol transport which can be measured *in vitro* by cholesterol-efflux capacity (1). Triglycerides are a major component of VLDL and other remnant lipoproteins such as chylomicrons, intermediate-density lipoproteins collectively termed triglyceride-rich lipoprotein cholesterol, which can also be atherogenic and often associate with low HDL cholesterol. Thus, measuring "non-HDL cholesterol" (total cholesterol minus HDL cholesterol) or apo-B concentration (the major apo of LDL and triglyceride-rich lipoprotein cholesterol) might provide a better index of atherogenic lipids and cardiovascular risk.

Cardiovascular disease due to atherosclerosis is the leading cause of death in patients with CKD. CKD dyslipidemia is highly atherogenic and characterized by increased small dense LDL cholesterol (an atherogenic form of LDL highly predisposed to oxidative damage), decreased HDL cholesterol, and increased triglycerides—specifically triglyceride-rich lipoprotein cholesterol. However, other factors that accompany CKD—such as diabetes, insulin resistance, metabolic syndrome, obesity, and marked proteinuria—may potentiate dyslipidemia and elevated triglyceride-rich lipoprotein cholesterol, making a causal independent effect of CKD on lipid abnormalities difficult to ascertain. Under normal physiologic conditions, lipoprotein lipase hydrolyzes the triglyceride content of triglyceride-rich lipoprotein cholesterol. In CKD, increased production of VLDL, diminished lipoprotein-lipase activity coupled with downregulation of glycosylphosphatidylinositol HDL binding protein 1, recruitment of monocytes, and induction of proinflammatory cytokines result in diminished clearance of atherogenic triglyceride-rich lipoprotein cholesterol, promoting atherosclerosis (2).

Triglycerides are the most diverse class of lipids, consisting of short to very long acyl chains with varying degrees of unsaturation that profoundly alter by CKD stage (3). Whether hypertriglyceridemia is a cause of atherosclerotic cardiovascular events has been a matter of long-standing debate, in part due to the unique methodologic considerations pertaining to the quantification of triglycerides. Some of these technicalities include high variability of measurements especially at higher levels of triglycerides, lack of distinction of structural diversity of triglycerides with traditional enzymatic methods, skewed distribution which necessitate categorization of data or data transformation, and collinearities with other prognostic lipid fractions (*e.g.*, HDL cholesterol) which mask their independence even after delicate multivariable adjustments. These issues have led to paradoxic results on the net effect of triglycerides on cardiovascular outcomes (2). For example, in a 2009 meta-analysis of 68 long-term prospective observational studies including 302,430 people, the association of high triglyceride level with coronary heart disease was no longer statistically significant after adjusting for HDL-cholesterol and non-HDL-cholesterol lipid fractions (2).

To overcome challenges with reverse causality and confounding issues inherent to observational epidemiologic approaches, a number of genetic approaches (which do not suffer the aforementioned limitations) including mutational analysis and exome sequencing, genome-wide associations, and Mendelian randomization studies were applied in recent years as alternative approaches to assess causality (4–6). In an exome sequencing analysis of 6721 patients with myocardial infarction compared with 6711 controls, a mutation in the gene encoding apoA5 was associated with increased triglyceride levels and 2.2-fold higher odds of myocardial infarction (4). In a meta-analysis of 14 genome-wide association studies of coronary artery disease which compared 22,223 individuals with and 64,762 without coronary artery disease, 13 loci including regions associated with increased triglycerides were associated with a 6%–17% increased risk of coronary artery disease (5). In a Mendelian randomization meta-analysis of 17 studies including 62,199 participants with 12,099 coronary events, each 1-log unit increase in triglycerides was associated with a higher coronary event using both an unrestricted allele score related to 67 triglyceride-related single nucleotide polymorphisms (odds ratio, 1.62; 95% CI, 1.24 to 2.11), and a restricted allele score related to 27 triglyceride-related single nucleotide polymorphisms that were not associated with LDL cholesterol

or HDL cholesterol (odds ratio, 1.61; 95% CI, 1.00 to 2.59) (6).

Finally, the question of whether alteration of triglyceride levels can modify the risk of atherosclerosis can be best answered in adequately powered randomized controlled clinical trials. In a 2019 meta-analysis of 49 randomized controlled clinical trials of lipid-lowering agents which spanned over 43 years, a total of 374,358 patients from 24 trials of nonstatin therapies and 25 trials of statin therapies with a total of 46,180 major cardiovascular events were analyzed (7). Using a multivariable meta-regression model in a pooled analysis, relative risk of major cardiovascular outcome was 0.84 (95% CI, 0.75–0.94; P=0.0026) per each 1 mmol/L (40 mg/dl) reduction in triglycerides. In a sensitivity analysis and after exclusion of the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) trial as an outlier, the preventive relative risk of the triglyceride-lowering agents remained statistically significant despite attenuation of the effect. Unfortunately, there was an under-representation of CKD in this analysis.

In this issue of *CJASN*, Lamprea-Montealegre *et al*. (8) evaluated the association of apo-B and markers of triglyceride-rich lipoprotein cholesterol with cardiovascular events in a secondary analysis of the participants of the Study of Heart and Renal Protection (SHARP) trial. They used data from 6245 patients who were not receiving dialysis and 3025 patients who were receiving dialysis. The baseline characteristics were gathered at the time of randomization. Samples from baseline and 2.5 years (1.5 years for those initially randomized to simvastatin) were used in the measurement of the lipid markers. Multivariable adjustments by the baseline characteristics using Cox regression models report statistically higher risk of atherosclerotic cardiovascular events with each 1 SD increase in apo-B, triglycerides, ratio of triglyceride to HDL cholesterol, and triglyceride-rich lipoprotein cholesterol. However, an inverse association was found between these markers with the nonatherosclerotic cardiovascular outcomes and no association was found with the nonvascular events. The study raises the possibility for targeting triglyceride-rich lipoprotein cholesterol in this vulnerable CKD population which has high risk for cardiovascular events and mortality.

The investigators should be commended for this important work, the major strengths of which include systematic analysis in a large cohort of patients with moderate-to-advanced CKD, a group that has been traditionally underrepresented in cardiovascular trials, and their use of state-of-the-art analytical strategies. Important limitations inherent to this study are not any different from other observational studies of the association of triglyceride levels with cardiovascular outcomes. After adjusting the triglycerides with lipoproteins such as LDL cholesterol and HDL cholesterol, the association was significantly attenuated. This is likely because of the high degree of collinearity reported between apo-B, LDL cholesterol, and non-HDL cholesterol (ρ=0.9). The measured lipids are also time-varying variables with dynamic levels. In absence of repeated measurements of time-varying variables in Cox models, application of the baseline values alone may not accurately reflect the corresponding risk associated with change in the level of time-varying lipids (8), a limitation that is mitigated by application of regression dilution ratios. Although the original source of the data is from a clinical trial, the observational nature of the secondary analysis does not allow for the inference of casualty.

Overall, the collective body of evidence supports a causal role for triglycerides and trigylceride-rich lipoprotein cholesterol as modifiable risk factors of atherosclerosis. The Statin Residual Risk Reduction with Epanova in High CV Risk Patients with Hypertriglyceridemia (STRENGTH) trial (NCT02104817) is another randomized trial assessing the effect of triglyceride-lowering treatments on major cardiovascular events that is expected to complete in 2020 and will provide further evidence for the effect of triglyceride-lowering therapies on atherosclerotic cardiovascular events. Further, randomized controlled clinical trials are needed to assess the effect of triglyceride-rich lipoprotein cholesterol–modifying agents on major cardiovascular events in patients with CKD. Finally, with the advent of high-throughput technologies (lipoprotein particle size and number, lipidomics, and proteomics), it is now possible to characterize lipoprotein abnormalities across the size spectrum to lipid diversity such as saturation, chain length, and protein cargo (3,9,10). Importantly, it is increasingly clear that levels of lipoproteins do not correlate with function. For example, recent studies demonstrate cholesterol-efflux capacity of serum HDL cholesterol (serum depleted of cholesterol-rich atherogenic lipoproteins) is an independent and better predictor of incident and prevalent cardiovascular risk than HDL cholesterol (1). In a study of patients with CKD in whom plasma lipoprotein levels were similar, we recently identified a plasma lipidomic signature of impaired mitochondrial β-oxidation across CKD stages as well as a predictor of diabetic CKD progression (3,9). Other key issues are the effects of lipoprotein particle size and concentration and the relationship of those changes to function and cardioprotection. Such in-depth characterization beyond traditional measures of cholesterol and triglyceride measurements, along with linking these lipoprotein structural measures to function, will provide a biologic context and identify patient-specific disease risk for cardiovascular diseases. In an era of precision medicine, these issues will need to be addressed with further research to identify novel patient-specific risk markers and targets for individualized therapy.

Disclosures

Dr. Afshinnia and Dr. Pennathur have nothing to disclose.

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References

1. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, Neeland IJ, Yuhanna IS, Rader DR, de Lemos JA, Shaul PW: HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med* 371: 2383–2393, 2014
2. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S; American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism; Council on

Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease: Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association. *Circulation* 123: 2292–2333, 2011
3. Afshinnia F, Rajendiran TM, Soni T, Byun J, Wernisch S, Sas KM, Hawkins J, Bellovich K, Gipson D, Michailidis G, Pennathur S; Michigan Kidney Translational Core CPROBE Investigator Group: Impaired β-Oxidation and altered complex lipid fatty acid partitioning with advancing CKD. *J Am Soc Nephrol* 29: 295–306, 2018
4. Do R, Stitziel NO, Won HH, Jørgensen AB, Duga S, Angelica Merlini P, Kiezun A, Farrall M, Goel A, Zuk O, Guella I, Asselta R, Lange LA, Peloso GM, Auer PL, Girelli D, Martinelli N, Farlow DN, DePristo MA, Roberts R, Stewart AF, Saleheen D, Danesh J, Epstein SE, Sivapalaratnam S, Hovingh GK, Kastelein JJ, Samani NJ, Schunkert H, Erdmann J, Shah SH, Kraus WE, Davies R, Nikpay M, Johansen CT, Wang J, Hegele RA, Hechter E, Marz W, Kleber ME, Huang J, Johnson AD, Li M, Burke GL, Gross M, Liu Y, Assimes TL, Heiss G, Lange EM, Folsom AR, Taylor HA, Olivieri O, Hamsten A, Clarke R, Reilly DF, Yin W, Rivas MA, Donnelly P, Rossouw JE, Psaty BM, Herrington DM, Wilson JG, Rich SS, Bamshad MJ, Tracy RP, Cupples LA, Rader DJ, Reilly MP, Spertus JA, Cresci S, Hartiala J, Tang WH, Hazen SL, Allayee H, Reiner AP, Carlson CS, Kooperberg C, Jackson RD, Boerwinkle E, Lander ES, Schwartz SM, Siscovick DS, McPherson R, Tybjaerg-Hansen A, Abecasis GR, Watkins H, Nickerson DA, Ardissino D, Sunyaev SR, O'Donnell CJ, Altshuler D, Gabriel S, Kathiresan S; NHLBI Exome Sequencing Project: Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature* 518: 102–106, 2015
5. Schunkert H, König IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AF, Barbalic M, Gieger C, Absher D, Aherrahrou Z, Allayee H, Altshuler D, Anand SS, Andersen K, Anderson JL, Ardissino D, Ball SG, Balmforth AJ, Barnes TA, Becker DM, Becker LC, Berger K, Bis JC, Boekholdt SM, Boerwinkle E, Braund PS, Brown MJ, Burnett MS, Buysschaert I, Carlquist JF, Chen L, Cichon S, Codd V, Davies RW, Dedoussis G, Dehghan A, Demissie S, Devaney JM, Diemert P, Do R, Doering A, Eifert S, Mokhtari NE, Ellis SG, Elosua R, Engert JC, Epstein SE, de Faire U, Fischer M, Folsom AR, Freyer J, Gigante B, Girelli D, Gretarsdottir S, Gudnason V, Gulcher JR, Halperin E, Hammond N, Hazen SL, Hofman A, Horne BD, Illig T, Iribarren C, Jones GT, Jukema JW, Kaiser MA, Kaplan LM, Kastelein JJ, Khaw KT, Knowles JW, Kolovou G, Kong A, Laaksonen R, Lambrechts D, Leander K, Lettre G, Li M, Lieb W, Loley C, Lotery AJ, Mannucci PM, Maouche S, Martinelli N, McKeown PP, Meisinger C, Meitinger T, Melander O, Merlini PA, Mooser V, Morgan T, Mühleisen TW, Muhlestein JB, Münzel T, Musunuru K, Nahrstaedt J, Nelson CP, Nöthen MM, Olivieri O, Patel RS, Patterson CC, Peters A, Peyvandi F, Qu L, Quyyumi AA, Rader DJ, Rallidis LS, Rice C, Rosendaal FR, Rubin D, Salomaa V, Sampietro ML, Sandhu MS, Schadt E, Schäfer A, Schillert A, Schreiber S, Schrezenmeir J, Schwartz SM, Siscovick DS, Sivananthan M, Sivapalaratnam S, Smith A, Smith TB, Snoep JD, Soranzo N, Spertus JA, Stark K, Stirrups K, Stoll M, Tang WH, Tennstedt S, Thorgeirsson G, Thorleifsson G, Tomaszewski M, Uitterlinden AG, van Rij AM, Voight BF, Wareham NJ, Wells GA, Wichmann HE, Wild PS, Willenborg C, Witteman JC, Wright BJ, Ye S, Zeller T, Ziegler A, Cambien F, Goodall AH, Cupples LA, Quertermous T, März W, Hengstenberg C, Blankenberg S, Ouwehand WH, Hall AS, Deloukas P, Thompson JR, Stefansson K, Roberts R, Thorsteinsdottir U, O'Donnell CJ, McPherson R, Erdmann J, Samani NJ; Cardiogenics; CARDIoGRAM Consortium: Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet* 43: 333–338, 2011
6. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, Dale CE, Padmanabhan S, Finan C, Swerdlow DI, Tragante V, van Iperen EP, Sivapalaratnam S, Shah S, Elbers CC, Shah T, Engmann J, Giambartolomei C, White J, Zabaneh D, Sofat R, McLachlan S, Doevendans PA, Balmforth AJ, Hall AS, North KE, Almoguera B, Hoogeveen RC, Cushman M, Fornage M, Patel SR, Redline S, Siscovick DS, Tsai MY, Karczewski KJ, Hofker MH, Verschuren WM, Bots ML, van der Schouw YT, Melander O, Dominiczak AF, Morris R, Ben-Shlomo Y, Price J, Kumari M, Baumert J, Peters A, Thorand B, Koenig W, Gaunt TR, Humphries SE, Clarke R, Watkins H, Farrall M, Wilson JG, Rich SS, de Bakker PI, Lange LA, Davey Smith G, Reiner AP, Talmud PJ, Kivimäki M, Lawlor DA, Dudbridge F, Samani NJ, Keating BJ, Hingorani AD, Casas JP; UCLEB consortium: Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J* 36: 539–550, 2015
7. Marston NA, Giugliano RP, Im K, Silverman MG, O'Donoghue ML, Wiviott SD, Ference BA, Sabatine MS: Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: A systematic review and meta-regression analysis of randomized controlled trials. *Circulation* 140: 1308–1317, 2019
8. Lamprea-Montealegre JA, Staplin N, Herrington W, Haynes R, Emberson J, Baigent C, de Boer IH; SHARP Collaborative Group: Apolipoprotein B, triglyceride-rich lipoproteins, and risk of cardiovascular events in persons with CKD. *Clin J Am Soc Nephrol* 15: 47–60, 2020
9. Afshinnia F, Nair V, Lin J, Rajendiran TM, Soni T, Byun J, Sharma K, Fort PE, Gardner TW, Looker HC, Nelson RG, Brosius FC, Feldman EL, Michailidis G, Kretzler M, Pennathur S: Increased lipogenesis and impaired β-oxidation predict type 2 diabetic kidney disease progression in American Indians. *JCI Insight* 4: 130317, 2019
10. Shao B, de Boer I, Tang C, Mayer PS, Zelnick L, Afkarian M, Heinecke JW, Himmelfarb J: A cluster of proteins implicated in kidney disease is increased in high-density lipoprotein isolated from hemodialysis subjects. *J Proteome Res* 14: 2792–2806, 2015

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See related article, "Apolipoprotein B, Triglyceride-Rich Lipoproteins, and Risk of Cardiovascular Events in Persons with CKD," on pages 47–60.