Routinely measured lipids show contrasting associations with risk of coronary artery disease, diabetes

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An analysis using genetics finds that increased low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and possibly triglyceride (TG) levels are associated with a lower risk of diabetes, and increased LDL-C and TG levels are associated with an increased risk of coronary artery disease, according to a study published online by *JAMA Cardiology*.

Understanding the interplay between circulating lipids and the risk of type 2 diabetes and coronary artery disease (CAD) is of emerging public health importance and has implications for drug development for cardiovascular disease prevention. Low-density lipoprotein cholesterol is causally related to CAD, but the relevance of HDL-C and TGs is uncertain. Lowering of LDL-C levels by statin therapy modestly increases the risk of type 2 diabetes, but it is unknown whether this effect is specific to statins.

Michael V. Holmes, M.D., Ph.D., of the University of Oxford, England, and colleagues examined the associations of LDL-C, HDL-C, and TG levels with CAD and diabetes through mendelian randomization (MR) using conventional MR and making use of newer approaches using genetics. Published data from genome-wide association studies were used.

The researchers write that their comprehensive MR investigations identified distinct associations between major lipids and the risk of CAD and diabetes. Increased LDL-C and TG levels increased the risk of CAD. Increased LDL-C, HDL-C, and possibly TG levels were associated with a lower risk of diabetes.

"Although further studies are needed to examine whether specific pathways or lipid subtypes are implicated, our findings inform potential expected downstream consequences of interventions affecting lipid traits and provide cautionary evidence that therapeutics that lower LDL-C and TG levels may have dysglycemic [abnormal blood sugar levels] effects," the authors write.

"Although all 3 lipids were associated with reduced risk of diabetes, it does not necessarily follow that lowering of LDL-C or TG levels through use of drugs that target specific proteins will alter the risk of diabetes. Large-scale genetic and clinical investigations are needed to clarify the effects of pharmacologic lowering of LDL-C and TG levels to gauge dysglycemic associations."

The researchers add that this information will be relevant to the design of clinical trials of lipid-modifying agents, which should carefully monitor participants for dysglycemia and the incidence of diabetes.

"The findings from White et al will no doubt fuel the controversy on the causal association of major plasma lipids with type 2 diabetes (T2D)," write Danish Saleheen, M.B.B.S., Ph.D., of the University of Pennsylvania, Philadelphia, and colleagues in an accompanying editorial.

"While MR studies have been successful in solving the causal relevance of major lipids in coronary heart disease (LDL-C and TG, yes, and HDL-C, no), it seems that other approaches are required to further evaluate the causal relevance of each of these lipid fractions in association with T2D. The importance of this issue is clear: it has the potential to provide new insights into the pathogenesis of T2D and has implications for the effect of specific lipid-altering therapies on the development of T2D."

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