Abstract

Elevated Remnant Cholesterol Causes Both Low-Grade Inflammation and Ischemic Heart Disease, While Elevated Low-Density Lipoprotein Cholesterol Causes Ischemic Heart Disease without Inflammation.

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BACKGROUND: Elevated nonfasting remnant cholesterol and low-density lipoprotein (LDL) cholesterol are causally associated with ischemic heart disease (IHD), but whether elevated nonfasting remnant cholesterol and LDL cholesterol both cause low-grade inflammation is presently unknown.

METHODS AND RESULTS: We studied 60,608 individuals from the Copenhagen General Population Study, the Copenhagen City Heart Study, and the Copenhagen Ischemic Heart Disease study, of which 10,668 had IHD diagnosed between 1977 and 2011. We genotyped for variants affecting levels of 1) nonfasting remnant cholesterol, 2) LDL cholesterol, 3) C-reactive protein by CRP alleles, and 4) C-reactive protein by interleukin 6 receptor alleles. Using a multi-directional Mendelian randomization design, we investigated possible causal associations between the lipoproteins and C-reactive protein, and between the lipoproteins and IHD. A 1mmol/L (39mg/dL) higher level of nonfasting remnant cholesterol was associated observationally with a 37%(95%CI:35-39%) higher C-reactive protein level, and causally with a 28%(10-48%) higher level. For LDL cholesterol, a 1mmol/L (39mg/dL) higher level was associated observationally with a 7%(6-7%) higher C-reactive protein level, but we found no causal association. Likewise, higher levels of C-reactive protein did not associate causally with elevated nonfasting remnant cholesterol or LDL cholesterol. Finally, the causal risk ratio for IHD for a 1mmol/L (39mg/dL) higher level was 3.3(95%CI: 2.1-5.2) for nonfasting remnant cholesterol and 1.8(1.5-2.2) for LDL cholesterol. The causal associations for remnant cholesterol were present even in those without diabetes mellitus and obesity.

CONCLUSIONS: Elevated nonfasting remnant cholesterol is causally associated with low-grade inflammation and with IHD, while elevated LDL cholesterol associated causally with IHD without inflammation.

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