COMMENT ON HUH ET AL.

Remnant Cholesterol Is an Independent Predictor of Type 2 Diabetes: A Nationwide Population-Based Cohort Study. Diabetes Care 2023;46:305–312

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Diabetes Care 2023;46:e203 | https://doi.org/10.2337/dc23-0774

Huh et al. (1) performed what is to date the biggest population-based cohort study aimed at evaluating the association between remnant cholesterol (remnant-C) and the risk of developing type 2 diabetes (T2D). Their main conclusion was that there was a strong relationship between remnant-C levels and the risk of T2D. The validity of this result needs some consideration.

First, some aspects of the methodology raise questions. In the study, remnant-C was calculated as total cholesterol minus LDL cholesterol (LDL-C) minus HDL cholesterol (HDL-C). It seems that LDL-C was calculated using the Friedewald formula, but the authors also mentioned that LDL-C was measured using the enzymatic method. Which method was used? The term "remnant-C" for cases in which LDL-C is calculated and not measured might be somewhat misleading: remnant-C would simply be fasting triglycerides (TG) divided by 2.17. Indeed, this estimate of remnant lipoprotein cholesterol includes cholesterol in TG-enriched lipoproteins not yet processed to remnants.

Second, there are some issues with the association of baseline lipid values with incident T2D. There is a mistake in Table 2: 0.26 mmol/L does not correspond to 10 mg/dL for TG, and 0.1 mmol/L does not correspond to 10 mg/dL for non–HDL-C. Another important question is whether remnant-C levels have a predictive value independent of TG. The increments selected for hazard ratios seem to be arbitrary and even biased to highlight the association of remnant-C with T2D over TG. The highest hazard ratio for each increase of 1 SD was for TG. Moreover, TG were not included in the fully adjusted model used for estimating the risk of T2D across quartiles of remnant-C.

Establishing which mechanisms are involved in explaining how remnant-C levels contribute to the development of T2D is a challenge. As the authors indicated, the most reliable explanation is that remnant lipoproteins load β-cells with cholesterol, generating lipotoxicity, but there are no major studies that prove this hypothesis. Mendelian randomization studies do not support a role for raised circulating TG levels in influencing T2D, glucose levels, or insulin resistance (2). In the case of remnant-C, Mendelian randomization studies are needed to confirm or refute the conclusions obtained in observational studies.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

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