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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Huh et al. (1) claimed that calculated remnant cholesterol (remnant-C) at baseline was associated with increased risk of type 2 diabetes onset after 9.28 years, with a fourth-quartile hazard ratio versus first-quartile hazard ratio of 1.95 (95% CI 1.93–1.97). However, their conclusion is tenuous because the authors calculated remnant-C instead of directly measuring it. Calculated and directly measured remnant-C are poorly correlated (2). Furthermore, the equation that these authors used to calculate remnant-C produces a value that is almost completely correlated with simple triglyceride (TG) level.

According to their methods section, remnant-C equals total cholesterol (TC) minus HDL cholesterol (HDL-C) minus LDL cholesterol (LDL-C), with the latter term itself having been calculated using the Friedewald formula, namely, LDL-C equals TC minus HDL-C minus (TG divided by 2.19). Inserting the Friedewald LDL-C into their remnant-C equation yields the following: remnant-C equals TC minus HDL-C minus (TC minus HDL-C minus [TG divided by 2.19]), which reduces to remnant-C equals TG divided by 2.19. Thus, the calculated remnant-C value is directly proportional to TG divided by the Friedewald constant. This nonindependent relationship is clearly revealed in Table 1, in which the TG level divided by calculated remnant-C in quartiles 1, 2, 3, and 4 is 2.17, 2.16, 2.14, and 2.13, respectively, i.e., essentially the Friedewald constant in all cases (2). In other words, the calculated remnant-C is directly related to the simple TG level, and the authors are merely confirming that TG level predicts onset of type 2 diabetes, which is well known (3). Although their multivariate model adjusted for numerous confounders, TG was not among them. Their analysis should therefore be repeated with adjustment for TG levels.

While it may prove to be true that remnant-C predicts future diabetes onset, this cannot be concluded from the work of Huh et al. (1). New assays that directly measure remnant-C (4) may be more valid for this type of study. However, these direct methods are expensive, not widely available, and not clinically standardized. In the meantime, readers, reviewers, and editors should be cautious with reports focusing on calculated remnant-C due to its limited added value over directly measured TG. When faced with a choice between a direct laboratory measurement, i.e., TG, and a tightly correlated derived value, i.e., calculated remnant-C, why would a clinician or researcher choose the latter?

Duality of Interest. R.A.H. reports consulting fees from Acasti, Aegerion, Akcea/Ionis, Amgen, Arrowhead, Boston Heart, HLS Therapeutics, Pfizer, Novartis, Regeneron, Sanofi, and Ultragenyx, all unrelated to the theme of this article. No other potential conflicts of interest relevant to this article were reported.

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