LDL Cholesterol and Dysglycemia: an Intriguing Physiological Relationship

Jordi Merino[1,2,3,4] and Jerome I. Rotter[5,6,7]

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COMMENTARY

It is an unexpected but pleasant surprise when new clinical relationships are identified, and one of the most interesting is the inverse association between LDL cholesterol (LDLc) and type 2 diabetes (T2D) risk. Evidence from both randomized clinical trials and genetic studies indicates that regulation of plasma lipids and glycemic control is more closely linked than previously assumed, yet in a counterintuitive, one could even say paradoxical, manner. Meta-analyses of randomized clinical trials have found that drugs designed to reduce LDLc, in addition to their hypolipidemic and cardioprotective effects, appear to also modestly increase T2D risk (1,2). Furthermore, naturally occurring genetic variation in molecular targets of LDLc-lowering therapy, such as genetic variants in or near *HMGCR*, *NCP1L1*, and *PCSK9* genes, have been found to be associated with impaired insulin sensitivity and new-onset T2D, particularly among people with impaired fasting glucose levels (3–6). Further supporting that this is a fundamental biologic relationship, individuals with familial hypercholesterolemia, a dominantly inherited disease characterized by high plasma levels of LDLc due to genetic mutations in *LDLR* or *APOB* genes, appear to have a lower prevalence of diabetes than unaffected relatives (7). However, not all genetic variants that raise LDLc have similar effects on glycemic control (8). This suggests that the mechanism by which LDLc is reduced might have relevant implications for glycemic deterioration and reveal potential important mechanisms for diabetogenesis in general.

As reported in this issue of *Diabetes*, Klimentidis et al. (9) conducted a study to examine the phenotypic and genotypic relationships between LDLc and T2D (Fig. 1). Using data from the UK Biobank (n = 431,167), they confirmed findings from previous reports that LDLc is inversely associated with T2D prevalence, in this case with an odds ratio of 0.41 [95% CI 0.39, 0.43] per each mmol/L increase in LDLc, which they term an "opposite direction of effect." Although the magnitude of their observed association was higher than in other studies considering T2D incidence as opposed to T2D prevalence (1,2,10,11), these findings remained similar in several sensitivity analyses taking into account potential bias such as incomplete case ascertainment or the presence of a collider. The phenotypic associations also showed a paradoxical relationship of increased LDLc with increased HbA_{1c}, which may be an indication of the difficulties of studying the relationship between these complex phenotypes in a cross-sectional study.

To identify genetic variants with opposite effects on LDLc and T2D prevalence, Klimentidis et al. conducted a cleverly designed two-stage genome-wide association study. They first identified genetic variants associated with LDLc in UK Biobank. Then, to confirm those dual LDLc-T2D variant associations, they used T2D summary statistics data from the Diabetes Genetics Replication and Meta-Analysis (DIAGRAM) consortium (n = 898,130). This led to the initial identification of 44 genomic regions with opposite associations between LDLc and T2D, and 31 of them then replicated in the independent data sets for their association with LDLc. A number of the genomic regions identified by Klimentidis et al. were previously known or suspected to be inversely associated with circulating LDLc and T2D (*HMGCR*, *NPC1L1*, *APOE*), but the authors also identified 14 genomic regions without evidence of previous association with LDLc or T2D. Thus, first of all, this is a novel way to identify new LDLc and T2D loci. Computational characterization of identified genomic regions suggests that genetic variants that have an

[1]Diabetes Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA
[2]Programs in Metabolism and Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA
[3]Department of Medicine, Harvard Medical School, Boston, MA
[4]Research Unit on Lipids and Atherosclerosis, Universitat Rovira i Virgili, Institut d'Investigació Sanitària Pere Virgili, Reus, Spain
[5]Institute for Translational Genomics and Population Sciences, Torrance, CA
[6]Division of Genomic Outcomes, Departments of Pediatrics and Medicine, Harbor-UCLA Medical Center, Torrance, CA
[7]Departments of Pediatrics and Human Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA
Corresponding author: Jordi Merino, jmerino@mgh.harvard.edu

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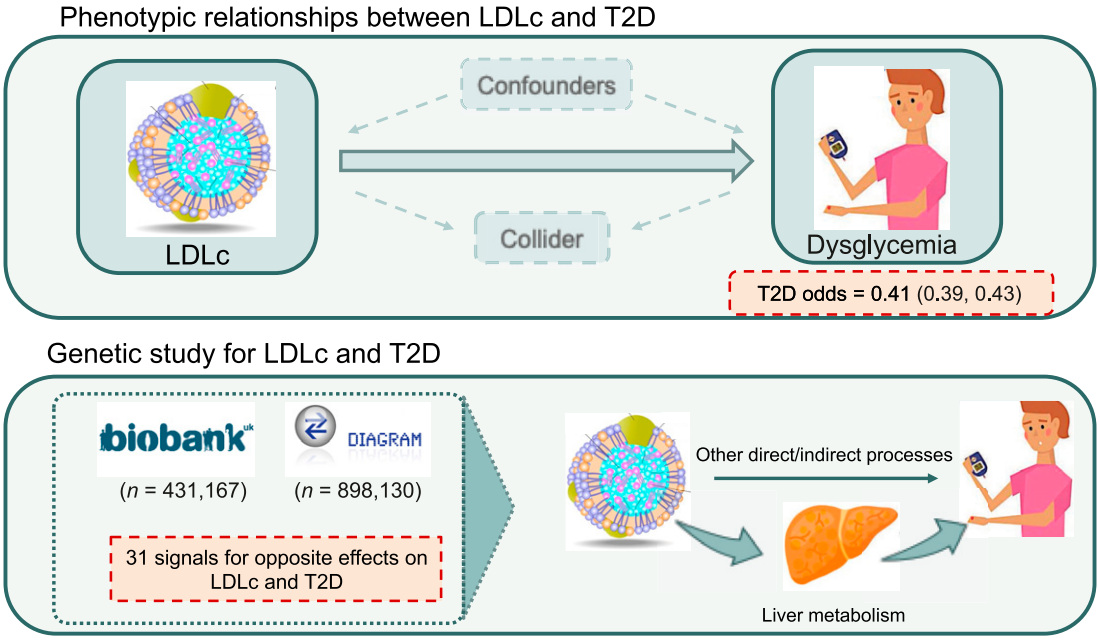

Figure 1— Overview of main study findings. In a cross-sectional study within the UK Biobank (n = 431,167), Klimentidis et al. (9) reported that LDLc is inversely associated with T2D prevalence (odds ratio 0.41 [95% CI 0.39, 0.43] per each mmol/L increase in LDLc). Using genetic data from UK Biobank and DIAGRAM (n = 898,130), Klimentidis et al. identified 44 genomic regions, with opposite associations between LDLc and T2D (31 of them then replicated) enriched for genes associated with NAFLD. Their findings suggest that the diabetogenic effect of lipid-lowering medications is in part mediated by increased liver fat content.

opposite effect on LDLc and T2D are enriched for genes associated with nonalcoholic fatty liver disease (NAFLD). Of particular interest is the observation that for some of the identified genomic regions, the same exact variant that has the joint effect on LDLc and T2D is the variant associated with increased NAFLD (i.e., *GCKR*, *PNPLA3*, *PPP1R3B*, or *TM6SF2*), highlighting the relevance of liver metabolism on plasma lipids and glycemic control.

There are some limitations to the study. First, this version of UK Biobank is a cross-sectional study, and it will be of interest to repeat these analyses when prospective data become available. For example, it is possible that T2D cases are more likely to be newly diagnosed patients not yet under lipid-lowering therapy, those with intolerance to lipid-lowering medications, people misreporting lipid-lowering medications, or older T2D individuals not requiring lipid-lowering medications. Propensity score analyses were implemented to account for this potential bias, but confounding could still exist (12). Second, this is not a traditional joint-phenotype genetic study in which the same participants have the phenotype of interest. By including data for LDLc from participants within the UK Biobank, and a separate data set to investigate whether these genetic variants associated with LDLc have a divergent effect on T2D, it is possible that differences in genome-wide association study characteristics may introduce some noise. Third, while mapping variants to genes is difficult, and only some of these loci exhibited colocalization of the association signals, it is still the case that we often infer that the closest gene is the most likely causal gene. Emerging data indicate that this is not always the case (13).

Overall, findings from Klimentidis et al. provide a new perspective on the debate regarding the intriguing physiological relationship between lipids and dysglycemia and put liver metabolism in the spotlight. Animal and human physiological studies have found that fat accumulation in the liver leads to hepatic insulin resistance and that direct and indirect mechanisms exist to control insulin's regulation of hepatic glucose and fat production (14,15). The observation that T2D signals identified for their dual association with low LDLc are mainly insulin-resistance loci, as opposite to the growing number of T2D loci primarily associated with insulin secretion, is well aligned with previous physiological data linking insulin resistance with hepatic fatty acid uptake and adipose tissue dysfunction. In this context, lipid-lowering strategies promoting adipose tissue expandability might have relevant implications to reduce glycemic deterioration associated with reducing LDLc, as it has been recently demonstrated for both gain- and loss-of-function variants in the LPL gene and T2D risk (16). Evidence from the current study may foster new lines of investigation to gain insights, not only into the underlying mechanisms responsible for the diabetogenic effect of LDLc-lowering medications, but into the etiology of T2D itself. Such knowledge will hopefully be used to inform public health and individual strategies to leverage more personalized and efficient approaches to

manage dyslipidemia among people with impaired fasting glucose levels.

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