# Does low lipoprotein(a) increase the risk of diabetes? New research suggests it does not

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New research has shown that, contrary to some previous studies, low levels of lipoprotein (a)—a parcel of fats and protein in the blood—do not cause type 2 diabetes.

The findings may alleviate concerns that drugs aimed at reducing lipoprotein (a) [known as Lp(a)] might be increasing patients' risk of diabetes. High levels of Lp(a) are known to increase the risk of a range of cardiovascular diseases, such as clogged arteries, heart attack and stroke, and so doctors usually try to reduce Lp(a) but may be worried about a possible link with diabetes.

In a study presented by Professor Tadeusz Osadnik from Medical University of Silesia in Katowice, Poland, at the ESC Congress today and published simultaneously in *Cardiovascular Diabetology*, researchers have used a genetic method called Mendelian randomization (MR) to show that, in fact, it is high levels of fasting insulin (hyperinsulinemia) that cause the reduction in Lp(a). Hyperinsulinemia leads to the development of pre-diabetes and type 2 diabetes.

Prof. Osadnik told the Congress, "Our findings suggest that hyperinsulinemia, triggered by insulin resistance, can partially explain the inverse relationship between low Lp(a) concentrations and an increased risk of type 2 diabetes. They show that insulin produced by the body has a slight tendency to reduce levels of Lp(a)."

Prof. Osadnik and Maciej Banach, Professor of Cardiology at the Medial University of Lodz, Poland, and Johns Hopkins University School of Medicine, Baltimore, U.S., published a study earlier this year that used MR to show there was no correlation between genetically predicted Lp(a) concentrations on the incidence of type 2 diabetes. However, they wanted to investigate further as there was some evidence that other factors might be involved.

MR is a method that uses measured variations in inherited genes to see if a particular risk factor [such as low Lp(a)] causes an effect on health (in this case, hyperinsulinemia), rather than just being associated with it, and reduces the likelihood of reverse causation.

The researchers used information from UK Biobank to identify genetic variants, called single-nucleotide polymorphisms or SNPs, that were strongly associated with fasting insulin levels. They conducted several statistical analyses to understand the relationship between the SNPs and fasting insulin.

Prof. Banach, who was also at the ESC Congress, said, "Our analyses show that higher genetically predicted fasting insulin levels cause a decrease in Lp(a) concentration, and there is no evidence of reverse causality, in which it would be the other way round.

"The question now is whether these observations may have any important clinical relevance? First, we can confirm that the relationship between Lp(a) and diabetes exists, but Lp(a) is unlikely to be a risk factor for the development of diabetes, independent of pre-existing hyperinsulinemia and insulin resistance. Second, the observational relationship between low Lp(a) and diabetes risk may not translate to possible adverse effects of therapies that reduce Lp(a) levels. More research is needed to investigate this further."

Prof. Osadnik said, "Although therapies aimed at reducing insulin resistance, high levels of insulin in the blood and high blood sugar levels may increase Lp(a), it is almost certain that their cardiometabolic benefits outweigh the increased cardiovascular risk caused by an increase in Lp(a). This is demonstrated by the fact that good control of blood sugar levels improves patient survival. As elevated Lp(a) is an independent and incremental risk factor for outcomes for patients with coronary artery disease, with and without diabetes, we should do our best to reduce elevated Lp(a)."

Prof. Banach concluded, "This study also clearly shows that our patients can be complicated, and often have other concurrent risk factors and medical conditions. We should always take a holistic approach to their

health, looking at all these other factors as well. We should not be focused just on Lp(a), or cholesterol levels or diabetes, but try to identify all other residual cardiovascular risk factors. We need to look at the whole patient; this is the only way to reduce cardiovascular disease effectively in our patients."

Limitations of the study include: it relied on summary data from UK Biobank and so it was not possible to analyze the influence of non-genetic factors that might affect Lp(a), such as sex, hormones or diet; bias may have been introduced because it included patients with diabetes ; the data came from people of European descent, so it might not be possible to generalize the findings to people of different ethnicities; and insulin and blood sugar levels are complex and interconnected, so further research is required to understand if indirect effects of insulin on Lp(a) levels exist.

**More information:** Causal associations between insulin and Lp(a) levels in Caucasian population: A Mendelian randomization study, *Cardiovascular Diabetology* (2024).

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Provided by Polskie Towarzystwo Lipidologiczne (Polish Lipid Association)