Belalcazar et al\textsuperscript{1} exploited a genetic variant (L446P)\textsuperscript{2} in the glucokinase regulatory (GCKR) gene, known to have inverse cardiometabolic effects, to investigate whether the effect of the 446L allele can be attenuated by an intensive lifestyle intervention (ILI) in the Look Action for Health in Diabetes (AHEAD) trial.\textsuperscript{3} Participants of Look AHEAD exhibited high adherence to the ILI, which demonstrated the success of an intensive lifestyle by significant weight loss,\textsuperscript{4} improved diabetes mellitus control,\textsuperscript{5} and reduced C-reactive protein (CRP) and triglyceride levels\textsuperscript{6} compared with usual care participants. The authors evaluated the interaction of the common variant in GCKR to treatment assignment and triglyceride or CRP levels in participants with type 2 diabetes mellitus (T2DM) and unfavorable metabolic profiles. In 3214 participants with triglyceride and 1411 with CRP levels, the GCKR 446L allele showed no benefit of participating in the ILI intervention on lowering triglyceride or CRP levels at the 1-year follow-up (49\% randomized to ILI and 51\% to usual care).

**Article see p 71**

Studying gene–environment interactions is a formidable challenge. Interactions require a generous sample size to identify significant interactions corrected for the multiple tests performed. Belalcazar et al\textsuperscript{1} used a well-founded hypothesis that the GCKR 446L raising affects on triglyceride and CRP could be modified by calorie restriction and increased physical activity. The next step in building the scientific evidence for a gene–lifestyle interaction would be to replicate the association in an independent study sample. Interestingly, an earlier study by Pollin et al\textsuperscript{7} reported that the GCKR 446L allele was associated with reduced triglyceride (interaction $P=0.04$) but no effect on CRP levels in the intensive lifestyle arm of the Diabetes Prevention Program\textsuperscript{7}—the lifestyle intervention that was adapted to more intensive calorie restriction and similar physical activity for Look AHEAD participants. Belalcazar et al\textsuperscript{1} ran comparable 2-way interaction analyses as reported in the study by Pollin et al\textsuperscript{7} without a significant effect from intensive lifestyle on 446L and triglyceride or CRP levels. The discrepancy in results of these 2 studies most likely has epidemiological and biological explanations.

Glucokinase is the key regulator in reducing blood glucose levels by initiating glycogenesis (glucose storage) in the liver. The GCKR 446L allele has been favorably associated with a reduction in glycemic traits and T2DM risk;\textsuperscript{8} however, levels of CRP and triglyceride\textsuperscript{9} are significantly increased with the most profound effect on triglyceride levels. This paradoxical observation mimics many pharmacological therapies for T2DM. For example, inhibitors of GCKR activity have shown promising results as new therapeutic targets for lowering glucose levels in individuals with diabetes mellitus; however, studies testing small molecules that target glucokinase reported increased triglyceride levels as well as increased severity and rates of hypoglycemia.\textsuperscript{10} Mechanistically, the 446L allele reduces GCKR-binding affinity for glucokinase,\textsuperscript{11} resulting in a reduced ability to inhibit glucokinase leading to increased hepatic glucose uptake, and synthesis of glycogen and triglycerides\textsuperscript{12,13} in a normoglycemic or hypoglycemic state.\textsuperscript{14} Recently, an encouraging study from Amgen reported glucose-lowering effects in diabetic and obese rodents; and importantly no effect on glucose in normoglycemic rats.\textsuperscript{15}

The 2 studies are similar by several epidemiological measures, for example, sample size, sex, and ethnicity; however, 1 primary difference in the design of the 2 trials is diabetes mellitus status. The Diabetes Prevention Program enrolled participants with impaired glucose tolerance while Look AHEAD participants were only eligible if they had T2DM at baseline. This could partially explain the difference in results reported by Belalcazar et al\textsuperscript{1} and Pollin et al.\textsuperscript{7} The increased glucokinase activity from 446L cannot be compensated in a diabetic state of decreased insulin secretion, and elevated glucose and triglyceride; whereas in a normoglycemic state increased glucokinase activity can still be modulated by weight loss through improved diet and exercise. Furthermore, studies assessing genetic risk scores containing GCKR P446L and interactions (or subgroup analyses) associated with T2DM risk have reported stronger effects in younger (<50 years)\textsuperscript{16,17} and leaner (<25 or 25 to <30 versus ≥30 kg/m\textsuperscript{2})\textsuperscript{18} individuals. The average age (59.0 versus 50.6 years) and body mass index (36.2 versus 34.0 kg/m\textsuperscript{2}) of participants at baseline were higher in Look AHEAD compared with the Diabetes Prevention Program, respectively.

The work by Belalcazar et al\textsuperscript{1} is intriguing and further contributes to the all-important understanding of gene–lifestyle interactions. Taking advantage of existing intervention and observational studies, their genotyped participants serves as a virtual clinical trial to efficiently gather evidence for the
potential adverse affects during drug development or modifying lifestyle to blunt the effects of our genes. Furthermore, these results can be used to inform the design of future trials. More work will need to be done to confirm the gene–lifestyle interaction on cardiometabolic outcomes in other studies and to further elucidate the in vivo effects of GCKR 446L by diabetes mellitus status.

Disclosures

None.

References


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