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Zinc–rs13266634 and the Arrival of Diabetes Pharmacogenetics: The "Zinc Mystique"

Advances in our understanding of the genetics of type 2 diabetes have been astronomical over the past decade with more than 100 single nucleotide polymorphisms (SNPs) associated with modest increases in diabetes risk and differences in related traits such as fasting glucose (1,2). However, these SNPs have contributed more to elucidating biologic pathways than predicting diabetes risk (3). Nonetheless, the most promising work suggests that we are on the cusp of being able to use genetic information to individualize treatment for type 2 diabetes prevention and management (4,5). The promise of pharmacogenetics is predicated on the existence of known individual variation in response to interventions and the strong biologic basis for genetic variation as a primary, immutable difference between individuals.

rs13266634 is one of the most consistently replicated diabetes risk variants (odds ratio of 1.14 for the R allele) (6). This SNP encodes a C→T base substitution in the *SLC30A8* gene, resulting in a change in the coded protein (Arg325Trp or R325W). The frequency of the diabetes risk R allele is 91.5%, 71.7%, and 56.7% in Africans, Europeans, and Asians, respectively (1,000 Genomes).

The *SLC30A8* gene encodes zinc transporter-8 (ZnT8). This transporter is specific to pancreatic islets and is mainly expressed in β-cells that transport zinc from the cytoplasm into insulin secretory vesicles (7). This zinc stabilizes insulin hexamers, prevents insulin degradation, and is cosecreted with insulin, proinsulin, and C-peptide during the early stage of glucose-stimulated insulin secretion (GSIS) (7,8). Cosecreted zinc also passes through the portal vein with the other contents of the insulin secretory vesicle and appears to inhibit hepatic clearance of insulin (8). Although preclinical studies consistently show structural abnormalities of insulin secretory vesicles in the absence of ZnT8 (9–11), they are not consistent regarding the impact of ZnT8 abnormalities on GSIS (9–12). The few human studies that evaluated quantitative traits suggest that carriers of the R risk allele have abnormalities in both GSIS and insulin processing (13–16).

In this issue, Shan et al. (17) suggest that plasma zinc concentrations are associated with diabetes in a genotype-specific fashion, a finding that highlights the potential of rs13266634 as a strong genetic candidate for individualizing diabetes care. The authors first measured zinc levels in 1,776 Chinese people with normal glucose tolerance (*n* = 793), newly diagnosed impaired glucose tolerance/impaired fasting glucose (*n* = 218), and newly diagnosed type 2 diabetes (*n* = 785) and observed lower plasma zinc concentrations in those with diabetes. The novel finding, however, was a statistical interaction between zinc levels and rs13266634 such that the benefit of higher zinc levels on the odds of diabetes decreased with increasing copies of the R (risk) allele (WW>RW>RR).

Shan et al. provide the first published data on the potential interaction between zinc levels and rs13266634 on diabetes risk. A major strength of the new report is its focus on a biologically plausible interaction: rs13266634 is a coding variant that affects a specific zinc transporter that is directly involved in insulin secretion in the β-cell. One could therefore hypothesize that the impact of available zinc would vary across its genotype. In fact, these findings are consistent with a prior meta-analysis of five cross-sectional studies that showed higher zinc intake seemed to reduce the fasting glucose-raising effect of rs11558471; rs11558471 is an *SLC30A8* SNP in tight linkage disequilibrium with rs13266634 (18). Of course, plasma zinc levels are unlikely to reflect zinc exposure at the level of the β-cell, and zinc levels assessed at a single point in time may not reflect

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COMMENTARY

the zinc relevant to the biological interaction important for understanding the potential therapeutic application of zinc for diabetes prevention. More important, these findings need to be replicated with larger sample sizes that assess zinc status prior to diabetes diagnosis, an approach that will address reverse causality.

If these associations hold up, the most logical and useful extension of this work would be a clinical trial of zinc supplementation to evaluate its therapeutic potential and safety, ultimately aiming for prevention or treatment of type 2 diabetes based on rs13266634 genotype. At a population level, understanding the implications of dietary patterns (and their zinc content) on this interaction is also extremely important given that other micronutrients, including iron and copper, are also important for the action of zinc in the body (19). Also, zinc is ubiquitous throughout the body. Supplementation could therefore have far-reaching effects because zinc serves as an essential component of numerous proteins, including enzymes, transcription factors, and growth factors, and it acts independently in autocrine, paracrine, and neurotransmitter roles (20).

The early chapters of the zinc–rs13266634 story raise several questions for diabetes genetic epidemiology, especially issues related to nutrigenetics and pharmacogenetics. Historically, zinc has been of interest in diabetes because it has been linked to lower diabetes risk in observational studies (21), and has reduced fasting glucose and hemoglobin A_{1c} in some randomized trials (22). The interaction under study may explain some of this "zinc mystique." However, while accumulating evidence suggests that rs13266634 impacts diabetes risk and insulin secretion traits in humans and is affected by total zinc intake and circulating zinc levels, the functional implications of the rs13266634 variant remain unclear. Indeed, a recent study found that rare loss-of-function variants in *SLC30A8* are actually protective against diabetes (23), and another suggests that rs13266634 may impact regulation of hepatic insulin clearance (8). If the findings of Shan et al. (17) are confirmed and genotype-guided zinc interventions show promise for diabetes, at what point do we consider the evidence to be substantial enough to warrant clinical use? And how will we implement this individualized care? These and other questions are ripe for investigation.

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