JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 15, 2018
© 2018 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

MINI FOCUS ON DIABETES

EDITORIAL COMMENT

# SGLT1 and Sweet Genetic Insights Into Cardiometabolic Risk*

Ferhaan Ahmad, MD, PhD,[a,b] Zhao Li, PhD,[a] Kamel Shibbani, MD[a,c]

There are 2 families of glucose transporters, the facilitative (GLUT) and the sodium-dependent (SGLT) transporters (1). The SGLTs function by secondary active transport using the $Na^+$ gradient. The SGLT1 isoform is present in small intestinal enterocytes and renal proximal tubule cells, where it mediates glucose uptake (2). Homozygous loss-of-function variants in *SLC5A1*, the gene encoding SGLT1, lead to glucose/galactose malabsorption with life-threatening diarrhea in newborns. In this issue of the *Journal*, Seidelmann et al. (3) show that heterozygosity for a haplotype of 3 common missense variants in *SLC5A1* (N51S/A411T/H615Q) that cause a modest decrease in SGLT1 function and are present at a frequency of 6.7% in the population is associated with a decreased prevalence of impaired glucose tolerance on oral glucose tolerance tests and obesity in subjects of European and African origin. In subjects of European origin, *SLC5A1* variants are also associated with a decreased prevalence of hypertension, lower diastolic blood pressure, decreased heart rate, and lower uric acid levels. In addition, the investigators show that the haplotype is associated with a decreased incidence of diabetes mellitus, heart failure, and death over a median follow-up period of 25 years.

The study design by Seidelmann et al. (3) in this issue of the *Journal* was robust, and its findings have potentially broad implications. A discovery cohort of 8,478 subjects and a replication cohort of 6,784 subjects were analyzed. The discovery cohort included subjects of European origin from 4 U.S. communities. The replication cohorts were subjects of African origin from the same U.S. communities and subjects recruited from at least 6 Finnish communities. The principal associations identified by the investigators were present in both racial groups and in geographically distant communities. The discovery cohort had excellent longitudinal follow-up with a median of 25 years.

SEE PAGE 1763

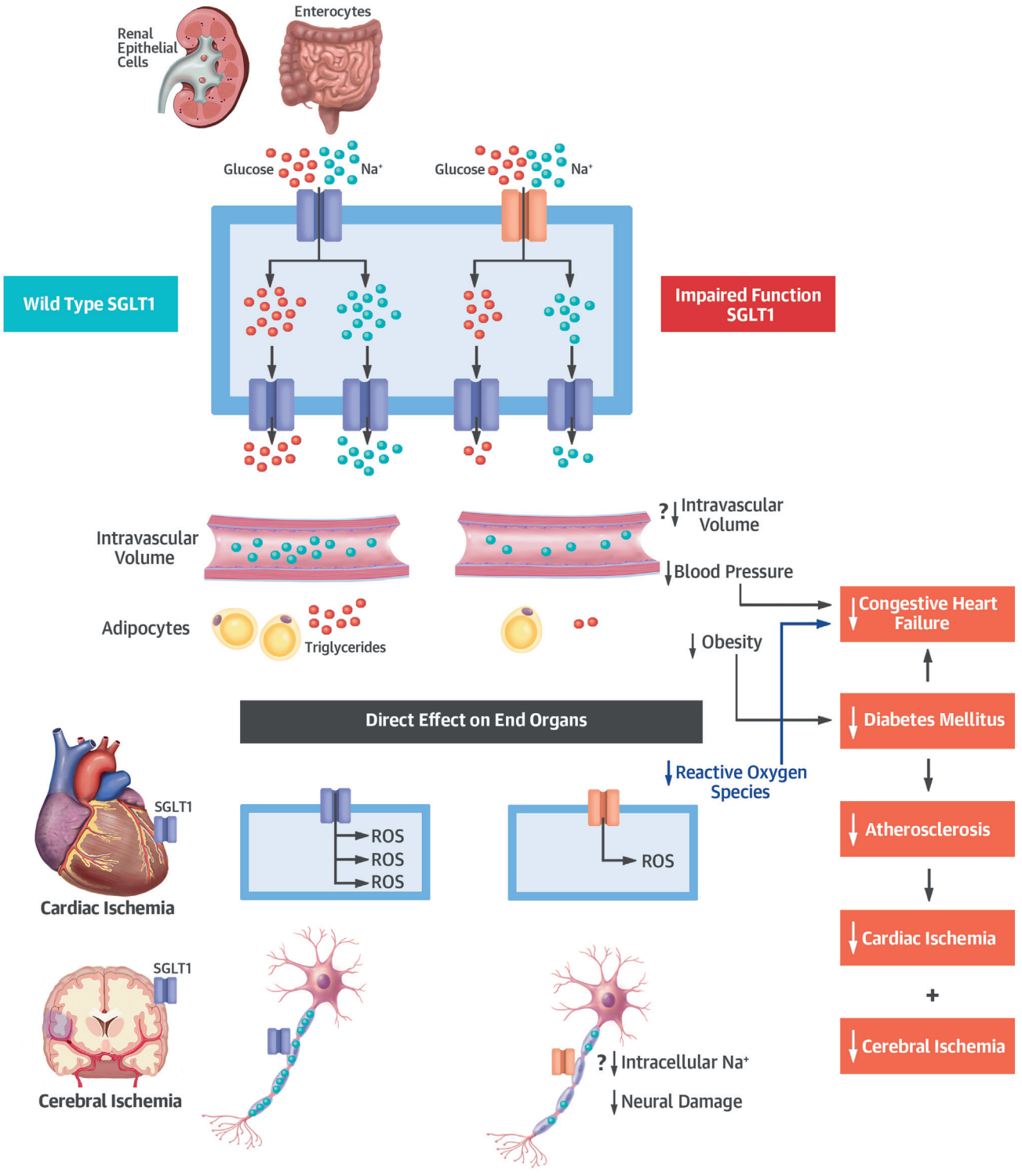
The design of this study (3) is appropriate to find associations between gene alleles and disease outcomes. However, alone, it can be used only to infer causation between exposures and outcomes, and it cannot prove the biological mechanisms that drive such causation. The simplest mechanistic pathway to explain the influence of *SLC5A1* variants on outcomes would be that decreased intestinal glucose and galactose absorption and possibly decreased renal reuptake of glucose from the ultrafiltrate lead sequentially to lower net caloric balance, decreased obesity, improved insulin sensitivity, improved glucose tolerance, and less heart failure (**Figure 1**). However, the association of the *SLC5A1* haplotype with impaired glucose tolerance remains significant after inclusion of obesity as a covariate, suggesting the presence of other mechanistic pathways in addition to obesity. Indeed, the investigators propose several plausible explanations for the protective effect of the identified haplotype, including increased levels of beneficial hormones such as glucagon-like peptide-1, decreased fibrosis secondary to low glucose levels, and a direct cardioprotective role.

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the [a]Division of Cardiovascular Medicine, Department of Internal Medicine, and Abboud Cardiovascular Research Center, [b]Department of Radiology and Department of Molecular Physiology and Biophysics, and the [c]Stead Family Department of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, Iowa. This research was supported by grants from the National Institutes of Health (R01 HL135000) and the American Heart Association (15GRNT25650003, 16POST27770035). Dr. Ahmad has received support from MyoKardia, Inc., for research unrelated to this editorial. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.07.060

**FIGURE 1** **Model of *SGLT1* and Cardiometabolic Risk**




Potential mechanisms by which sodium-glucose cotransporter 1 (SGLT1) contributes to cardiometabolic risk. ROS = reactive oxygen species.

Download English Version:

https://daneshyari.com/en/article/11014907

Download Persian Version:

https://daneshyari.com/article/11014907

Daneshyari.com