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EDITORIAL COMMENT

Understanding Heart Failure With Preserved Ejection Fraction in a Diabetic Way*

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Diabetes is associated with adverse outcomes in patients with heart failure, notably in those with heart failure with preserved ejection fraction (HFpEF). Although several mechanisms have been proposed as contributing to these worse outcomes, proven treatments for diabetic HFpEF, or for HFpEF more generally, are still lacking. Systematic analysis of differences in patients with both diabetes and HFpEF compared to those with HFpEF alone could provide insight into the unique pathophysiology of this condition and identify new therapeutic targets.

In this issue of *JACC: Basic to Translational Science*, Hanff et al. (1) examined plasma proteins in HFpEF patients with or without diabetes to identify candidates contributing to worse outcomes in patients with diabetes. SomaScan (SomaLogic Inc., Boulder, Colorado), a multiplexed, modified aptamer-based proteomic assay, was used to measure almost 5,000 proteins in plasma from patients in the PHFS (Penn Heart Failure Study) and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial) studies. Proteins that differed between diabetic and nondiabetic HFpEF patients in each cohort were identified, including 361 proteins in PHFS and 36 proteins in TOPCAT. Among these proteins, 10 were associated with diabetes and concordantly changed in both cohorts. Using adaptive least absolute shrinkage and selection operator regression, Hanff et al. (1) found that 6 of these 10 proteins contributed independent information regarding the presence of diabetes before adjustment for clinical covariates, and 3 of these (alpha-1-microglobulin/bikunin precursor protein; apolipoprotein M [ApoM]; cartilage intermediate layer protein 2) remained significant after adjustment for clinical covariates. Hanff et al. (1) are to be applauded for systematically delineating, for the first time, the plasma proteomes in HFpEF patients with or without diabetes.

Hanff et al. (1) further found that even after adjustment, ApoM was the only protein significantly associated with adverse outcomes as a composite of time to cardiovascular death, aborted cardiac arrest, and heart failure hospitalization. Interestingly, diabetes was associated with worse outcomes in unadjusted models but was no longer significant after adjustment for ApoM. This finding suggests that ApoM is colinear with the association between diabetes and adverse HFpEF outcomes. This association was further confirmed by mediation analysis, which suggested 72% of the association between diabetes and adverse outcomes was mediated by ApoM. The directionality of these associations is supported by previous work showing that although serum ApoM is reduced in patients with Type 2 diabetes, genetic deletion of ApoM in mice fed a standard chow diet has no impact on blood glucose and insulin sensitivity (2). Thus, it appears that diabetes leads to a reduction in ApoM, rather than the converse, and the current study suggests reduced ApoM mediates much of the increase in adverse outcomes seen in patients with HFpEF with diabetes. Whether restoration of ApoM

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levels could mitigate those adverse outcomes in diabetic HFpEF remains to be determined.

ApoM is a lipocalin primarily secreted from the liver and is a carrier of sphingosine-1-phosphate. Plasma ApoM binds to and positively correlates with high-density lipoprotein (HDL) cholesterol. Although ApoM clearly has effects on circulating cholesterol and HDL with possible implications for atherosclerosis, ApoM is reduced in both patients with heart with reduced ejection fraction (HFrEF) and those with HFpEF (3). Interestingly, genetic deletion of ApoM exacerbates lipopolysaccharide-induced cardiac dysfunction (4). Moreover, serum ApoM levels are lower in patients with type 2 diabetes and are inversely correlated to body mass index and insulin resistance index (2). In mice, genetic deletion of ApoM exacerbates insulin resistance, whereas adeno-associated viral gene transfer of ApoM improves insulin secretion and insulin sensitivity in high-fat diet-induced obesity (2). Together, these studies suggest that ApoM may protect against diabetes and cardiac dysfunction. Hanff et al. (1) now provide evidence that reduced ApoM contributes to the increased risk of adverse outcomes in patients who have both conditions. These studies also add to the evolving literature raising the possibility that HDL levels can predict risk and may influence outcomes in patients with heart failure.

This interesting work provides new insights into the mechanisms mediating adverse outcomes in patients with diabetes and HFpEF. First, patients with diabetes with HFpEF exhibit distinct plasma proteomes compared to patients with HFpEF in the absence of diabetes, in which alpha-1-microglobulin/bikunin precursor protein is increased while cartilage intermediate layer protein 2 and ApoM are decreased in diabetic HFpEF. Second, reduced ApoM is responsible for much of the increase in adverse outcomes seen in patients with diabetes and HFpEF. Altogether, this study underscores the importance of diabetes in the pathobiology of HFpEF and implicates ApoM as a potential therapeutic target in diabetic HFpEF.

As with all provocative analyses, the study by Hanff et al. (1) raises multiple questions that warrant further investigation. First, the current study did not distinguish between type 1 and type 2 diabetes, so it is possible that the role of ApoM in adverse heart failure outcomes differs between these conditions. Second, the current study focused on HFpEF. Because ApoM is reduced in both HFrEF and HFpEF (3), it would be interesting to examine whether the strong correlation of ApoM with adverse outcomes in diabetic heart failure also applies to HFrEF and how ApoM changes with the HFrEF treatments shown to improve outcome. Third, in PHFS, the patients with diabetes were older than the nondiabetic patients (age 65 vs. 59 years of age), whereas in TOPCAT, the reverse was true (age 69 vs. 76 years of age). Elderly patients with diabetes have a greater risk of developing heart failure compared to younger patients, and diabetes severity is associated with the risk of heart failure in the elderly. Thus, it is not clear whether the protein differences between the 2 cohorts (361 in PHFS vs. 36 in TOPCAT) are related to the differences in age distribution or differences in diabetes severity. Finally, although the current study examined plasma proteins, other macromolecules likely also play important roles. For example, noncoding ribonucleic acids such as microribonucleic acids have been implicated in the pathophysiology of diabetic cardiac dysfunction (5) and could also contribute to worse outcomes in diabetic HFpEF.

Despite these issues, Hanff et al. (1) have admirably provided evidence of the impact of diabetes on adverse HFpEF outcomes and highlighted the potential role of ApoM in this process. Their observations provide valuable insights into the molecular correlates of diabetic HFpEF with possible implications for therapeutic intervention in HFpEF. Exploring the potential of ApoM-directed therapies in diabetic patients with HFpEF will be an exciting opportunity for future investigation. Toward this goal, validation of its functional role and elucidation of the underlying mechanisms in experimental HFpEF animal models would be important next steps.

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