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EDITORIAL COMMENT

An (Auto)Taxing Effort to Mechanistically Link Obesity and Calcific Aortic Valve Disease*

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Calcific aortic valve disease (CAVD) is a critical pathology that ultimately results in cardiac failure. There are currently no Food and Drug Administration–approved drugs for CAVD, and invasive valve replacement options are the only effective treatment, making this a major unmet medical need. CAVD typically develops over decades of life and does not always associate with other common cardiovascular diseases, including atherosclerosis. Because of the apparent distinction between CAVD and other cardiovascular disorders, as well as the long duration between disease initiation and outcomes (e.g., cardiac failure), identifying biomarkers is an important aspect of CAVD drug development efforts. Apoliprotein(a) (*LPA* gene) is a genetic risk factor associated with CAVD, and elevated circulating levels of this gene's lipoprotein product, lipoprotein(a), are associated with aortic valve calcification (1). Lipoprotein(a) contains several lipids and proteins, including the lipid lysophosphatidylcholine and the protein autotaxin, an enzyme that converts lysophosphatidylcholine to lysophosphatidic acid. Lysophosphatidic acid stimulates inflammation and calcification in aortic valve interstitial cells (2), supporting the role of autotaxin-mediated lipid metabolism in CAVD pathogenesis. In this issue of *JACC: Basic to Translational Science*, Bourgeois et al. (3) suggest an association of CAVD with elevated autotaxin and lipoprotein(a) complexes and associate autotaxin and lipoprotein(a) complexes with increased body mass and CAVD risk.

As pointed out in the Bourgeois et al. study (3), there are several major risk factors associated with CAVD, including age, sex, hypertension, type 2 diabetes mellitus, low-density lipoprotein, smoking, and obesity. Key biological processes, including inflammation, act as shared mechanistic links between these main CAVD risk factors. However, these major CAVD risk factors may stimulate CAVD inducers, like inflammation, by different mechanisms. Calcification can occur in the valve and/or arteries and involves different genetic and environmental stimuli. Therefore, it is currently unclear if cardiovascular calcification is a single pathology or multiple distinct pathologies with some shared disease mechanisms. If different, several therapeutic approaches may be necessary to treat this disorder in multiple patient populations. Although a difficult task, obtaining a detailed mechanistic understanding of how calcification is initiated in cardiovascular tissues is paramount for early identification of the patient populations that could likely benefit from targeted therapeutic approaches.

Obesity and cardiovascular calcification are multifaceted diseases. Linking risk factors of these diseases could identify molecular mechanisms that can be

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therapeutically targeted to lower cardiovascular risk in the increasing worldwide obese patient population. By supporting a connection of calcification genetic risk factors to obesity, we previously showed that a genetic risk factor for vascular calcification—sortilin—also contributed to obesity in a female mouse model of vascular disease (4). Whether similar connections between obesity and CAVD genetic risk factors exist is largely unknown. Increased abundance of the major CAVD genetic risk factor, lipoprotein(a), has not been consistently shown to be linked to obesity. However, Bourgeois et al. (3), present an interesting aspect to this by reporting increased autotaxin and lipoprotein(a) complexes that were associated with increased body mass and CAVD risk in a small patient population.

Lipoprotein(a) is produced in the liver, whereas a large portion of autotaxin is produced by adipose tissue, together with smaller levels being made by several other tissues and aortic valve interstitial cells (2). Bourgeois et al. (3) did not identify the tissue source of the increased autotaxin that they observed complexing with lipoprotein(a); however, the most likely candidate source would appear to be adipose tissue. Although yet to be a proven CAVD mechanism, these new findings suggested increased adipose tissue in obesity might likely increase the release of autotaxin that complexes with lipoprotein(a). Lipoprotein(a) localized lysophosphatidylcholine conversion to lysophosphatidic acid by autotaxin could then stimulate inflammation and calcification in aortic valve cells, leading to CAVD.

The findings of Bourgeois et al. (3) also support the potential of autotaxin and lipoprotein(a) complexes to be used as a CAVD biomarker, particularly in obese patients. Autotaxin was previously proposed as a CAVD biomarker in conjunction with lipoprotein(a), but this assessment produced mixed results that both supported (2) and found no association (1) with autotaxin abundance and CAVD risk. The reason for these seemingly inconsistent findings is unclear. One possible explanation might be that autotaxin activity is a key factor to assess rather than protein abundance (1). In the current study, autotaxin activity was found to associate with CAVD risk, whereas in another 2020 study (1) that did not examine autotaxin activity, no association was seen with autotaxin abundance and CAVD risk. Future studies will be needed to assess autotaxin activity in larger patient populations to clarify these contrasting findings. In addition, how autotaxin activity might be potentially increased in the absence of protein abundance changes, as may be the case in some conditions, requires further investigation.

Based on the Bourgeois et al. (3) results, obese patients are a critical patient population to focus on to clarify the association of autotaxin complexed with lipoprotein(a) with CAVD risk. If increased autotaxin activity is consistently observed to be associated with obesity and CAVD risk, therapeutically targeting autotaxin may present an additional strategy to the apolipoprotein(a) antisense therapies currently being evaluated in clinical trials. In addition, apolipoprotein(a) antisense trials raise mechanistic possibilities that could be further explored in relation to autotaxin and lipoprotein(a) complexes. A 2020 apolipoprotein(a) antisense study found reduced pro-inflammatory activation in circulating monocytes in patients with elevated lipoprotein(a) (5). As such, increased lysophosphatidic acid production might also act to increase circulating immune cell inflammation.

Although autotaxin can directly act on promoting inflammation in aortic valve interstitial cells (2), it is possible that it may also regulate circulating monocyte inflammation that contributes to CAVD. Whether inflammation induction of immune cells by lysophosphatidic acid acts to increase CAVD is unknown and was not addressed in the current study. It would also be interesting to assess whether autotaxin and lipoprotein(a) complexes contribute to inflammation in adipose tissue directly or via immune cell-driven inflammation. If this is the case, autotaxin and lipoprotein(a) complexes may similarly act to increase obesity via inflammation, which, in turn, drives a cardiometabolic disease cycle that further increases CAVD progression.

In summary, although the results of Bourgeois et al. (3) support the potential of autotaxin and lipoprotein(a) complexes as a possible biomarker for CAVD, further studies are needed to fully validate this claim and to clarify existing discrepancies. The current study puts forth an intriguing connection among autotaxin and lipoprotein(a) complexes, obesity, and CAVD risk that strongly supports further translational, mechanistic, and therapeutic assessment of autotaxin inhibition in cardiometabolic diseases.

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