Indoxyl Sulfate: Long Suspected But Not Yet Proven Guilty

Tammy Sirich and Timothy W. Meyer


The action of colon microbes on undigested proteins gives rise to a variety of indoles and phenols that are conjugated by the liver before excretion by the kidney. Among the most abundant of the excreted compounds is indoxyl sulfate (IS), which was shown more than 100 years ago to accumulate in the blood when kidney function is lost (1,2). Because it is abundant and relatively easy to measure, IS has long attracted the attention of researchers seeking to explain the ill effects of kidney failure. Early interest was focused on its potential contribution to the symptoms of uremia, including particularly cognitive dysfunction. Subsequently, Niwa and Ise (3) assembled evidence that rising blood IS levels contribute to progressive loss of kidney function in chronic kidney disease (CKD). Most recently, attention has been focused on the prevalence of vascular disease in CKD, and IS has been identified as a potential vascular toxin (4).

The report by Yu et al. (5) in this issue of CJASN adds to the evidence that IS impairs vascular function. The case against IS, however, should be described as suggestive, not proved. Because so many solutes accumulate in renal failure, it is very difficult to distinguish the contribution of individual compounds to clinical outcomes. Bergstrom (6) suggested for identifying toxic solutes criteria that are analogous to Koch’s postulates for identifying infectious agents. According to these criteria, not only must the toxic solute be present in high concentration but also

● the high concentration should be related to specific effects that are ameliorated when the concentration is reduced

● the effects observed in patients should be replicated by raising the solute concentration in normal people, experimental animals, or in vitro systems

High concentrations of IS in patients with CKD are indeed related to ill effects, including vascular disease. Reporting in this journal, Baretto et al. (7) described a significant correlation between IS levels and both cardiovascular and overall mortality in patients with estimated GFR (eGFR) ranging from 10 to 90 ml/min, but such associative studies have so far not shown that IS is a better predictor of adverse outcomes than the numerous other solutes whose plasma levels rise as the GFR falls. An important strength of the study of Yu et al. (5) is that the investigators have assessed the effect of reducing IS levels. Very few previous studies of the ill effects of retained solutes have taken this important step. Yu et al. (5) were able to reduce IS levels by 24 weeks of oral treatment with AST-120, a formulation of activated carbon that absorbs the IS precursor indole in the colon and leads to its excretion in the feces. They found that IS treatment partially reversed the impairment in flow-mediated dilation in the brachial artery observed in a group of 39 patients with average eGFR of 21 ml/min. The effect of AST-120 on flow-mediated dilation suggested that IS limits production of vasodilator nitric oxide by endothelial cells.

The absence of a control group is a weakness in this report of the effect of AST-120. The investigators show that AST-120 did not change the eGFR or hemoglobin level, but inclusion in the study could conceivably have led to improved adherence to dietary and antihypertensive control or other changes that influence vascular function independent of IS. The complexity of potential influences on the vasculature is illustrated by the recent report that high phosphate levels impair flow-mediated dilation in the brachial artery (8). The lack of specificity in the effect of AST-120 is a second weakness in the case against IS. AST-120 absorbs many organic compounds, and, as recently documented by Kikuchi et al. (9), it thus reduces the plasma levels of retained solutes, including hippurate, phenyl sulfate, and p-cresol sulfate, as well as IS. This does not weaken the evidence that AST-120 is beneficial but only limits our ability to attribute its effect to reduction in IS levels. Vascular injury in renal disease has been related to high p-cresol sulfate levels, and AST-120 could, for instance, protect the vasculature by lowering levels of this compound rather than IS (10).

Yu et al. (5) provide evidence that IS itself is toxic by showing that it reduces proliferation and nitric oxide production, measured as the sum of nitrite and nitrate production over 2 days, in cultured human vascular endothelial cells. Other in vitro studies have shown that IS promotes leukocyte interactions, impairs wound repair, and induces oxidant stress in endothelial cells and has additional effects on cultured smooth muscle cells (4,11). These studies move us toward fulfillment of Bergstrom’s criteria that the putative toxic effects of retained solutes must be replicated by raising solute concentrations in normal people, experimental animals, or in vitro systems. An important consideration in evaluating these results is...
that protein binding reduces the free concentration of plasma IS to <10% of its total concentration. The IS concentrations proved effective in vitro are thus likely in many cases to have been higher than the free IS concentrations to which vascular cells are exposed in patients with CKD. Further studies of the administration of IS to intact animals may provide stronger evidence for the vascular toxicity of IS (12). These results also make us look forward to the ultimate test of larger clinical trials. Because they are made in an isolated compartment by microbes, the levels of colon-derived compounds such as IS may prove easier to manipulate than those of most retained solutes. Potential suppressive maneuvers include not only binders such as AST-120 but also nutritional and prebiotic treatments. If IS and/or other colon-derived solutes are indeed vascular toxins, then such treatments should provide a valuable addition to BP control in reducing the burden of vascular disease in CKD.

Disclosures
None.

References

Published online ahead of print. Publication date available at www.cjasn.org.