The Role of Bicarbonate in Cognition

Acidosis May Be Corrosive to the Brain

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Acidosis is a common complication of CKD, and it may play a pivotal role in many aspects of its associated high morbidity and mortality. Acidosis has been associated with multiple complications, including mortality (1), CKD progression (2), and functional limitations (3) in recent literature. Correction of acidosis through supplementation may slow the progression of CKD and improve nutritional status (4,5). Understanding the causes and consequences of acidosis is, therefore, important from pathophysiologic, prevention, and treatment perspectives.

Although we understand that acidosis has a potential link to bone and muscle health as well as the previously mentioned hard clinical outcomes, it is not known whether it is associated with other complications seen in patients with CKD that are not routinely measured in clinical practice. One complication that is both prevalent and more studied recently in CKD surrounds cognitive impairment. Studies have found an association between CKD and cognitive impairment that occurs early in CKD and is seen across multiple domains of cognition (6). These domains may include a global score, which links to cognitive impairment and dementia, or specific subdomains, including executive function, processing speed, orientation, attention, and language. Although studies have examined the role of CKD in cognitive function, very few studies have explored the role of acidosis in cognitive function. Animal studies suggest that acidosis may affect brain function first by upregulating the excitatory synaptic transmission on γ-aminobutyric acid–ergic neurons (7). This subsequently impairs sequential spikes at the neuron, leading to neuronal dysfunction (8). These mechanisms in animals have not been confirmed in humans, but there are potential links seen between acidosis and cognitive function. There is also a link between cognitive impairment and frailty in patients with kidney disease (9), a pattern that may represent shared factors affecting both cognitive and physical health, such as those occurring in acidosis.

In the manuscript published in this issue of the *Clinical Journal of the American Society of Nephrology*, Dobre *et al.* (10) explore the association between serum bicarbonate concentration and cognitive function using 2853 participants in the Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT-MIND) cohort. The Systolic Blood Pressure Intervention Trial (SPRINT) is a multicenter trial that evaluated target BP and its effect on cardiovascular events and mortality, and it enrolled patients with and without CKD. The SPRINT-MIND cohort is a subset of the SPRINT that was enriched with older participants who underwent extended cognitive battery testing. Although not a hard cardiovascular outcome, cognitive function may be affected in either a positive way (*i.e.*, reduction in vascular-type events) or a negative way (*i.e.*, side effect of aggressive therapy) by BP treatment. Measurement of cognitive function was, therefore, included for all SPRINT-MIND participants.

In this analysis of the SPRINT, Dobre *et al.* (10) evaluate the cross-sectional association of serum bicarbonate levels with cognitive function as measured by a battery of tests around global cognitive function, executive function, memory, attention/concentration, and language. They find that lower bicarbonate level is independently associated with lower performance on tests evaluating either global cognitive or executive function. They report that a 1-mEq/L lower serum bicarbonate level had similar associations as being approximately 4–5 months older. This association persisted after adjustment for several brain magnetic resonance imaging (MRI) findings that may correlate with cognitive function and after adjustment for eGFR and albuminuria, suggesting a distinct pathophysiologic process. In addition, sensitivity analyses looking at clinical subgroups revealed similar findings as did categorical cutoffs of serum bicarbonate level. These findings were not seen in other cognitive tests around memory, attention/concentration, or language.

This study has several key features. The standardization of cognitive ascertainment across participants is essential, because something as difficult to measure as cognitive function needs trained staff and a consistent protocol. A prospective study achieves this. Including MRI results in a subset of patients affords the investigators the opportunity to see if their findings are explained by other mechanisms by which cognitive function may be lower, such as white matter changes; the addition of MRI results is rarely seen in the literature, and they help to clarify the pathophysiologic pathway. A large multicenter study also allows the investigators to perform sensitivity and subgroup analyses. Most importantly, because cognitive

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impairment can present across any number of domains, including either globally or in specific domains, measurement of a large battery of tests is useful to see specific aspects that are affected. A systematic review found that both global cognitive function and language function were particularly impaired in CKD (6). However, this study by Dobre *et al.* (10) found that lower bicarbonate was associated with lower scores on both global and executive function tests, but there was no association seen with language domains or other domains. The exact domains potentially affected by the shared issues of CKD and acidosis are, therefore, still unknown.

If global cognitive impairment and executive function are the primary areas where acidosis leads to cognitive impairment, this is clinically important. Lower scores on tests evaluating global cognitive impairment may lead to clinically apparent cognitive impairment or even dementia; therefore, preventing this is an important clinical end point. Executive function is essential for higher-order organization and processing abilities, such as activities of daily living or even navigating the health care system, and therefore, understanding and preventing impairments in this domain are important for our patients. Because the SPRINT enrolled hypertensive adults, actions, such as understanding BP, its treatment, and its potential side effects, require some higher-order processing abilities.

Several items are still unknown after this study. Although cross-sectional relationships have the potential to reveal important correlations, we still do not know whether low bicarbonate causes cognitive impairment or whether they just share an underlying pathophysiology. A longitudinal study is needed to evaluate this and clarify the temporality of this association. We also do not know whether treatment of acidosis prevents or reverses cognitive impairment. In addition, the nature of any management strategy for acidosis also needs exploration; it may be through alkali supplementation or dietary changes focused on fruits and vegetables, because there are data to support either as a potential therapy (4,5). Is it important to reduce net endogenous acid production through focusing on fruits and vegetables? Or is the level of serum bicarbonate the important part? Dietary pattern is an area that the investigators could have included to strengthen their findings. In addition, it is not known whether a high bicarbonate level is associated with cognitive impairment in a J- or U-type relationship, similar to how high bicarbonate is associated with high mortality in humans (1) or impairment in neuronal function in animals models (8). The authors did not see such a relationship using categorical cutoffs or in their spline analyses, although this needs confirmation in future studies. Finally, the differences in cognitive function between those with low bicarbonate and those with high bicarbonate were small and potentially explained by residual or unmeasured confounding, suggesting that the 1-mEq/L lower level of bicarbonate was equivalent to being 4–5 months younger in cognitive health. Whether correction of bicarbonate level translates into meaningful clinical differences in cognitive function is unclear and would take a large trial to discover.

In summary, the study by Dobre *et al.* (10) adds another piece of evidence that acidosis is harmful. In addition to its previously studied associations with mortality, kidney disease progression, and other clinical outcomes, we can now add cognitive impairment to the areas that acidosis likely affects. Understanding, preventing, and treating acidosis in patients with and without CKD have the potential to improve both hard clinical end points and quality of life.

Disclosures

None.

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See related article, "Serum Bicarbonate Concentration and Cognitive Function in Hypertensive Adults," on pages 596–603.