

Conclusions

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Future of Hyponatremia Research

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Despite the many advances made in understanding the manifestations and consequences of hyponatremia, and the availability of effective pharmacologic therapies for the treatment of hyponatremia, it is obvious that we do not yet have a uniformly accepted consensus on how and when this disorder should be treated. To achieve this consensus, additional translational and clinical research will be necessary to establish the knowledge base upon which evidence-based recommendations can be made with confidence.

Basic/Translational Studies That Have High Priority

Mechanisms Responsible for Bone Loss with Chronic Hyponatremia

Published studies now provide compelling evidence that osteoclasts directly sense and respond to low $[Na^+]$. Likely, this serves to liberate stored sodium from bone, and thus represents an adaptation to mitigate the effects of sodium deficiency on brain, heart, testis, and likely other organs. The molecular mechanisms underlying this response represents an exciting target for future investigation, with the promise of uncovering a potential low $[Na^+]$ sensing receptor or sodium channel on the plasma membrane of osteoclasts, along with the associated downstream activated signaling pathways.

Mechanisms Responsible for Gait Instability and Falls with Chronic Hyponatremia

Studies in both humans and experimental animals have documented gait disturbances that are likely responsible for the increased rate of falls in hyponatremic patients, and more recent studies have found decreased nerve conduction velocity. Whether

these are manifestations of the decreased brain osmolyte levels, including important excitatory motor neurotransmitters such as glutamate, or other neurophysiological changes, remains to be ascertained. As well, whether the gait instability is completely reversible after correction of chronic hyponatremia, as suggested by short-term studies in humans and animals, remains to be determined.

Effects of Hyponatremia on Malignant Cells

It is becoming more and more evident that hyponatremia negatively affects the prognosis of cancer patients, both with and without metastatic disease. Although this association with worse outcomes has been documented in multiple clinical studies, the potential mechanisms through which this might occur are not understood. *In vitro* and *in vivo* studies on the effects of low sodium concentrations on malignant cell proliferation, invasiveness, and alterations of signaling pathways would be illuminating in order to better understand this strong association.

Effects of Chronic Hyponatremia on other Body Organs

Although significant progress has been made in understanding the effects of hyponatremia on the brain and bone, it is apparent that other organs are affected as well. Aged male hyponatremic rats have hypogonadism, as indicated by marked decrease of testicular weight and abnormal testicular histology, decreased body fat, skeletal muscle sarcopenia by densitometry, and cardiomyopathy, manifested as increased heart weight per body weight, histomorphometric evidence of reduced myocyte number, and marked perivascular and interstitial fibrosis. The functional consequences of these findings remain to be studied, as well as the intriguing hypothesis that hyponatremia may exacerbate multiple manifestations of senescence thereby speeding the aging process.

Clinical Research Studies That Have High Priority

Improvement of Symptomatic Hyponatremia

Although it is clear that correction of hyponatremia can improve many of the neurological symptoms associated with hyponatremia and is life-saving in cases with severe neurological symptomatology, assessment of symptomatic improvement of the more subtle neurocognitive symptoms associated with milder degrees of hyponatremia is challenging. This is further complicated by the fact that these symptoms often occur in older patients with varying degrees of baseline dementia and in patients with other comorbidities such as heart failure, cirrhosis, pulmonary disease, cancer, and psychiatric disease that can also cause neurocognitive impairments. Assessment of neurocognitive deficits and improvements with correction of hyponatremia is essential if we are to develop scientifically valid guidelines to identify which patients will benefit from active treatment of both acute and chronic hyponatremia.

Improvement of Clinical Outcomes

The strong independent association of hyponatremia with a variety of adverse clinical outcomes makes randomized controlled trials of the impact of more effective treatment of hyponatremia in hospitalized patients a high priority for the many diseases in which hyponatremia is known to be associated with adverse outcomes. Hyponatremia has a strong and independent association with a variety of serious adverse clinical outcomes, such as hospitalization rate and mortality. This makes randomized controlled trials of the impact of more effective treatment of chronic hyponatremia a high priority for the many diseases in which chronic hyponatremia is strongly associated with adverse outcomes.

Effectiveness and Safety of Different Treatments for Hyponatremia

The indications for the use of vasopressin receptor antagonists by regulatory agencies differ substantially worldwide, and various treatment guidelines published to date also differ substantially in regard to appropriate hyponatremia management, including recommendations of therapies with inadequate evidence databases. There are many reasons for this failure to achieve consensus, but primarily it is the lack of prospective controlled studies comparing different treatments in various groups of patients.

Prevention of Falls, Osteoporosis, and Fractures

The strong association of hyponatremia with increased fracture rates as independently documented in diverse geographic areas has established hyponatremia as a previously unrecognized risk factor for fractures. Although this association is clear and the mechanisms whereby hyponatremia could increase the risk of falls and fractures is becoming known, whether treatment of chronic hyponatremia with more effective therapies can improve bone health and reduce falls and fracture rates, particularly in older patients, remains to be studied prospectively.

Improvement of Quality of Life

It is clear that the potential benefits of treating hyponatremia cannot be assessed adequately simply by measures of improvements in mortality. It is equally important from a clinical perspective to assess quality of life measures, particularly in older patients who have the highest incidence of hyponatremia as well as the greatest burden of co-morbidities. Multiple studies have suggested improvement of a variety of patient-reported symptoms following improvements in the serum sodium concentration of hyponatremic patients, but larger studies using better defined instruments to evaluate the known symptoms associated with chronic hyponatremia would provide valuable input with regard to indications to treat relatively asymptomatic patients with chronic hyponatremia.

Reduction of Hospital Resource Utilization

Given the substantial economic burden associated with hyponatremia, whether more effective treatment of hyponatremia can reduce the increased costs that have been found to be associated with hyponatremia is a crucial question. This is particularly important for assessing the cost-benefit ratio of new therapies for hyponatremia, such as the vaptans, in view of their high costs.

Conclusions

Until the above questions can be answered via additional high quality translational and clinical research studies, physicians must recognize the primary role that clinical judgment must continue to play in making decisions about the management of hyponatremia in individual patients. Their recommendations should take into account appropriate appraisals of evidence by authoritative experts in the field, the decisions of regulatory agencies based on critical reviews of the efficacy and safety data for approved treatments for hyponatremia and, most importantly, the specialized needs of individual hyponatremic patients.

However, the future of hyponatremia research is bright. Scientific disciplines and funding agencies are beginning to appreciate the magnitude of the clinical and economic burden of hyponatremia, and are no longer relegating low sodium levels to the category of a “clinically insignificant” laboratory abnormality. Recognition that an absence of clinical symptoms does not mean that a metabolic disorder is not having significant adverse effects on body organs and functions, as has been long recognized for other metabolic disorders such as diabetes and hypertension, will inevitably lead to a re-assessment of appropriate treatment recommendations for chronic hyponatremia, even when mild and minimally symptomatic. There is every reason to believe that the steady increase in hyponatremia publications shown in Figure 1 (in the Introduction, pp 1–7) will continue into the foreseeable future, and with that will come a fuller and richer understanding of the many ways in which hyponatremia affects the human body, many of which we likely are not even aware of at the present time. The editors look forward eagerly to the next two decades of research and the knowledge that it will bring to scientists and clinicians everywhere.

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