REVIEW ARTICLE

Sodium and Growth in Preterm Infants: A Review

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Abstract

Aim: This article is intended to review the relationship between sodium homeostasis and growth, outline reasons why preterm infants may become sodium deficient, and share data from our group and others regarding the potential benefits of dietary sodium supplementation.

Background: Despite tremendous efforts over the past 20 years to optimize neonatal nutrition, postnatal growth failure in preterm infants remains a significant problem. Compelling associations have been identified between in-hospital growth failure and cardiometabolic and neurodevelopmental disorders, heightening the need to further identify the optimal nutritional needs of preterm infants.

Results: The impact of sodium deficiency may have on somatic growth is poorly studied and reported upon within the human literature. In contrast, animal studies dating back almost 100 years highlight the nutritional importance of dietary sodium. Sodium homeostasis during early postnatal life is understudied and underappreciated by neonatologists.

Conclusion: Insufficient sodium intake during early life is likely a critical yet underappreciated contributor to growth failure. Total body sodium depletion may be an important risk factor driving complications of premature birth.

Clinical significance: Increased awareness of sodium homeostasis in preterm infants may improve outcomes in this population. Sodium intake recommendations are provided based on the interpretation of currently available literature.

Keywords: Growth, Human, Postnatal, Premature, Preterm, Review, Sodium.

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Aim

From soon after admission to a neonatal intensive care unit until often near the time of hospital discharge, clinicians prescribe the amount of protein, lipid, carbohydrate, and fluid an infant receives. A primary focus of care is achieving optimal growth of patients, with the knowledge that postnatal growth failure is linked with increased risk of morbidity, including neurodevelopmental impairment.[1,2] Thus, extensive study has occurred regarding the optimal intake of various components of nutrition. One area of parenteral and enteral nutrition that has been overlooked is a mineral intake and in particular sodium intake. For almost 100 years, the importance of adequate dietary sodium intake to achieve maximal growth has been recognized.[3] Subsequent studies in animals and human infants have repeatedly demonstrated that inadequate sodium intake early in life impairs growth and may impact other physiological functions. The purpose of this review is to highlight the importance of sodium intake early in life, the gaps in our understanding of how to identify sodium deficiency, and our lack of recognition of what sodium requirements for preterm infants over the first few months of life.

Background

Why would a Preterm Infant become Sodium Depleted?

Newborn infants are in a precarious state of sodium balance. For term infants who receive strictly breastmilk for the first months of life, sodium intake is obviously limited to that within breastmilk. Beyond the first postpartum week following term delivery, the sodium content in breastmilk is typically no more than 10 mEq/L.[4] Assuming a daily intake of 150–175 mL/kg of milk, an infant would receive approximately 1.5–1.75 mEq/kg/per day of sodium. Since >98% of ingested sodium is likely absorbed and sweat production is minimal, sodium losses during infancy are primarily urinary. The mature kidney displays redundant sodium transport systems that allow for a high degree of renal tubular sodium reabsorption (thus a low fractional excretion of sodium and urinary sodium concentration). Assuming a urine production of 50 mL/kg/d (approximately 2 mL/kg/hour) and a urine sodium concentration of 10 mEq/L (a conservative value assuming a well-functioning kidney), urine sodium losses average 0.5 mEq/kg/d. Thus, the net sodium balance, assuming no stool or skin losses, would be 1–1.25 mEq/kg/d. If one further assumes that infant growth averages 25 g/d, with total body water at this stage of development is being approximately 70% of body weight, and with equal distribution of intracellular and extracellular compartments, an infant requires 1.225 mEq/d of sodium for growth. This calculation is as follows: (A) 25 g/d growth, of which 70% is water = 17.5 g (mL); (B) 50% of this water is (8.75 mL) extracellular; (C) Sodium concentration

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of extracellular water is 140 mEq/L; (D) 8.75 mL × 140 mEq/L = 1.225 mEq. Thus, any decrease in sodium intake or increase in sodium losses may put the infant at risk for sodium deficiency and suboptimal growth.

For the preterm infant, the mother's milk is insufficient to meet the sodium needs for growth. Milk samples obtained over the first month after birth from mothers delivering at approximately 28 weeks gestation contained approximately 30–35 mg/dL of sodium (1.3–1.52 mEq/dL).[5] Assuming an intake of 160 mL/kg/d, this would result in a sodium intake of only 2.08–2.42 mEq/kg/d. As will be discussed below, this sodium intake is insufficient due to the higher obligate urine sodium losses in preterm compared to term infants. Donor breastmilk, even with added commercial fortifiers is also insufficient to meet the sodium needs of the preterm infant. Perrin et al. measured the sodium content of 300 samples of donor human milk and estimated the sodium content resulting from fortification with 3 different human milk fortifiers and feeding volumes of 160 mL/kg/d.[6] They reported a sodium content of approximately 100 mg/L (range 40–570) (4.35 mEq/L, range 1.74–24.78 mEq/L in donor human milk samples. Depending on the type of fortifier used (Similac Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid, Abbott Laboratories), bovine-based fortifier to 24 kcal/ounce (Enfamil Liquid Human Milk Fortifier High Protein; Mead Johnson), and human-milk-based fortifier (Prolacta + 6; Prolacta Bioscience), the expected mean sodium intake from donor human milk was 1.6–3.4 mEq/kg/d.

We have recently argued that term babies are capable of protecting themselves from a sodium deficit in the first few months of life (in the absence of significant pathology) by utilizing stores of osmotically inactive sodium which develop in utero.[7] These stores result from sodium binding negatively charged glycosaminoglycans with skin and other tissues. Studies from rats demonstrate that such stores can be mobilized for growth early in life and during conditions of sodium depletion.[8] Using data from previously published literature, we estimated the term fetus may 'store" up to 80 mEq Na, the vast majority of these stores being accumulated during the last 10 weeks of gestation. The term newborn may then these stores as necessary to achieve optimal growth in the first few months after birth. The absence of these osmotically inactive sodium stores in the preterm infant may be one of the risk factors for the development of sodium deficiency, and thus postnatal growth failure in this vulnerable population.

In contrast to the mature kidney, kidneys from preterm infants have a limited capacity for sodium reabsorption due to the immaturity of renal tubular sodium transporters (recently reviewed by Gattineni and Baum).[9] In preterm infants, fractional excretion of sodium (FENa) and urine sodium excretion (UNaV) are inversely associated with gestational age at birth and postnatal age.[10,11] Longitudinal study of preterm infants reveals FENa exceeded 6% in infants <28 weeks of gestation on the day of life 3, decreasing to about 4% by the end of the first week of life and to 2% at a month of age.[12] We previously calculated expected urinary sodium losses in preterm infants across a range of gestational and postnatal ages.[13] Even at 6 weeks of postnatal age, infants 23–27 weeks gestational age are estimated to lose 5–5.5 mEq/kg of sodium per day, likely exceeding the sodium intake of many preterm infants at this postnatal age. Losses at earlier postnatal ages were greater. More recently, we confirmed these findings by longitudinal examination of sodium balance in infants 22–23 weeks of gestation from 2 to 10 weeks of postnatal age.[14] Urine sodium losses exceeded 6 mEq/kg/d until 31 weeks postconceptional age. These losses were not driven by high sodium intakes as sodium balance was not significantly positive until 33 weeks of post-conceptional age. Serum sodium values for the cohort remained in the normal range despite a negative sodium balance, while no significant relationship was identified between sodium intake and serum sodium values. This finding emphasizes that serum sodium values are more reflective of body water homeostasis rather than sodium balance and that serum sodium values cannot be the sole factor in determining the prescription of sodium to preterm infants.

Though not extensively studied, dysregulated hormonal responses appear to contribute to high renal sodium losses early in life. In term infants, cord blood aldosterone and renin levels are significantly greater than paired maternal levels, though urine sodium losses are high and there is an absence of correlation between urine aldosterone and urine potassium concentrations and urine Na^+/K^+ ratio.[15] Thus, despite strong activation of the renin-aldosterone system, partial aldosterone resistance appears to be present. In a separate study involving preterm infants and using urine aldosterone concentration and urinary Na^+/K^+ ratio as an index of renal aldosterone sensitivity, Martinerie et al. concluded preterm but not term infants display aldosterone sensitivity.[16]

However, because the activity of the renin-angiotensin-system may be impacted by numerous factors early in life, and urine aldosterone excretion may not truly reflect aldosterone secretion, the conclusions for this study have been refuted.[17] Atrial natriuretic peptide (ANP) may also play a role in sodium homeostasis early in life. In preterm infants with mean gestational ages of approximately 31 weeks, mean daily Na intakes of 1.4–1.8 mEq/kg/d from weeks 1–5 after birth resulted in sustained levels of plasma ANP whereas infants receiving sodium intakes of 4.6 +/-1.0 mEq/kg/d demonstrated a steady decrease in ANP levels.[18] However, Shaffer et al. found no correlation between plasma ANP concentrations and sodium excretion or fractional sodium excretion.[19] Other investigators have demonstrated that ANP levels are elevated during postnatal adaptation, are greater in preterm than term infants, and may be impacted by respiratory status.[19–21] Thus, whether ANP significantly affects renal function during the postnatal period remains unclear.

What Are the Potential Mechanisms by Which Sodium Depletion Results in Growth Failure?

Studies in young animals have been revealed an understanding the need for sufficient sodium intakes early in life. In young growing rats, sodium-deficient diets impair weight and length gain, impair bone growth, diminish nitrogen retention, and decrease muscle protein synthesis.[22,23] Sodium supplementation to sodium-depleted animals restore normal rates of weight and length gain and protein synthesis. Fine et al. placed weanling rats on diets with sodium intakes ranging from 30 to 900 μeq/day for 5 weeks.[24] Doses less than 300 μeq/day were associated with decreased weight gain, nitrogen accretion, and fat-free dry weight. Doses greater than 300 μeq/day were not associated with further weight gain. Importantly, total body water, as a percent of body weight, and serum sodium values were similar across groups at the end of the 5-week study, despite 30-fold differences in sodium intake. These findings suggest chronic differences in sodium intake do not impact total body water (i.e., water retention) and that serum sodium values may be normal even in the face of significant total body sodium depletion. Sodium-deficient animals ingested a greater amount of food per gram weight gain than animals on higher sodium diets, consistent

with alterations in energy efficiency (weight gain (grams)/energy absorbed.

The mechanisms by which sodium depletion may impair somatic growth remain to be fully elucidated. Haycock suggested that depletion of extracellular sodium decreases Na^+/H^+ antiporter activity, thus altering intracellular pH and the cell's ability to respond bind and respond to various growth factors.[25] Indeed, alkalinization of the cytoplasm by stimulation of the antiporter by mitogens appears necessary for cell proliferation.[26] Work from our own laboratory using a mouse model of early life sodium depletion similarly found impaired somatic growth when sodium intake was less than a critical value but not enhanced by excess dietary sodium.[27] Additionally, sodium depletion impaired energy efficiency (efficiency in which an animal uses absorbed energy for growth) but not digestive efficiency (efficiency of absorbing ingested energy) or caloric intake, suggesting energy expenditure is increased in association with sodium depletion. Preliminary findings from our laboratory using indirect calorimetry support the idea that total aerobic energy expenditure is increased in mice fed a low-sodium diet even after correction for body composition.[28] These findings provide strong evidence that early-life sodium supply impacts energy homeostasis and growth kinetics and prompts an increased focus on identifying optimal sodium supplementation for prematurely born and low-birthweight infants.

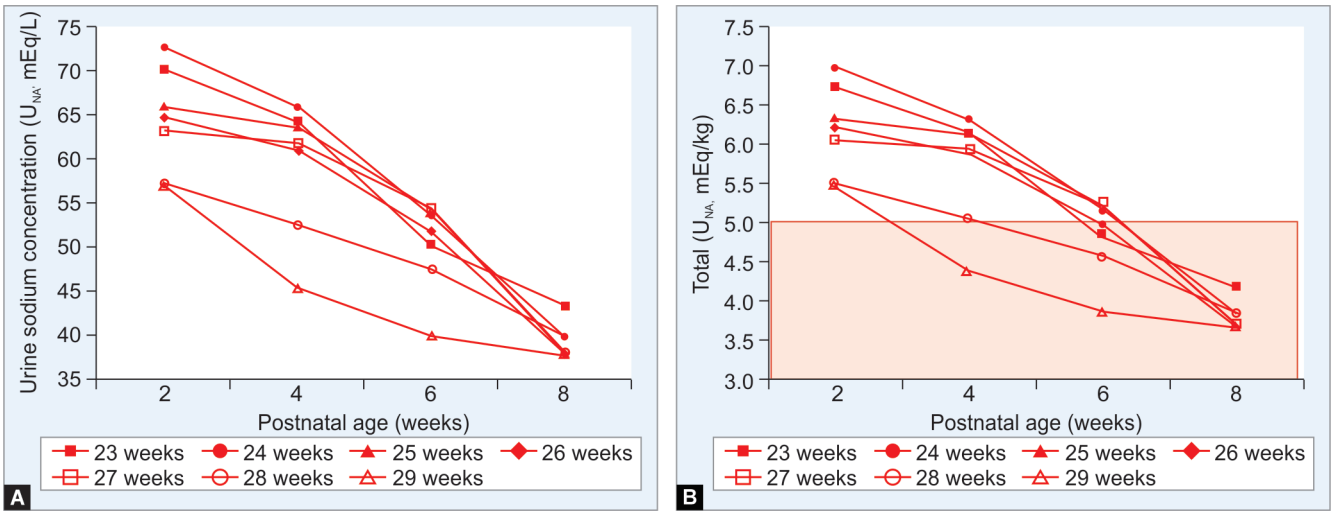
Does Sodium Supplementation Result in Improved Postnatal Growth in Preterm Infants?

Studies in preterm infants, though limited, support a beneficial effect of sodium supplementation above that is typically provided in the diet to optimize postnatal growth. Vanpée et al. randomized infants 29–34 weeks gestation to oral NaCl supplementation of 4 mEq/kg/d from 4 to 14 days of age or routine nutritional care, including enteral feedings and parenteral nutrition (n = 10 per group).[29] Average daily sodium intake over this period was 5.0 =/–0.9 mEq/kg/d in the supplemented group and 1.7 +/– 0.6 mEq/kg/d in control group. At two weeks of age, supplemented infants weighed more than birthweight (+5.8 +/–7.2%), whereas control infants had not regained birthweight (–1.6 +/– 4.6%). Fluid intake and urine output were similar between the control and supplemented infants, suggesting that weight gain was not a result of water retention. Al-Dahhan et al. similarly supplemented 22 infants born at 27–34 weeks gestation to a total daily sodium intake of 4–5 mEq/kg/d on postnatal days 5–11.[30] Compared to the control group (n = 24) with sodium intakes of slightly less than 2 mEq/kg/d during this period, the supplemented group showed increased weight gain. After 2 weeks of age, the supplemented group had a slight but significantly increased average daily sodium intake of approximately 0.8 mEq/kg /d compared to the control group, while continuing to display increased rates of weight gain. In a more recent study, Isemann et al. randomized infants <32 weeks gestation to receive 4 mEq/kg/d of Na, or placebo, from days of life 7–35, resulting in an average daily Na intake of 6.3 mEq/kg in the supplemented group and 2.9 mEq/kg in the placebo group.[31] Fifty-three infants were enrolled at an average gestational age of 28.5 weeks. NaCl was administered enterally (four times daily) if feedings equaled or exceeded 100 mL/kg/d. Unfortunately, only 29 infants completed the study related to death, transfer, and hospital discharge, approximately half <28 weeks of gestation. At 6 weeks of postnatal age, 79% of supplemented infants maintained their birthweight percentile (i.e., did not demonstrate postnatal growth failure) compared with only 13% in the placebo group. The difference in weight gain was particularly accentuated in the subgroup of infants born at <28 week's gestational age. Caloric intake was similar between groups, while sodium daily sodium intake for the 4-week intervention period averaged 6.3 ± 0.4 vs 2.9 ± 1.0 mEq/kg/d in the supplemented vs control infants, respectively. Collectively, these studies suggest that in the absence of sodium supplementation, human milk and currently available formulas fail to provide the nutritional sodium requirements to achieve optimal growth in preterm infants.

Table 1: Recommended sodium intake (mEq/kg/day) according to gestational and postnatal ages

	Postnatal age, days				
Gestational age, weeks	*1–2*	*7*	*14*	*28*	*56*
22–25	0–2	6–9	6–9	5–8	4–6
26–28	0–2	5–8	5–8	4–7	3–5
29–31	0–2	4–7	4–7	3–6	3–5
32–36	0–2	3–5	3–5	3–4	2–4

We previously described our approach to identify preterm infants at risk for sodium depletion and provide sodium supplementation based on urine sodium concentrations.[13] In sodium deficit states, urine sodium excretion falls too low levels, as renal tubular sodium transporters are activated to the extent possible by neurohumoral and tubuloglomerular mechanisms. Recognizing that there is no consensus regarding the interpretation of urine sodium concentration values, studies in populations of infants with ileostomies and cystic fibrosis demonstrated that sodium supplementation to maintain urine sodium concentrations above certain cut-off values, consistent with a sodium-replete state, is associated with improved weight gain. Using conservative estimates of expected urine sodium concentrations in preterm infants and attempting to account for the immaturity of renal sodium reabsorption mechanisms, we developed an algorithm which to drive sodium supplementation in preterm infants 25–29 weeks gestation (Table 1). Urine sodium concentrations were measured every 2 weeks, beginning at 2 weeks of age, (Fig. 1) and provided sodium supplementation based upon the algorithm until 8 weeks of postnatal age. We then compared the growth of the first 40 infants cared for by this protocol to a recent historical cohort. Sodium intake was on average 1.5–2.0 mEq/kg/d greater in the contemporary cohort (algorithm group) compared to the historical cohort, with 75% of the infants receiving supplementation based upon a low urine sodium concentration. Despite similar caloric, protein, lipid, and fluid intakes between cohorts, infants cared for using the algorithm demonstrated significantly improved growth between 2 and 8 weeks of postnatal age. We are now undertaking a randomized trial using the algorithm to determine its utility and validity in the care of preterm infants (ClinicalTrials.gov NCT03889197). While spot urine sodium concentrations cannot and should not replace more prolonged sampling of urine to measure urine sodium losses, they may be of particular use in infants who are failing to achieve growth goals despite the provision of adequate calories and protein. Additionally, the concomitant administration of drugs that promote natriuresis, such as diuretics, confounds the interpretation of urine sodium values.



Figs 1A and B:. Estimates of urine sodium (Na) concentration and daily urine sodium losses in sodium replete preterm infants based upon literature. Please note that the American Academy of Pediatrics currently recommends sodium intake of 3–5 mmol/kg/d for preterm infants during stable growth phase

Source: Adapted from Segar DE et al. Am J Perinat 2018

The importance of sodium homeostasis in optimizing additional outcomes of preterm infants has been highlighted by other investigators. Both hyper- and hyponatremia in the first week of postnatal life have been associated with increased mortality, risk of intraventricular hemorrhage, and neurodevelopmental impairment,[32–35] Interestingly, children born prematurely and supplemented to sodium intakes of 4–5 mEq/kg/d for days 4–14 of postnatal life had significantly improved neurodevelopmental performance (motor function, performance IQ, the general memory index) at 10–13 years of age compared to infants receiving 1–1.5 mEq/kg/d.[36] Whether the potential effects of sodium on neurocognitive development and brain growth are separate from those on somatic growth is not known. In a mouse model of sodium depletion, we identified that male mice exhibited early-life dietary sodium-dependent improvement in spatial learning and memory, though somatic growth was not different between the two sodium intakes (0.15 vs 0.30% sodium diet).[27] Large studies, we detail sodium intakes and balance, will be needed to address this issue. Late-onset hyponatremia (beyond 14 days of age), which may result from fluid overload or, more likely at this age from total body sodium depletion, has been associated with increased risk of hearing loss, bronchopulmonary dysplasia, and neuromotor and neurocognitive impairment.[37,38]

An area requiring further research is the potential role sodium homeostasis may play in immune function and the risk of infection in preterm infants. In the previously discussed study by Isemann et al., infants randomized to receive the sodium supplementation had significantly lower rates of necrotizing enterocolitis and late-onset sepsis.[31] Over the past decade, there has been emerging evidence regarding total body sodium concentration, including tissue sodium stores, on innate and adaptive immune responses.[39–41] While the majority of work has focused on the effect of high salt intake, Evans et al. identified that adult patients with salt-losing tubulopathies display impaired interleukin-17 responses which link T cell activation to neutrophil mobilization and activation.[42]

Also unknown is the impact of concurrent morbidities, such as bronchopulmonary dysplasia, on kidney function, kidney sodium handling, and ultimately sodium homeostasis. In addition to the state of systemic inflammation, many of the therapeutics used to treat these infants, including diuretics and corticosteroids may impact renal handling of sodium and negatively impact sodium homeostasis and growth. Along these lines, Tan et al. recently reported in infants <28 weeks gestation administration of hydrochlorothiazide and spironolactone for evolving or established bronchopulmonary dysplasia was associated with significant slowing of weight gain.[43]

Conclusion and Clinical Significance

As highlighted in the above text, there is a general lack of understanding of the sodium requirements of the preterm infant. Renal sodium handling in the newborn is inherently related to the stage of kidney development and as such the sodium needs differ based on gestational and postnatal age, as well as confounding medical and surgical conditions. Additionally, the requirements for optimal growth may differ from the requirements to achieve neurodevelopmental outcomes. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee of Nutrition recently published new recommendations for enteral nutrient intake in preterm infants, including for sodium.[44] Recognizing the high urine sodium losses that may be present in preterm infants, the Committee now states: "A Na intake of 3–8 mmoL/kg/d is recommended. The upper range of Na intake is slightly higher than in previous recommendations and should be considered in infants receiving high energy and protein intakes or with important sodium loss." These recommendations differ from those of the American Academy of Pediatrics (3–5 mEq/kg/d) which have remained similar for almost 40 years and fail reflect to needs of the extremely preterm infants.[45] We provide recommendations on the range of sodium intakes we believe, based upon currently available data, that meet the sodium requirements of most preterm infants needed to avoid growth failure associated with sodium deficiency. These recommendations are similar to the recommendations of others who have reviewed this topic.[46] We are optimistic that current and future studies will yield a better understanding of the sodium requirements necessary to achieve the full growth potential of preterm infants and develop approaches

to identify infants with sodium deficits who would benefit from additional sodium supplementation.

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