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Abstract
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Keywords
hyponatremia, osteopenia, endurance athlete

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Bone: An Acute Buffer of Plasma Sodium During Exhaustive Exercise?

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Abstract

Both hyponatremia and osteopenia separately have been well documented in endurance athletes. Although bone has been shown to act as a "sodium reservoir" to buffer severe plasma sodium derangements in animals, recent data have suggested a similar function in humans. We aimed to explore if acute changes in bone mineral content were associated with changes in plasma sodium concentration in runners participating in a 161 km mountain footrace. Eighteen runners were recruited. Runners were tested immediately pre- and post-race for the following main outcome measures: bone mineral content (BMC) and density (BMD) via dual-energy X-ray absorptiometry (DEXA); plasma sodium concentration ($[Na^+]_p$), plasma arginine vasopressin ($[AVP]_p$), serum aldosterone concentration ($[aldosterone]_s$), and total sodium intake. Six subjects finished the race in a mean time of 27.0±2.3 h. All subjects started and finished the race with $[Na^+]_p$ within the normal range (137.7±2.3 and 136.7±1.6 mEq/l, pre- and post-race, respectively). Positive correlations were noted between change (Δ; post-race minus pre-race) in total BMC (grams) and $[Na^+]_p$ (mEq/l) ($r=0.99$; $p<0.0001$), and between total sodium intake (mEq/kg) and %Δ lumbar spine BMD ($r=0.94$; $p<0.001$). Change in $[aldosterone]_s$ was positively correlated with: rate of total sodium intake ($r=0.84$; $p<0.05$); Δ total BMC ($r=0.82$; $p<0.05$); and Δ $[Na^+]_p$ ($r=0.88$; $p<0.05$). No significant pre- to post-race mean differences were noted in BMC or BMD. Robust associations between Δ BMC and Δ $[Na^+]_p$ suggest that sodium status and bone density may be inter-related during endurance exercise and should be considered in future investigations of athletic osteopenia.

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Introduction

In 1996, it was reported that 4 cyclists competing in the Tour de France lost an average of 25% of spinal bone mass over the 3-week event [1]. Subsequent cross-sectional studies demonstrated that competitive road cyclists had significantly lower spine bone mineral density (BMD) compared with recreationally active controls, with 25% of cyclists having lumbar t-scores in the osteopenic and 9% in the osteoporotic range [2]. Prospective studies of cyclists further demonstrated significant decreases in BMD in the hip region (nonsignificantly in the lumbar spine; $p=0.07$) over a 9 month competitive season with nonsignificant trends for BMD recovery noted in the ensuing 3-months off-season [3]. Larger cross-sectional studies performed on distance runners found similar trends in both males and females, with weekly running distance negatively correlated with lumbar spine bone mineral content (BMC) [4] and BMD [5]. In particular, lumbar spine BMC in elite male runners (>100 km/week) was 19% lower, with a 20–30% increase in bone turnover markers such as urinary pyridinoline, urine deoxypyridinoline, and serum alkaline phosphatase, when compared with age-matched nonrunning controls [4]. A single bout of running has also been documented to inhibit markers of bone formation such as PICP (carboxyterminal-propeptide of type 1 procollagen) and osteocalcin and to stimulate markers of bone resorption such as ICTP (carboxyterminal cross-linked telopeptide of type 1 collagen) and CTX (cross-linked-C-telopeptide of type 1 collagen) after 15 km [6], 28 km [6], and 246 km [7] races.

Hyponatremia, defined as a plasma sodium concentration ($[Na^+]_p$)<135 mEq/l, has recently been associated with the development of osteoporosis in humans, with substantial reductions in bone mass (30%) observed in rats with sustained hyponatremia over a period of 3 months [8]. Oxi-

dative stress associated with chronic hyponatremia appeared to be the primary mediator of the osteoclastogenesis that was seen in these animals [9], with significant decreases in lumbar spine (L1–L4) BMD seen in just 14 days [10]. In more acute settings, it has been hypothesized that osmotic inactivation of circulating sodium or the failure to mobilize osmotically inactive sodium from internal skin and/or bone stores may play a pathogenic role in the development of exercise-associated hyponatremia (EAH) in athletes participating in endurance races [11]. Thus, the purpose of this investigation was to evaluate if acute changes in bone mineral density could be detected by dual-energy X-ray absorptiometry within the context of fluid and sodium homeostasis in a cohort of runners participating in a long duration race.

Materials and Methods

Institutional Review Board approval was granted for this study and research was performed on human subjects according to the Declaration of Helsinki ethical principles for medical research. Eighteen runners participating in the 100 mile (161 km) Western States Endurance Run (WSER) were recruited and signed written informed consent. All pre-race measurements were obtained 1–2 days prior to race start. All post-race measures were performed at the finish line, within 2 h of race finish.

Bone mineral density (BMD) and content (BMC) were obtained using a dual-energy X-ray absorptiometry (DEXA) scan (Hologic Discovery A bone densitometer, Waltham, MA, USA). All scans were performed by a single technician following a standardized protocol procedure (www.tufts.edu/med/nutrition-infection/tnc-cdaar/protocols/DEXA2.doc). All subjects were positioned supine on a flat table within an air conditioned mobile DEXA van for 5 min before each scan was performed. The %CV was obtained on a single subject repositioned and measured 3 times at race start as well as 3 times at race finish (**Table 1**).

Pre- and post-race blood (10 mL) was obtained from an antecubital vein and analyzed for plasma concentrations of sodium ($[Na^+]_p$) and calcium ($[Ca^{++}]_p$) using a portable analyzer (I-Stat, Abbott, Princeton, NJ, USA). The remaining venous blood was then centrifuged at 3000 rpm within 10 min of collection, separated and then stored at −80 °C until analysis of plasma arginine vasopressin ($[AVP]_p$) [12], and serum aldosterone ($[aldosterone]_s$) analyses (enzyme immunoassay, ALPCO Diagnostics, Salem, NH, USA) could be performed.

Sodium intake during the race was obtained using methodology described previously [13] and assessed using Nutritionist Pro software (Axxya Systems, Stafford, TX, USA).

All data are presented as means ± SD. Analyses included paired *t*-tests and regression analyses. Statistical significance was set at $p < 0.05$.

Results

Only 6 of 18 subjects were able to complete the race with a mean finish time of 27.0 ± 2.3 h. The mean age of the finishers was 47.2 ± 4.7 years, with a pre-race weight of 67.4 ± 15.5 kg. The average total fluid intake during the race was 19.6 ± 6.7 l (742 ± 28 ml per hour) while the average total sodium intake was estimated at 780 ± 439 mEq (11.8 ± 6.7 mEq/kg).

There were no significant differences (pre- to post-race, respectively) in $[Na^+]_p$ (138.7 ± 2.3 to 136.7 ± 1.6 mEq/l) or $[Ca^{++}]_p$ (1.2 ± 0.2 to 1.1 ± 0.1 mEq/l) concentrations but significant increases were seen in $[AVP]_p$ (0.7 ± 0.4 to 2.7 ± 1.9 pg/ml; $p < 0.05$) and $[aldosterone]_s$ (141.4 ± 38.5 to 313.6 ± 110.7 pg/ml; $p < 0.05$).

No statistically significant pre- to post-race changes in BMD or BMC (**Table 1**) were noted. However, robust statistically sig-

Table 1 Bone mineral contents (BMCs) of different body regions measured in 6 race finishers at baseline (pre-race) and following the race as measured as an absolute change.

Region	Pre-Race BMC Mean ± SD (g) (*min–max*)	Absolute Δ BMC Mean ± SD (g) (*min–max*)	%Δ BMC Mean ± SD (%) (*min–max*)	CV (%)
Total body	2557.6 ± 617.6 (*1823.0–3340.9*)	−8.2 ± 56.4 (*−103.6–51.1*)	0.0 ± 0.0 (*−0.3–0.02*)	0.39
Head	521.1 ± 82.7 (*428.1–652.4*)	−18.0 ± 17.5 (*−42.5* to *−2.1*)	−3.6 ± 3.4 (*−8.5* to *−0.5*)	1.4
Thoracic spine	94.2 ± 25.5 (*65.9–138.9*)	4.2 ± 12.5 (*−9.9–22.5*)	4.6 ± 11.3 (*−8.9–19.0*)	2.1
Lumbar spine	62.8 ± 11.2 (*47.6–78.2*)	0.8 ± 3.5 (*−4.5–5.5*)	1.5 ± ± 6.0 (*−6.6–10.3*)	6.3
Pelvis	318.7 ± 84.0 (*228.1–437.3*)	3.0 ± 7.9 (*−1.7–19.0*)	1.2 ± 3.2 (*−0.7–7.7*)	1.0
Right arm	199.5 ± 65.1 (*116.7–260.1*)	−6.8 ± 6.3 (*−15.7* to *−0.7*)	−3.8 ± 3.2 (*−7.7* to *−0.3*)	2.3
Left arm	184.5 ± 57.6 (*109.2–243.3*)	1.1 ± 5.4 (*−3.9–10.2*)	0.4 ± 2.3 (*−1.9–4.0*)	1.5
Right rib	85.6 ± 23.0 (*60.9–124.5*)	10.3 ± 9.1 (*0.1–19.4*)	9.9 ± 8.7 (*0.1–19.7*)	1.2
Left rib	85.7 ± 25.5 (*57.7–132.0*)	4.3 ± 7.4 (*−7.7–12.1*)	5.1 ± 6.9 (*−6.2–12.5*)	1.4
Right leg	507.1 ± 138.8 (*328.8–679.3*)	−3.5 ± 20.2 (*−9.9–22.5*)	4.6 ± 11.3 (*−8.9–19.0*)	1.7
Left leg	498.4 ± 132.2 (*322.9–642.0*)	−3.5 ± 17.4 (*−18.3–26.7*)	−1.0 ± 3.5 (*−4.4–4.7*)	0.6

Δ: Post-race minus pre-race and percent change (%Δ) from baseline (post-race minus pre-race/pre-race). The coefficient of variation (%CV) was obtained using a single control subject that was repositioned and measured on the same DEXA machine 6 different times (3 pre- and 3 post-race measurements)

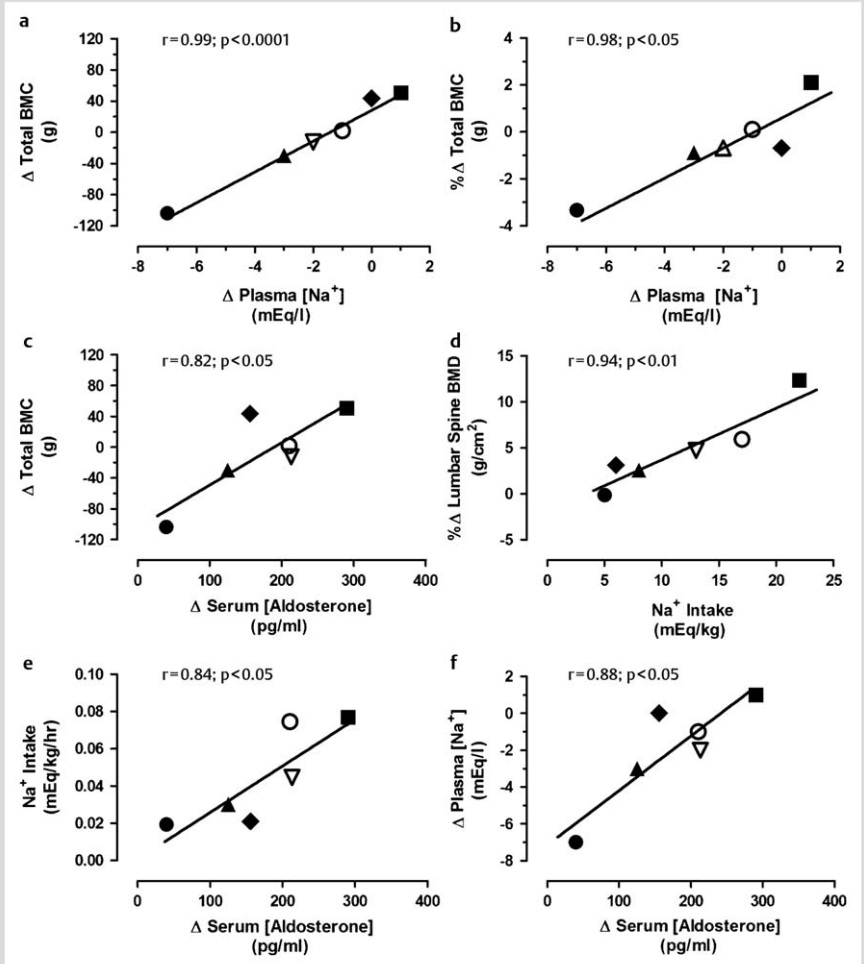

Fig. 1 Significant positive correlations (n = 6; open symbols represent female and closed symbols represent male subjects) for **a** the absolute change (Δ; post-race minus pre-race) in total bone mineral content (BMC) vs. the change in plasma sodium concentration ($[Na^+]_p$); **b** the relative (percent) change (%Δ; post-race minus pre-race/pre-race) in total bone mineral content (BMC) vs. the change in plasma sodium concentration ($[Na^+]_p$); **c** the absolute change in total mineral bone content (BMC) vs. the change in serum aldosterone concentration; **d** the percent change in lumbar spine bone mineral density (BMD) vs. total sodium (Na^+) intake during the race; **e** the rate of sodium (Na^+) intake during the race vs. the change in serum aldosterone concentration; **f** the change in plasma sodium concentration ($[Na^+]$) vs. the change in serum aldosterone concentration.

nificant correlations were noted between absolute and percent changes in BMC and BMD, total sodium intake and aldosterone (**Fig. 1a–f**). There was a statistically significant positive correlation between post-race [AVP] and post-race $[aldosterone]_s$ ($r = 0.90$; $p < 0.05$). Post-race $[Na^+]_p$ was positively correlated with total sodium intake when measured as a rate (mEq/h) of intake ($r = 0.84$; $p < 0.05$). Post-race $[Ca^{++}]_p$ was negatively correlated with both post-race $[Na^+]_p$ ($r = -0.95$; $p < 0.01$) and rate of sodium intake (mEq/h) ($r = -0.83$; $p < 0.05$). No significant relationships were noted between post-race $[Ca^{++}]_p$ or change in $[Ca^{++}]_p$ with the change in total BMC, BMD, lumbar spine, $[AVP]_p$ or $[aldosterone]_s$.

Discussion

The highly significant correlations between pre- to post-race changes in total and regional bone mineral content and density with key markers of water and sodium balance were unexpected given our low subject completion rate and negligible pre- to post-race changes documented in BMC (**Table 1**). In this cohort of 6 ultra endurance athletes, the pre- to post-race change in plasma sodium concentration appeared to explain 98% of the variance seen in the absolute change in total BMC (**Fig. 1a**) and 96% of the variance when expressed as a percent change (**Fig. 1b**). These findings would support the possibility that the skeleton acts as a dynamic buffer in response to acute changes in plasma sodium concentration, perhaps due to a mobilization of sodium from an osmotically inactive crystallized form into an osmotically active form to buffer declining extracellular $[Na^+]_p$ [14]. Conversely, bone mineral density increased in linear proportion to $[Na^+]_p$, suggesting that sodium ions may have mobilized into bone to accommodate rising extracellular $[Na^+]_p$ due to a surplus sodium intake (**Fig. 1a, b, d**). The plausibility of a true physiologic relationship between $[Na^+]_p$ and bone sodium stores is strengthened by regional data, with total sodium intake (mEq/kg) positively associated with changes in lumbar spine BMD, explaining 88% of the variance (**Fig. 1d**). Because the lumbar vertebrae are largely composed of metabolically active trabecular bone, bone density changes in this particular region would be the most reactive [8,15]. Over time, we speculate that a decrease in bone sodium stores (cumulative sweat sodium losses) may potentially manifest as decreased lumbar spine bone mineral density as a transient homeostatic response to protect $[Na^+]_p$ levels during chronic training and competition [1–5]. However, we are mindful that the sodium intake of most people living on a Western diet is high, so additional mechanisms are likely.

In further support of the mobilization of bone sodium stores in the broader context of sodium homeostasis, $[aldosterone]_s$, the body's main sodium-retaining hormone, was positively associated with $[Na^+]_p$ (**Fig. 1f**), rate of sodium intake (**Fig. 1e**) and $[AVP]_p$ ($r = 0.90$; $p < 0.05$). These key hormonal interrelationships highlight the preservation of fluid homeostasis by classic endocrine mediators of water (AVP) and sodium (aldosterone) balance during heightened physical stress. The change in $[aldosterone]_s$ was also positively associated with the change in

total BMC (**Fig. 1c**), which suggests that this sodium-retaining hormone may have a role in sodium mobilization in bone, as previously documented in the skin of rats (as another sodium reservoir) placed on high or low salt diets [16].

Data in support of bone as a potential reservoir for ~40% of total exchangeable body sodium stores have been known since 1954 [17]. The acute (2–4 h) and chronic (5 days) effects of marked derangements in $[Na^+]_p$ (severe hypernatremia and hyponatremia) on bone sodium content has been previously documented in animals [14,18]. Recent studies, however, indicated that the minimum time it would take for osteoclasts to become activated and demineralization to occur in response to low serum sodium (hyponatremia) would be 2 weeks [8,10]. Concomitantly, 1–4 weeks appeared necessary to detect a decreased skin charge density signifying mobilization of inactive sodium ions from glycosaminoglycans in rats in response to a low sodium diet [16]. Thus, these studies collectively suggest that the mobilization of sodium stores to augment blood sodium concentrations would require a minimum of 2 weeks before a significant physiological response could be detected. The present findings, however, support the possibility for accelerated changes in bone mineral content during daily or extreme physical activity in response to alterations in fluid and sodium homeostasis.

Finally, although it has been previously hypothesized that bone may serve as a buffer for changes in $[Na^+]_p$ [11], whether or not such changes could be detected by a DEXA scan, within a normal range of dynamically shifting blood sodium concentrations, over a short period of time (~30 h) did not appear plausible until now. These data thereby expose the possibility that DEXA scans may be useful tools in assessing acute changes in bone density, in relationship with other fluctuating homeostatic variables. The robust associations (**Fig. 1a–d**) underlying the unimpressive mean pre- to post-race changes in BMC (**Table 1**) highlights the need to reconsider not only the usefulness of the DEXA under acute conditions, but how we interpret DEXA results in the context of bone as a dynamic warehouse of shifting mineral stores under specialized conditions of stress. Therefore, it is evident by these data that in a period as short as 27 h, it is neither likely nor possible that major changes in BMC/BMD will be seen. However, this should not preclude the potential importance of smaller metabolically active changes occurring during shorter periods of time.

The major limitations of this study include the small sample size and relevance to normal human activity. The (unexpected) 66% attrition rate in our original sample cohort, however, demonstrates the extreme nature of this event while highlighting the exceptional physical and mental stamina of this small cohort of finishers. Despite the variability associated with the small sample size and measurement techniques, these data produced strong correlations in support of heightened sodium regulation during exhaustive exercise. These correlations also support previous observations suggesting that the composition of bone sodium is not fixed but rather reflective of a state of chemical equilibrium within the body [17].

In conclusion, these data suggest an alternative possible explanation for the dramatic and unexplained changes in lumbar spine density documented in competitive endurance athletes. Although the number of subjects was small, these data provide a provocative launching pad for future investigation of: 1) bone as an acute buffer of plasma sodium concentration during exhaustive endurance exercise and 2) DEXA scans as a useful tool to assess relationships – rather than absolute changes – between metabolic variables after shorter periods of significant physical stress. These data may also have important implications in trauma and disease.

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Conflict of Interest

The authors declare that they have no conflicts of interest in the authorship or publication of this contribution.

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