



Sarcopenia as a potential cause of chronic hyponatremia in the elderly

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ABSTRACT

Hyponatremia is the most frequent electrolyte disorder found in clinical practice, particularly in hospitalized elderly patients, where it is associated with fractures, falls, hospital readmission, prolonged hospital stay and increased mortality. Pathophysiologically, hyponatremia can be induced by the reduction in sodium or potassium body content, and/or the increase in water body content. Sarcopenia is an ageing-associated progressive and generalized loss of musculoskeletal mass and strength which leads to low physical performance, particularly in the frail elderly. Since muscle mass is the main potassium body store, this condition usually represents a reduced body potassium content.

In the present article it is hypothesized that sarcopenia, as a cause of low potassium body content, could induce or co-induce hyponatremia, particularly in elderly individuals suffering from frailty phenotype.

Introduction

Hyponatremia (serum sodium < 135 mmol/L) is the most frequent electrolyte disorder found in clinical practice, particularly in hospitalized elderly patients [1–3]. This electrolyte imbalance is associated with fractures, falls, hospital readmission, prolonged hospital stays and increased mortality (> 50%) compared with normonatremic admitted patients [3–9]. Most probably hyponatremia is both a marker of the severity of the underlying condition as well as a direct contributor to its prognosis. In a retrospective study performed on hospitalized patients, hyponatremia was found in 14.5% and its severity was independently associated with age and higher comorbidity, documented especially in frail patients and those suffering from heart disease, cancer or submitted to orthopedic procedures [10].

Regarding ageing-associated disorders, it is sarcopenia which has an estimated prevalence of 5–13% in people from 60 to 70 years of age, and of 11–50% in those over 80 years of age [11,12]. Even though hyponatremia has been described as a cause of sarcopenia, as far as we know there is no previous report in literature proposing sarcopenia as a hyponatremia inducing condition.

In the present article, we present the hypothesis that sarcopenia could induce or co-induce hyponatremia, particularly in frail elderly people.

Regarding hyponatremia pathophysiology, it is known that a significant salt and water depletion may generate real hypovolemia, and if this depletion involves a loss of salt and water in excess of salt, it can induce hyponatremia. Besides, salt and water retention in excess of water can induce hyponatremia (with or without edema), which may

present with hypervolemia (eg: severe renal failure, etc.) or effective hypovolemia (cardiac failure, etc.) depending on its etiologic mechanism [13–17].

Additionally, another factor which can modify the sodium/water ratio of the body is the body potassium content since its intracellular depletion induces hyponatremia by at least two main mechanisms:

- sodium shift to the intracellular compartment
- inappropriate anti-diuretic hormone release

Hyponatremia secondary to low potassium body content can be documented in severe malnourished patients [18]

Edelman equation, as well as its variant of Boling equation, summarized all these concepts in the following equation that describes the variables that determine natremia [14]: **Edelman equation** Natremia = 1.1 (total body sodium + total body potassium / total body water - 25.6 **Boling Equation** Natremia = 0.487 (total body sodium + total body potassium / total body water + 71.54. However, it is also known that not all body sodium and body potassium are osmotically active, since a portion of sodium is bound in bone and skin tissues and is therefore rendered osmotically inactive. Additionally, a portion of cellular potassium is reduced in its mobility and in its osmotic activity due to its association with anionic groups as is the case of carboxyl groups on proteins or to phosphate groups in creatine phosphate, proteins, ATP, and nucleic acids. Thus, since osmotically inactive sodium and potassium do not contribute to the distribution of water between the plasma and non plasma compartments, osmotically inactive sodium and potassium cannot contribute to natremia

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modulation. Therefore, the simplified form of Edelman-Boling natremia equation is:

$$\text{Natremia} = \frac{\text{osmotically active body sodium} + \text{osmotically active body potassium}}{\text{total body water}}$$

Based on these concepts hyponatremia is usually classified depending on its inducing mechanism [14]:

- 1) Body excess of free water: the increase of free water produces a dilutional effect leading to hyponatremia (e.g. syndrome of inadequate secretion of antidiuretic hormone).
- 2) Body deficit of sodium (e.g. low sodium diet, salt-losing nephropathy).
- 3) Potassium body deficit (e.g. potassium-losing nephropathy).
- 4) Combined mechanisms

It is clear from this equation that the levels of body sodium and potassium are closely related; and that any alteration in body potassium content would influence the resulting natremia. Thus, if the potassium reserve begins to decrease, it could induce hyponatremia.

The hypothesis

Based on the above exposed information, it is originally hypothesized in this article that sarcopenia, which represents a low body potassium status, could induce hyponatremia.

Consequences and discussion

Hyponatremia in the elderly

As mentioned earlier, hyponatremia is the most frequent electrolyte disorder found in hospitalized patients, particularly in elderly individuals. It can appear in any clinical setting which leads to a significant reduction in serum sodium/water ratio. It has even been proposed that ageing-associated inflammation (inflammaging) stimulates interleukin-6 release, inducing antidiuretic hormone release, and consequently a trend to hyponatremia installation in this population [13,14]. On the other hand, it has been documented in animal models that low serum sodium levels can increase the expression of oxidative stress biomarkers, thus accelerating the aging process [15]. Barsoney et al. based on their findings in hyponatremia animal models, has proposed that chronic hyponatremia could exacerbate (by increasing oxidative stress) multiple ageing manifestations such as osteoporosis, loss adiposity, sarcopenia, and cardiomyopathy [1].

It is worth mentioning that the prevalence of hyponatremia increases in frail patients, particularly during their hospital stay (from 18% on admission to 24% during hospitalization), as well as in nursing-home residents, where up to 53% of them suffer at least one episode of hyponatremia in the course of a year [16,17].

Even though, acute and severe hyponatremia (serum sodium < 125 mmol/L) usually shows neurologic symptoms secondary to cerebral edema, chronic hyponatremia is frequently considered to be asymptomatic [18]. However, recent reports indicate that chronic mild hyponatremia presents significant health problems in the elderly, such as cognitive disorders, gait instability, attention deficits, decreased reaction time, as well as being an independent risk factor of falls also associated with the development of osteoporosis [19–26].

Sarcopenia in the elderly

The term primary sarcopenia describes individuals with progressive and generalized loss of musculoskeletal mass plus the presence of alterations in strength and/or low physical performance related to age

[27–29]. It has been documented, that people usually lose muscle mass due to ageing at a rate of 1–2% per year after 50 years of age [30].

Several mechanisms contribute to the age-related decrease in muscle mass and strength, including altered hormonal status (hypogonadism, etc.), vitamin D deficiency, inflammatory processes, reduced physical activity, and malnutrition, particularly induced by low dietary intake of energy and protein [11]. The causal pathways for ageing-associated sarcopenia are incompletely understood, but it has been hypothesized that disproportionate atrophy of type IIa muscle fibres, decreases synthesis rate of myosin heavy chain proteins, decline of anabolic hormone levels, and voluntary inactivity may contribute [31].

As mentioned earlier, sarcopenia has an estimated prevalence of 5–13% in people from 60 to 70 years of age, and of 11–50% in those over 80 years of age [11,12]. This phenomenon is related to frailty, falls, poor quality of life, loss of functionality and autonomy, greater predisposition to getting sick and mortality [32,33]. Similarly, people with sarcopenia have 2–5 times more risk of having disability than those without sarcopenia [31].

In addition, Barsoney et al. documented that hyponatremia can induce or accelerate sarcopenia, finding a pronounced and progressive decrease in muscle mass of 17% in 10 weeks, which was mitigated with vitamin D prescription [1,15].

Relationship between body potassium content and muscle mass

The total body potassium content is around 3,500 mmol, being the most abundant intracellular cation in the organism, while its intracellular potassium concentration is about 150 mmol/L. In addition, body potassium stores can vary depending on subject weight, age, sex and muscle mass. Since potassium is mainly an intracellular ion, and muscles cells are the most abundant in the organism, body muscle mass constitutes the main body potassium reserve, and consequently the total body potassium content usually correlates with the skeletal muscle mass [1,29]. Several studies have reported a total body potassium decline with age, which has been correlated with the continuous muscle mass decline throughout adult life [1,34]. In addition, it has been described that, both men and women, lose 5% of the total body potassium with ageing. This observation shows that there is a natural correlation between body potassium content decline and sarcopenia installation during ageing [33–37].

A new hypothesis: Sarcopenia as a cause of hyponatremia

As was previously mentioned, there is a tight relationship between potassium, sodium and water body content which is clearly expressed in the Edelman-Boling equation (natremia = body sodium + body potassium/body water). This equation evidently shows that natremia is determined, not only by the body content of water and sodium, but also by the potassium content [38].

Since potassium is the main intracellular cation, and muscle cell is the most abundant cell in the organism, muscle mass is the main potassium reserve in the organism. Therefore, we here originally propose the hypothesis that sarcopenia, which implies a reduced muscle mass, and consequently a reduced body potassium content, according to Edelman-Boling equation, could induce hyponatremia.

This hypothesis could also explain the hyponatremia usually observed in malnourished patients and in sarcopenic elderly patients. Besides, since it has already been demonstrated in animal models that hyponatremia can induce sarcopenia by generating gait disorders and consequently muscle deconditioning, and we propose that sarcopenia can also induce hyponatremia, therefore a vicious circle could be initiated between these two entities. In this sense, since chronic inflammatory processes and oxidative stress factors can both generate muscle consumption, they could also induce hyponatremia by sarcopenic mechanism. Finally, it has already been postulated that hyponatremia induces osteoporosis, and consequently bone fractures [35–37].

However, since many osteoporotic hyponatremic elderly patients are also sarcopenic, this latter condition could also contribute (totally or partially) to the appearance of hyponatremia in this population.

Conclusion

In the present article it is hypothesized that sarcopenia, as a cause of low potassium body content, could induce or co-induce hyponatremia, particularly in frail elderly people.

Compliance with ethical standards

Conflict of interest: All the authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.03.029>.

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