Hyponatremia in Hospitalized Patients With Coronavirus Disease 2019

Nasser Mikhail*, and Soma Wali

Division of Endocrinology, Department of Medicine, Olive-View UCLA Medical Center, David-Geffen School of Medicine, CA, USA

*Corresponding author: Mikhail N, Division of Endocrinology, Department of Medicine, Olive-View UCLA Medical Center, David-Geffen School of Medicine, CA, USA; E-mail: nmikhail[AT]dhs[Dot]lacounty.gov

Abstract

Background: *The clinical significance of hyponatremia in hospitalized patients with coronavirus disease 2019 (COVID-19) is unclear.* *Objective:* *To clarify the frequency, mechanisms, and clinical implications of hyponatremia in patients admitted to the hospital with COVID-19.* *Methods:* *PUBMED search until January 15, 2021. Search terms include COVID-19, hyponatremia, interleukin-6, anti-diuretic hormone, severity, mortality, retrospective, prospective studies, and meta-analyses are included.* *Results:* *Several large retrospective studies and one prospective investigation indicate that prevalence of hyponatremia in patients with COVID-19 ranges from 9.9% to 35.8%. In most studies, hyponatremia represents the most common electrolyte abnormality in patients admitted with COVID-19 and is mostly mild in severity biochemically. Hyponatremia is associated with severe picture of COVID-19 as reflected by increased need for intensive care and mechanical ventilation. Hyponatremia on hospital admission is an independent factor implicated in increased mortality of patients with COVID-19. Mechanisms of hyponatremia in COVID-19 may include inappropriate anti-diuretic hormone activity, increased interleukin-6 (IL-6), and less frequently concomitant adrenal insufficiency.* *Conclusions:* *Hyponatremia is a common electrolyte abnormality in patients with COVID-19 that is linked to poor prognosis. Further studies are needed to elucidate whether hyponatremia plays a causative role in worsening outcomes of COVID-19 or it is a marker of bad prognosis.*

Keywords: *Hyponatremia; COVID-19; Prognosis; mortality, Anti-diuretic hormone, Interleukin-6.*

1. Introduction

Hyponatremia is the most common electrolyte abnormality in hospitalized patients and is linked to unfavorable prognosis [1,2]. Many case reports described patients with COVID-19 presenting with symptomatic hyponatremia [3-5]. This was followed by several studies, mainly retrospective, that confirmed the presence of hyponatremia among a substantial number of patients with COVID-19 admitted to the hospital (see below). The purpose of this review is to determine the extent and severity of hyponatremia in patients with COVID-19, and attempt to clarify its underlying

mechanisms, and clinical significance. Hyponatremia is defined as serum sodium levels below normal, i.e. below 135 mmol/L.

2. Prevalence of Hyponatremia in COVID-19

The HOPE-COVID-19 registry is a large retrospective study including 5,868 patients from 7 countries with major patient contribution from Spain (81.4%) and Italy (10.0%) admitted with COVID-19 pneumonia [6]. In the latter study, the prevalence of hyponatremia was 20.5%, and hypernatremia was 3.7% [6]. Another large study (n= 4,645) from New York City conducted by Frontera et al [7] reported that hyponatremia occurred in 31% of patients on hospital admission. They further categorized hyponatremia as mild (serum sodium 130-134 mmol/L), moderate (121-129 mmol/L), and severe (≤ 120 mmol/L) [7]. Thus, mild, moderate, and severe hyponatremia occurred in 22%, 7%, and 1% of patients, respectively [7]. In a third retrospective study from China by Hu et al [8] including 1,254 patients admitted for COVID-19, 9.9% (n=124) had hyponatremia. In the study of Tezcan et al [9] from Turkey, hyponatremia was the most common electrolyte abnormality among 408 patients admitted with COVID-19 occurring in 35.8% of subjects followed by hypocalcemia (9.5%) and hypokalemia (6.8%). However, in the smaller study of Wu et al [10] (n=125), frequency of hyponatremia was 17.6% being the third electrolyte abnormality after hypocalcemia (64.8%) and hypochloremia (30.4%). The high prevalence of hypocalcemia in the previous study was most likely due to lack of correction for concomitant hypoalbuminemia [10].

3. Hyponatremia and COVID-19 Severity

In the only available prospective study including 330 Algerian patients admitted with COVID-19 followed for a period ranging from 3 to 30 days, Bennour et al [11] examined several biological abnormalities that could predict severe COVID-19 (defined as admission to intensive care, use of mechanical ventilation or death). These authors found that hyponatremia on admission independently predicted COVID-19 progression to the severe form of disease with a sensitivity and specificity of 65% and 85%, respectively [11]. Thus, patients presenting with serum sodium < 133.6 mmol/L were 6 times more likely to develop severe COVID-19 (OR 6.0, 95% CI 2.0 to 17.4; P = 0.001) [11]. In addition to hyponatremia, they reported 5 other parameters independently related to the severe form of COVID-19, namely elevated urea nitrogen, lactic dehydrogenase (LDH), neutrophil to leucocyte ratio, C-reactive protein (CRP), and decreased albumin [11].

In addition, in the study of Hu et [8], 46.8% of patients with hyponatremia had severe or critical COVID-19 compared with 19.5% of patients with normal sodium levels (P value not reported).

The above results are in line with those reported by two meta-analyses of retrospective studies. In the first meta-analysis of 22 Chinese studies, Ghahramani et al [12] classified patients with COVID-19 admitted to the hospital into severe cases (defined as per World Health Organization criteria, or admission to intensive care unit) and non-severe cases. Serum sodium levels, which were reported in 9 of the 22 studies of the meta-analysis (number of patients not reported) were significantly lower in the severe group compared with the non-severe group, with a weighted mean difference of -1.95 mmol/L, 95% CI, -2.87 to –1.03; P <0.001) [12]. Meanwhile, differences in serum potassium concentrations between the severe and non-severe patients were not significant [12].

In the second pooled analysis of 5 studies including 1,415 patients with COVID-19 admitted to the hospital, Lippi et al [13] found that patients with severe disease (requiring mechanical ventilation or intensive care) had significantly lower serum sodium levels compared with subjects with non-severe disease, weighted mean difference being -0.91 mmol/L (95% CI, -1.33 to -0.50 mmol/L) [13].In the study of Wu et al [10], frequency of hyponatremia was significantly greater in patients with COVID-19 requiring long hospitalization (14 days or more) compared with patients requiring shorter hospitalization (<14 days), 27.1% and 9.1%, respectively (P=0.021).

However, not all investigations reported an association between hyponatremia and severity of COVID-19. In an early retrospective Chinese study (n=736) performed during the first 2 months of the COVID-19 outbreak, median serum sodium levels on admission were similar in patients with and without severe COVID-19, 138.4 mmol/L and 138,0 mmol/L, respectively [14].

4. Hyponatremia and Biochemical Markers of COVID-19 Severity

Several studies showed that hyponatremia was associated with biochemical markers of COVID-19 severity. Thus, Hu et al [8] found that compared with patients with normal serum sodium levels, those with hyponatremia exhibited higher leukocytic and neutrophils counts, and lower lymphocytes and platelet count (all P < 0.05). Tezcan et al [9] reported that serum levels of CRP, LDH, D-dimers, and ferritin levels were significantly higher in patients with hyponatremia compared with subjects who had normal sodium values.

5. Hyponatremia and COVID-19 Related Mortality

In the study entitled HOPE-COVID-19 registry mentioned above, hyponatremia emerged as an independent risk factor for increased mortality (OR 1.5, 95% CI 1.08-2.09; P=0.016) [6]. Hypernatremia was also an independent risk factor for higher mortality (OR 2.38, 95% CI 1.18-4.78; P= 0.015) [6]. In the study of Frontera et al [7], increasing severity of hyponatremia was associated with 43% increased risk of in-hospital mortality (odds ratio 1.43, 95% CI 1.08-1.88; p=0.012) after adjustment for pertinent variables such as age, gender, race, body mass index, renal failure, encephalopathy, mechanical ventilation and past medical history. Moreover, in the study of Hu et al [8], mortality rate was higher in patients with hyponatremia compared with those with normal serum sodium levels, 16.7% vs 6.3% (P < 0.001). Furthermore, in a fourth retrospective study from Turkey, Tezcan et al [9] showed that hyponatremia was an independent factor related to death from COVID-19 after adjustment for multiple variables (OR 10.33, 95% CI 1.62-65.62; p =0.01).

6. Hyponatremia and COVID-19 Clinical Outcomes Other Than Mortality

In the HOPE-COVID-19 registry analysis, hyponatremia was independent risk factor for development of sepsis (OR 1.87; 95% CI 1.32-2.66; P<0.001) and receiving intensive care (OR 1.35, 95% CI 1.02-1.78; P=0.035) [6]. In the study of Frontera et al [7], patients with serum sodium <130 mmol/L were significantly more likely to require invasive mechanical ventilation (OR 1.83, 95% CI 1.50-2.25; p<0.001) and were less likely to be discharged home (OR 0.64, 95% CI 0.53-0.77; p<0.001). Additionally, patients with serum sodium ≤120 mmol/L had eight-fold higher risk of having

encephalopathy (OR 8.35, 95% CI 4.29-16.27; p <0.01) [7]. In the study of Hu et al [8], the hyponatremic group exhibited more extensive pneumonia compared with patients with normal serum sodium.

7. Mechanisms of Hyponatremia in COVID-19

7.1 Syndrome of inappropriate antidiuresis

Many authors believe that the syndrome od inappropriate secretion of anti-diuretic hormone (SIADH) or its newer terminology "syndrome of inappropriate antidiuresis' (SIAD) may be a major cause of hyponatremia among patients with COVID-19 [4, 15-17]. The main reason for this belief is that most cases of hyponatremia are associated with COVID-19 pneumonia and pulmonary infection is a well-established cause of SIAD [1]. In fact, Frontera et al [7] examined the mechanisms of hyponatremia in the subgroup of patients with severe hyponatremia (serum sodium ≤120 mmol/L) (n=36). They found that the most common mechanisms were SIADH (36%) and hypovolemia (36%), followed by "Tea and Toast" (22%), and hypervolemia (6%) [7].

7.2 Interleukin-6

Interleukin-6 is a pro-inflammatory cytokine that generally correlates with severity of COVID-19 [18]. Growing body of data suggests that IL-6 may directly stimulate secretion of anti-diuretic hormone (ADH) causing hyponatremia. Indeed, the earlier experiments of Mastorakos et al [19] showed that intravenous administration of recombinant IL-6 in humans produced rapid rise in serum ADH peaking within 30 minutes [19]. Conversely, inhibition of IL-6 activity by the IL-6 receptor antibody tocilizumab corrected hyponatremia and SIADH in a girl with juvenile idiopathic arthritis [20]. Several lines of evidence suggest that the same mechanism may be pertinent to COVID-19 associated hyponatremia. Thus, in the study of Frontera et al [7], there was a small, but significant correlation between hyponatremia and IL-6 levels (Spearman rho, -0.069; p=0.017). Likewise, Habib et al [3] recorded an inverse correlation of moderate strength between serum sodium and IL-6 levels in their small series of 29 patients admitted with COVID-19 (correlation of coefficient R= -0.60, P =0.006). Furthermore, tocilizumab administration was associated with significant rise in mean serum sodium values from 132.4 to 139.6 mmol/L over 48 h [3].

7.3 Endocrine disorders: Adrenal insufficiency and hypothyroidism

Adrenal insufficiency is well-known cause of hyponatremia due to cortisol and aldosterone deficiency [21]. Few case reports described adrenal insufficiency due to bilateral adrenal hemorrhage associated with hyponatremia [22]. Other endocrine disease that may lead to reversible hyponatremia is hypothyroidism [23]. Normalization of adrenal and thyroid function will lead to correction of hyponatremia.

8. Conclusions and Current Needs

Hyponatremia is a common electrolyte disorder in patients with COVID-19 admitted to the hospital. The degree of hyponatremia is generally mild. Accumulating evidence strongly suggests that hyponatremia is associated with poor outcome and high mortality in patients with COVID-19. However, it is still unclear whether hyponatremia in hospitalized patients with COVID-19 plays a causative role in disease severity and complications, or simply is a marker of poor prognosis. The management of hyponatremia in the setting of COVID-19 requires further studies. Some

unanswered questions include the rate of sodium correction, and possible use of sodium-raising agents. In this respect, the role of vasopressin receptor antagonist therapy (e.g conivaptan, tolvaptan) and IL-6 receptor antagonists (e.g. tocilizumab) should be evaluated in randomized trials.

9. Conflict of Interest

The authors do not have any conflict of interest to declare.

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