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ACE2 Engagement In Virus Internalization Could Lead to Reduced Efficiency of RAAS Pathway Causing Hyponatremia as Negative Prognostic Factor Among COVID-19 patients

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Abstract

SARS-CoV-2 utilizes host ACE2 for cleaving S1 subunit of Spike Protein for its entry into the cell. This can lead to reduced cell surface availability of ACE2, affecting the efficient maintenance of RAAS pathway resulting into poor reabsorption of Sodium in kidney leading to hyponatremia. Our study of 1940 cases showed that in recovered patients (Year 2020), 23.5% had hyponatremia of which 25.9% had many comorbidities. Among deceased patients, 44.1% had hyponatremia as single morbidity factor. In year 2021, among recovered patients 16.8% had hyponatremia, whereas among the deceased patients, 31.2 % reported hyponatremia of which 73.9 % had hyponatremia as single co-morbidity associated with death. We report hyponatremia as the single negative prognostic factor and more importantly the possible fact that hyponatremia could be caused due to engagement of ACE2 in virus internalization, thereby impacting efficiency of RAAS pathway responsible for sodium reabsorption.

Keywords: RAAS, Sodium, Hyponatremia, Mortality, SARS-CoV-2.

Introduction

Hyponatremia, irrespective of a specific infection has been reported as common risk factor associated with the increased risk of mortality among patients (1). In particular, it has been reported that among hospitalized patients of COVID-19, sodium alterations have been reported to appear frequently (2, 3). However, earlier workers report unavailability of sufficient data to establish the increased risk of Hyponatremia among COVID-19 patients (4). The further detailed studies have reported that among COVID-19 patients, infection causes specific dysfunction of the proximal tubule of the kidney (5). In present paper we addressed two specific research contentions, one to study association of hyponatremia with mortality of patients of COVID-19 and other to reveal possible mechanism of causation of hyponatremia among severe patients. The study was undertaken among 2,563 COVID-19 patients which included recovered as well as deceased patients during pandemic years of 2020 through 2021. The present paper reports details of work done.

Materials and Methods

The records of indoor patients of COVID-19 admitted in Sharda Hospital, Greater Noida, India were studied as part of the study supported by the Indian Council of Medical Research, Govt of India (Grant id: 2021-6369). A total number of 1,940 indoor patients of COVID-19 were studied (1320 reported in the

year 2020 and 620 in the year 2021 pandemic). The patients were divided in two groups in each year of study; Recovered patients and Deceased patients. Each category of patients were subdivided into patients with comorbidities of Diabetes, Respiratory infections, Tuberculosis, cardiac problems, Renal problems and Diabetes etc.

Results and Discussion

Of the total 1320 patients of COVID-19, admitted to the hospital during the pandemic of 2020, 1243 were recovered whereas 77 patients were deceased. In recovered group, 293 (23.5%) had hyponatremia (Serum sodium <135mmol/l) among which 76 (25.9%) has one or many co-morbidities whereas 217 (74.06%) had no comorbidity. Among deceased patients, out of 77 patients studied, 34 (44.1%) had hyponatremia. In patients admitted during 2021, 398 patients studied in recovered group, of which only 64 (16.8%) had hyponatremia. On other hand, among 222 deceased patients, 69 (31.0%) had hyponatremia. Of 69 patients having hyponatremia, only 18 (28.0%) had some co-morbidities whereas 51 (73.9%) patients showed hyponatremia as single co-morbidity (Table 1).

Table 1. Blood Sodium level among survived and deceased patients of COVID-19

Patients status	Year of pandemic	Number of patients studied	No of patients with low sodium	No. of patients with low sodium and comorbidity	No. of patients with low sodium without co-morbidity
Recovered	2020	1243	293 (23.5%)	76 (25.9%)	217 (74.0%)
Deceased	2020	77	34 (44,15%)	22 (64.7%)	12 (35.29%)
Recovered	2021	398	64 (16.3%)	16 (25.0%)	48 (75.0%)
Deceased	2021	222	69 (31.0%)	18 (26.0%)	51 (73.9%)
Total		1940			

Discussion

Angiotensin Converting Enzyme 2(ACE2) has been reported to be present in number of human tissues and organs. A histological presence of ACE2 in smooth muscles, oral and nasal mucosa and in organs such as lungs and kidneys has been reported (6). In the cells constituting proximal convoluted tubule of nephron and descending region of Henley's loop, cell surface presence of ACE2 ensures reabsorption of sodium ions from outgoing urinary discharge by virtue of RAAS pathway. Engagement and metabolic utilization of this enzymatic protein (ACE2) by invading SARS-CoV-2 virions to ensure their entry into cells of the patients is likely to bring down the availability of ACE2 affecting one of its important functions of reabsorption of sodium in the kidney. Angiotensin Converting Enzyme is the central actor of Renin-Angiotensin-Aldosterone-System (RAAS pathway). Deficiency of ACE2 in COVID-19 patients has been reported to be positively associated with the delivery of harmful contents among smokers (7). We report here first time that reduced availability of this enzyme could be directly responsible for hyponatremia among COVID-19 patients as ACE-2 regulates the reabsorption of Sodium from outgoing urinary fluids and reabsorbed sodium is pumped back into blood through sodium/potassium pumps. Few earlier studies also have reported the role of Anti Di Uretic Hormone (ADH) and RAAS pathway as possible mechanisms involved in Hyponatremia (8, 9). However, water reabsorption at distal convoluted tubule of nephron by secretion of hormone ADH by posterior pituitary alone may not be sufficient reason for net urinary concentration of sodium but more important issue will be tubular reabsorption of sodium through RAAS pathway. In present paper we resolve that RAAS pathway involves secretion of Angiotensinogen by liver and of Angiotensin Converting Enzyme by endothelial cells of

lungs and kidney which converts ACE-I into ACE-II. We therefore pin point the crucial role of ACE-II deficiency in hyponatremia instead of broad mention of RAAS pathway which could be a useful clue for the clinical management of serious patients of COVID-19.

Hyponatremia has been reported by earlier workers as possible negative prognostics factor among patients of COVID-19 and that therapeutic solution for management of hyponatremia among COVID-19 patients should be found (2). Many other studies also have reported occurrence of hyponatremia and other factors associated with the COVID-19 patients (10, 11, 12, 13, 14, 15). While earlier workers have reported group of co-morbidities associated with mortality of COVID-19 patients, based on our study of 2563 patients including survivors and non survivors, for the first time we report that serum sodium deficiency or hyponatremia could be a single negative prognostic factor associated with the mortality. We further report that hyponatremia could be caused by deficiency of important enzyme ACE2 being involved in virus internalization during phase of spread of infection of SARS-COV-2 within human system. The imbalanced salt homeostasis as could be possibly caused by inefficient RAAS pathway appears to be the main mechanism of hyponatremia among COVID-19 patients.

Conclusion

We conclude two points based on our study. First that Hyponatremia is the single co-morbidity associated with the mortality of the patients and the observation need to be given prime attention during clinical management of serious patients. Second is that possible mechanism of low serum sodium could be due to the reduced level of ACE2 among patients infected with SARS-CoV-2. The paper thus sensitizes, that maintaining the normal serum sodium level among COVID-19 patients will reduce the mortality of serious patients.

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