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ROLE OF MICRONUTRIENTS IN ASSOCIATION WITH SEVERITY AND MORTALITY OF COVID-19 PATIENTS

Biochemistry

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ABSTRACT

Introduction: The micronutrients in our body play a pivotal role in combating infection. Of them, Zinc, Vitamin C, and Vitamin D have crucial roles. COVID infection results in raised CRP (C-reactive protein) and D-dimer in response to infection. This study aimed to know the progression of disease in the individuals who consumed and who did not consume these micronutrients before admission. Along with this, the effects of high-dose steroids in this study population with no comorbidities have also been analyzed. **Materials And Methods:** It is a hospital-based observational study. The study group includes 1130 cases who were diagnosed and confirmed with COVID-19. Blood samples were processed on the day of admission for CRP, and D-dimer values. Patients administered steroids have been followed during treatment. **Results:** The clinical parameters recorded during the study period CRP (2.36+/-1.46 mg/dl), (9.16+/-6.44mg/dl) and D-dimer (1.20+/-5.99mg/L), (2.48+/-3.13mg/L) for the consumed group, and non-consumed group respectively, with 95% confident interval and p-value less than 0.05 were statistically significant. **Conclusion:** A patient who had taken micronutrients before admission had statistically shown mild disease progression and fewer side effects of steroids compared to their counterparts.

KEYWORDS

Zinc, vitamin C, vitamin D, covid pneumonia, steroid side effects.

INTRODUCTION

The COVID-19 pandemic that hit Globally has left devastating effects economically, physically, and psychosociologically since March 2020.[1] The effects of the virus and its treatment protocols have been extensively studied, and published in various journals but sequelae post- treatment and post-survival have been limited especially in this third-world countries like India.[2] As the nutritional status of the patient is of utmost importance in combating the viral infection, especially those viruses having a predilection to respiratory epithelium, SARS CoV-2 is also not different. [3]

The micronutrients in our body play a pivotal role in combating infection by different mechanisms.[4] Of them, Zinc, ascorbic acid, and vitamin D have a crucial role in controlling the entry of viruses into host cells and modifying the inflammatory markers in response to body immunology. [5,6] As the COVID infection results in multiorgan involvement with raised CRP (C-reactive protein) and D-dimer in response to infection [7,8] Therefore the steroids like dexamethasone, and methylprednisolone, played a vital role in preventing the harmful effects of the inflammatory cascade, but the high doses that have necessitated to control the storm of inflammation, lead to short-term and long-term side effects in patients.[9] So, this study was designed to know the progression of disease in the individuals who consumed and who did not consume these micronutrients before admission. Along with this, the effects of high-dose steroids in this study population with no comorbidities have also been analyzed.

MATERIALS AND METHODS

This will be an observational study conducted in a tertiary care hospital of the Govt of Andhra Pradesh in the Department of Biochemistry, King George Hospital. Ethical clearance for the study was obtained from the Institutional ethical committee before the commencement of the study.

Study Design: Hospital-based observational study.
Study Period: April 2021- August 2021
Sample Size:1130 Cases.

Inclusion Criteria

All patients of age between 18-55yrs admitted in KGH, CSR block for mild to moderate covid disease after RT-PCR positivity.

Exclusion Criteria

1. Paediatric age group (age < 18years) & Elderly age group (age >55 years)
2. Pregnant women
3. Severe COVID pneumonia with SPO2 <80% On admission
4. On admission ventilatory support
5. Previous comorbidities (HTN, TYPE-2 DM, COPD, Bronchial Asthma, On steroid dependency for any reason)

Methods

1. Patients' Blood samples have been processed on the day of admission for CRP, and D-dimer values.
2. Patients who have progressed from mild to moderate disease and who have been administered steroids have been followed during treatment.
3. CRP AND D-dimer levels are estimated by immunoturbidimetric assay in the HORIBA PENTRA autoanalyzer.
4. SPSS software Version 24.0 was used for statistical analysis.

RESULTS

In this study total of 1130 patients of which 757 (67%) males and 373 (37%) females got admitted after 07 days of home isolation following RT-PCR positivity for COVID-19 were analyzed.

Age-wise distribution is shown in [Table:2] Out of which 764 (67.61%) have not consumed any medication except Tab. Paracetamol 500 mg thrice daily for fever control. 366 patients (32.39%), consumed either vitamin C and Zinc combination or, vitamin C, Zinc, and vitamin D3, following which they presented to the hospital due to the progression of disease severity. The clinical parameters recorded during the study period showed below [Table 1].

Table 1: Comparison Of Inflammatory Markers Between Consumed And Non-consumed Groups)

	Non-Consumed group (mean ± SD)	Consumed group (mean ± SD)	p-value
CRP (mg/dl)	9.16 ± 6.44	2.36 ±1.46	0.001
D-dimer (mg/L)	2.48 ± 3.13	1.20 ± 5.99	0.001

Out of 764 patients who have not consumed vitamin C, zinc, or vitamin D3, 231 patients had mild disease corresponding to 20.44%, and were discharged. 301 patients (26.63%) progressed to moderate disease, and 202 (17.87%) progressed to severe disease, despite IV Antibiotics and

steroid supplementation. 24 patients succumbed to illness (2.1%), and 06 patients (0.5%) had > 7 days of ventilator support. [Fig:2]

Out of 366 patients (32.39%) who have consumed vitamin C, zinc, or vitamin D3, 245 developed the mild disease (21.68%), 100 developed moderate disease (8.8%), 16 developed severe disease (1.4%), 05 succumbed to illness (0.4%).

Out of 1130 patients, 533 patients (47.17%), who have not consumed any of the micronutrients from the day of positive RT-PCR to admission had progressed to moderate to severe disease and been on steroids, out of which 503 patients recovered and were discharged, 30 succumbed to illness. Out of 503 patients who had recovered after IV antibiotic and steroid therapy, 36 (6.75% of 533), developed B/L spontaneous pneumothorax, and 64 (12% of 533), developed pleural effusion for which they have been treated with intercostal drain placement. [Fig: 2,4]

Out of 366 patients who had taken micronutrients either zinc, vitamin C, or vitamin D3 121 patients (10.6%), progressed from moderate to severe disease and were on steroids, out of which 116 (95.86% out of 121) recovered and 05 (4.1%out of 121) succumbed to illness. Among 116 patients who got recovered 04 developed a spontaneous pneumothorax (3.3%) and were treated with intercostal drain placement. Out of 1130, 35 succumbed to illness despite all efforts of IV antibiotic and steroid supplementation constituting 2.6% of the total in the unconsumed group, and 0.44% in the consumed group. [Fig: 3,5]

654 out of 1130 excluding 35 deaths were 619 patients who have been treated with steroids and have been followed for 2 months to evaluate the steroid aftereffects. [Fig:1]

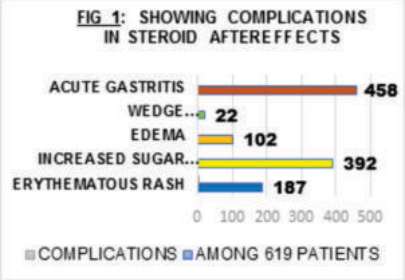
Accordingly, we found 187 patients (30.2%) had erythematous rash, high sugar levels (250mg/dl) in 392 Patients (63.3%), dependant edema in 102 patients (16.4%), wedge compression fracture of vertebrae (spontaneous nontraumatic osteopenic) in 22 constituting (3.55%) and acute gastritis in 458, accounting for (73.9%) of all ill effects caused by steroid therapy.[Table 3]

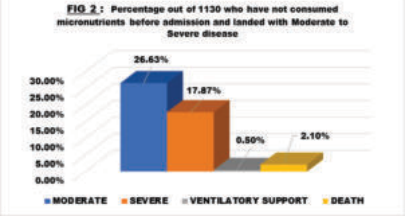
Table 2: Age-wise Distribution

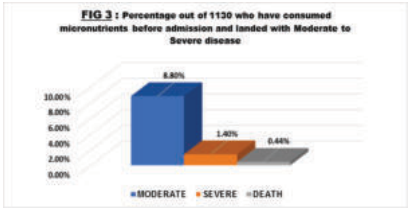
AGE GROUP (YRS)	No. OF PATIENTS	% OF DISTRIBUTION
20 - 30	116	10.26%
31 - 40	210	18.58%
41 - 50	541	47.87%
≥ 51	263	23.27%

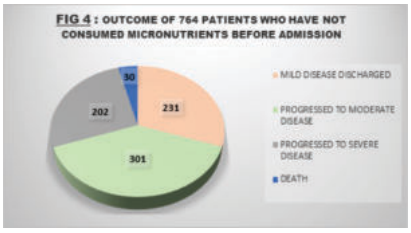
Table 3: Showing Complications In Steroid Aftereffects

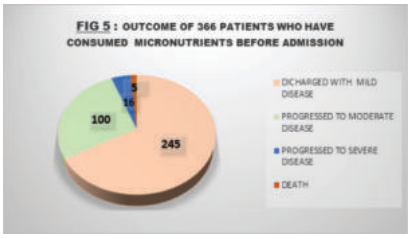
COMPLICATION	AMONG 619 PATIENTS	
ERYTHEMATOUS RASH	187	30.2 %
INCREASED SUGAR LEVELS	392	63.3 %
EDEMA	102	16.4 %
WEDGE COMPRESSION FRACTURES	22	3.55 %
ACUTE GASTRITIS	458	73.9 %











DISCUSSION

Zinc is an important trace element performing many biological processes where it involves its role in immunoregulatory and antiviral properties. In a study, it was found that 16% of respiratory diseases are linked to a deficiency of zinc.[10] In vitro studies performed found that spike protein of SARS-CoV-2 directly interacts with the host cell surface ACE2 (angiotensin-converting enzyme 2) and the cellular protease TMPRSS2 (transmembrane protease serine 2) permitting its entry and replication, and spike protein levels were inversely related to Zinc.[11] Zinc also shows its effects by inhibition of RNA synthesis, DNA polymerase, viral replication, and reverse transcriptase. Therefore, it may be hypothesized that Zn supplementation in older people and those who are at risk of COVID-19 infections would be benefited most from zinc supplementation.[14]

To clear viral particles, the body's immune system mainly depends on IFN & Cytotoxic T lymphocytes, for which zinc plays a key role. Zinc deficiency decreases the levels of serum thymulin, which helps in the differentiation of immature T cells to Mature T cells and the functionality of mature T cells.[12] Zinc also plays important role in enhancing cell resistance to apoptosis by inhibiting Caspases, 3, 6, and 9, and by increasing the BCL-2/Bax ratio, such as anti-apoptotic properties resulting in increased levels of Mature T-cells. [12] Zinc induces alteration in capillary epithelium which inhibits transcapillary movement of plasma proteins, leading to local edema, inflammation, exudation, and mucus secretion, further preventing the development of pleural effusion superadded bacterial infection pneumonic consolidation. [13]

Ascorbic acid is known to be a powerful antioxidant and various studies point to its effects on the immune system, assisting in normal neutrophil function, scavenging ROS, activating pro-inflammatory transcription factors, activating the signaling cascade, nuclear factor B (NFB), regulating inflammatory mediators, gene regulation, phagocytosis, and signaling pathways in T cells, and increasing neutrophil motility to the site of infection., where decreased levels lead to susceptibility to viral pneumonia. [15,16] Studies have shown administration of high doses is effective against the common cold. [17] Recent Meta-analysis has shown that the administration of a high dose of vitamin C at the onset of the common cold decreases the progression to severe disease in COPD, Bronchial asthma patients give a hypothetical hope that the levels of vitamin C and the immunological effects are closely associated and the effectiveness of which has been analyzed in this study. [18,19,]

Levels of 25-hydroxy cholecalciferol (vitamin D) levels and acute respiratory infection are inversely related in both children and adults as reported in the National Health and Nutrition Survey (NHANES)

2001–2006. [20] As per a study conducted in Indonesia, vitamin D deficiency (serum 25-hydroxy vitamin D level of 20 ng/mL or lower) and insufficiency (serum 25-hydroxy vitamin D level of 21 to 29 ng/mL) are associated with increased mortality in COVID-19. [20,21,22]

Levels of vitamin D plays important role in the body's defensive mechanism especially in the respiratory epithelium by the production of proteins for tight junctions, adherens, and gap junction vitamin D is also involved in the production of Anti-microbial peptides like cathelicidin and defensins which are effective against a wide variety of bacteria and viruses affecting respiratory epithelium. [24]

Vitamin D prevents cytokine storm, which is the culprit involved in immunological damage to the endothelium, and denudation of the alveolar membrane, which then causes a vicious cycle in moderate to severely ill COVID-19 patients causing mortality. [23]

Though many therapies aiming at mitigation of the inflammatory response are being evaluated, strong evidence of benefit is lacking. Corticosteroids offer benefits in subsiding hyperinflammation, and ARDS but the disadvantages are dose-dependent on acute and delayed side effects like delayed viral clearance, and opportunistic infections. [25] In the RECOVERY TRIAL, dexamethasone use versus usual care was found that the use of dexamethasone reduced 28-day mortality in patients requiring oxygen therapy, and mechanical ventilation. A prospective meta-analysis consisting of seven randomized control trials showed administration of corticosteroids lowers 28-day mortality in COVID patients. The surviving sepsis guidelines modified for COVID-19 management recommend systemic corticosteroid administration to patients with ARDS on mechanical ventilation and refractory shock. [28]

Glucocorticoids increase the risk of adverse GI effects, such as gastritis, gastric ulcer formation, and GI bleeding. [25,26] Glucocorticoid-induced acute neuropsychiatric impairment may present with a wide variety of behavioral symptoms including euphoria, aggression, insomnia, mood fluctuations, depression, manic behavior, and even frank psychosis these psychiatric disturbances tend to wear off with time on cessation of glucocorticoid therapy. [29, 30]

CONCLUSION

In the study of these patients, we have found that the micronutrients like Zinc, Vitamin C, and vitamin D played a major role in not developing severe disease & early recovery in patients who used steroids. The study group consists of patients who have no comorbidities but the difference existed between both groups with consumption of Zinc, vitamin C, and vitamin D for a period of 7 to 10 days from the day of RT-PCR positivity till the day of admission therefore it is being postulated that these micronutrients can be taken prophylactically which are more beneficial than giving them as a therapeutic strategy to prevent more severe disease and lethality of the COVID virus.

Conflict Of Interest: The author declares no conflict of interest.

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