Micronutrients and COVID-19 Patients' Outcome

INTRODUCTION

Micronutrients involve in the continuum of host immune responses to the virus from the initial virus-host interaction, innate immune activation to adaptive immune responses. The healthy immunity requires the synergistic contribution from multiple micronutrients and single nutrient barely drives the whole immune machinery. However, the viral-host resistance relies on the support from a dominant group of nutrients, including vitamins A, C, D, E, B6, B12, folate, iron (Fe), zinc (Zn), copper (Zn), selenium (Se) and magnesium (Mg).[1]

Healthy immunity eventually proceeds to the production of SARS-CoV-2 specific antibodies that neutralise the virus and resolve the infection. Vitamins A, C, D, E, B6, B12, and folate, and the trace elements Zn, Fe, Cu, Se, as well as the mineral Mg comprise a group of nutrients that support the entire continuum of virus-host immune responses. Their contributions range from the regulation of number and function of innate immune cells, the production of pro- and anti-inflammatory cytokines, the responses to inflammation, the oxidative burst function, the reductive-oxidative haemodynamics to the responses of adaptive immunity, including differentiation, proliferation, and functions of T-cells, the interactions with the presenting viral antigens and the production and development of virus-specific antibodies.[1]

Despite their synergistic contributions to virus-host responses, the deficiency state of specific nutrients increases an individual susceptibility to the severe clinical manifestation of SARS-CoV-2 infection.[1] Important nutrients that support the immune function include vitamins A and D, the B vitamins (folate, vitamins B6 and B12) and vitamin C, and the minerals and trace elements Zn, Fe, Se and Cu.[2] Hence, this report is to provide rapid review on the association between micronutrients and Covid-19 patients' outcome.

EVIDENCE on EFFECTIVENESS and SAFETY

Effectiveness

A total of 15 titles were retrieved from the scientific databases such as Medline, EBM Reviews, EMBASE via OVID and PubMed. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 4 December 2020.

There were three studies included in this review: a systematic review and two observational studies.

Based on the systematic review, there were very limited evidence on micronutrients and Covid-19 patients' outcome. The results for the systematic review are as follow:

i. <u>Vitamic C</u>

Two systematic reviews concluded that the evidence that **vitamin C was likely to benefit Covid-19 patients was weak or absent**.[3]

ii. Zinc

A retrospective study reported that addition of zinc sulfate did not impact the length of hospitalisation, duration of ventilation or ICU duration. In univariate analyses, zinc sulfate increased the frequency of patients being discharged home, and decreased the need for ventilation, admission to the ICU and mortality or transfer to hospice for patients who were never admitted to the ICU. After adjusting for the time at which zinc sulfate was added to the protocol, an increased frequency of being discharged home (OR=1.53, 95% CI 1.12 to 2.09) reduction in mortality or transfer to hospice remained significant (OR=0.449, 95% CI 0.271 to 0.744). **These data provide initial in vivo evidence that zinc sulphate may play a role in therapeutic management for Covid-19.**[3]

iii. Vitamin D

1. A retrospective cohort study in Switzerland **showed significantly lower 25-hydroxyvitamin D (25OHD) levels (p=0.004) were found in polymerase chain reaction (PCR)-positive** for SARS-CoV-2 (median value 11.1 ng/mL) patients compared with negative patients (24.6 ng/mL).
2. In a study of 499 hospitalised patients or health care workers in the United States of America (USA) (Chicago) with a Covid-19 test result and vitamin D status measurement (in the past year) there was **no difference between Covid-19 positive and negative cases (p=0.11)**. An expanded analysis that sought to categorise the vitamin D status of an individual based on their vitamin D status test result and vitamin D treatment regimen in the previous two years found that participants **who were predicted 'vitamin D deficient' had an increased risk (RR=1.77, p<0.02) of testing positive** for Covid-19 compared with participants with predicted vitamin D status of likely sufficient.
3. In a different approach, Haustie et al. used baseline United Kingdom (UK) Biobank data from 348,598 participants collected 10 to 14 years ago of whom 449 had a positive Covid-19 test in between March and April 2020. After inclusion of other factors such as season, ethnicity and other health conditions there was **no significant association between 25OHD and Covid-19 infection (OR=1.00; 95% CI 0.998-1.01)**.
4. A study from the Philippines found that in 212 Covid-19 hospitalised patients, **vitamin D status was associated with clinical outcomes** such that for each standard deviation increase in 25OHD concentration, the odds of having a mild clinical outcome rather than a severe or critical outcome were 7.94 and 19.61, respectively (CI not reported).
5. A study of 780 Covid-19 positive hospital patients found that after correction for age, sex and comorbidity the **odds ratio of death was 10.2 p<0.0001 (95% CI not reported) in cases with vitamin D deficiency (VDD) (defined as <50 nmol/L) compared with normal vitamin D status (defined as 75 nmol/L)**.[3]

An observational study of 50 Covid-19 patients in Korea showed **VDD was the most prevalent, with a deficiency (≤20 ng/dl) in 76% of the patients and a severe VDD (≤10 ng/dl) in 24%**. Regarding the other nutrients, a **deficiency of selenium was observed in 42%** of the patients, **pyridoxine in 6.1%** and **folate in 4.0%**. No patient was deficient in B1, B12, or zinc. In the comparison between the two groups, the average 25OHD level among those with Covid-19 was 15.73 ng/dl, which was significantly lower than the average level in the control group, which was 25.03 ng/dl. **The deficiency rate was 74.0% in the Covid-19 group and 43.3% in the control group**. In terms of severe deficiencies, there were also differences between the two groups (24.0% and 7.3%, respectively). Among the patients with mild Covid-19 (without pneumonia), vitamin D and selenium deficiencies were present in 66.7% and 44.4%, respectively.[4]

A retrospective observational study on 186 consecutive subjects with PCR-confirmed SARS-CoV-2 infection evaluated the VDD rates in Covid-19 patients as a function of radiologic stage. There was **a remarkably high fraction (59%, 109/186) of patients with Covid-19 were VDD (25OHD <20 ng/mL) on admission**: 47% of women and 67% of men. Male patients with Covid-19 showed progressively lower median 25OHD with advancing stage, resulting in VDD rates increasing from

55% in stage 1, 67% in stage 2, to 74% in stage 3 (p=0.0010). However, no such stage-dependent 25OHD variations were seen in female patients with Covid-19 **(see Figure 1)**.[5]

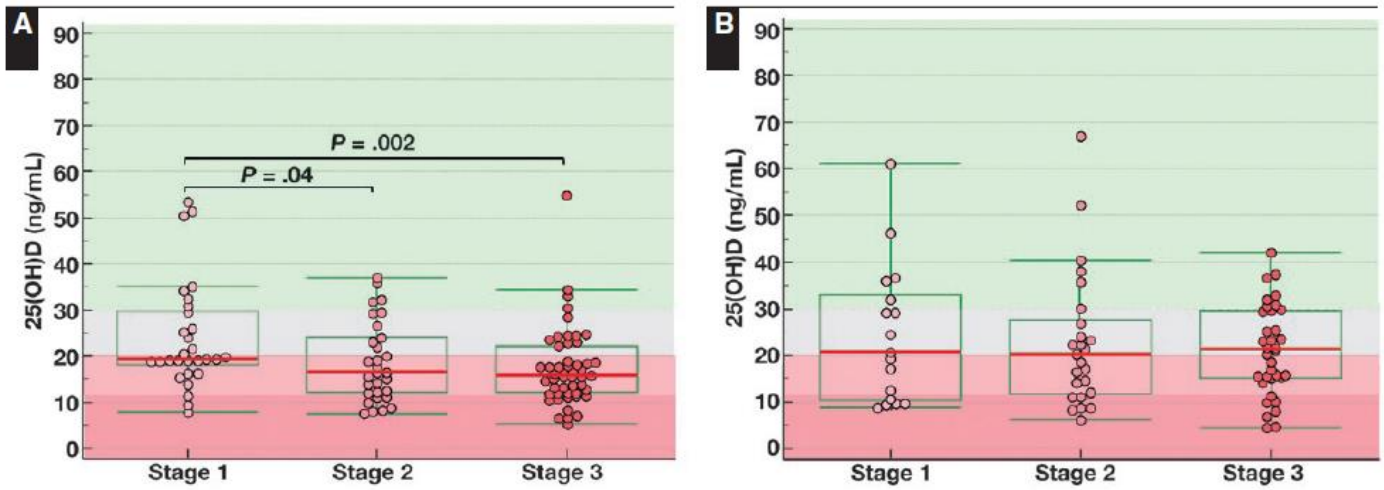

Figure 1: Box-and-whisker plots of 25-hydroxyvitamin D (25OHD) in male patients with coronavirus disease 2019 (Covid-19) **(A)** and female patients with Covid-19 **(B)** grouped according to radiologic stage (stage 1, early stage groundglass opacities; stage 2, progressive stage, crazy paving pattern; stage 3, peak stage, consolidation). Background colour in boxplots indicates normal vitamin D status (green, 25OHD >30 ng/mL), vitamin D deficiency (pale red, 25OHD <20 ng/mL), severe vitamin D deficiency (darker red, 25OHD <12 ng/mL), and a gray zone (20 ng/mL ≤ 25OHD ≥ 30 ng/mL). P values indicate statistical differences between groups calculated by the Mann-Whitney test.[5]

Safety

There was no retrievable evidence on its safety.

CONCLUSION

There was very limited retrievable evidence on association between micronutrients and outcome in patients with Covid-19. The limited evidence showed more patients who were diagnosed with Covid-19 were vitamin D deficient. However, direct association between vitamin D and the outcome in Covid-19 patients cannot be determined. Thus, more studies involving larger population or RCT are needed.

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Based on available evidence up to 4 Disember 2020

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Disclaimer: This rapid assessment was prepared to provide urgent evidence-based input during COVID-19 pandemic. The report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.

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