NICE National Institute for Health and Care Excellence

Medicines evidence commentary

Commentary on important new evidence from medicines awareness weekly

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Vitamin D supplementation for preventing intensive care admissions in people with COVID-19 associated pneumonia

A new study (Castillo et al. 2020) found that vitamin D supplementation in hospitalised adults with COVID-19 may reduce admission to intensive care. However, the study has many confounders so the results should be interpreted with caution. The clinical management of patients with COVID-19 should not be changed based on the results of this study. Further studies are underway which will provide further evidence on the place of Vitamin D in treating COVID-19, NICE is reviewing new evidence on this topic as it becomes available. The information in this medicines evidence commentary should be read alongside the existing NICE advice on vitamin D for COVID-19.

Overview and current advice

Vitamin D is important for bone and muscle health and may also have a role in the body's immune response to respiratory viruses. Two forms of vitamin D (vitamin D2 ergocalciferol and vitamin D3 colecalciferol) are licensed for the prevention and treatment of vitamin D deficiency but are not specifically licensed for preventing or treating any infection including the novel coronavirus that causes COVID-19. In June, NICE published a COVID-19 rapid evidence summary on vitamin D for COVID-19 which found that there was no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19. NICE advises that, in line with UK Government advice, everyone should have vitamin D intake equivalent to an average daily

intake of 10 micrograms (400 international units) to protect bone and muscle health. This advice suggests that everyone should consider taking a daily vitamin D supplement during autumn and winter. Also, people with little or no exposure to sunlight (including those shielding or self-isolating) or from an ethnic minority group with dark skin should consider taking a supplement all year round.

New evidence

A Spanish pilot randomised controlled trial has examined whether supplemental calcifediol (a vitamin D3 analogue), given to 76 adults (45 men and 31 non-pregnant women, mean age 53 years) consecutively hospitalised with COVID-19, affected intensive care unit (ICU) admission rates and mortality (Castillo et al. 2020). Diagnosis of SARS-CoV-2 with acute respiratory infection was by Polymerase Chain Reaction (PCR) test and radiographic evidence of pneumonia.

All study participants were given the treatments: hydroxychloroquine (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 5 days), azithromycin (500 mg orally for 5 days) and only for those patients who also had confirmed diagnosis of pneumonia and a NEWS score of at least 5, ceftriaxone (2 g intravenously every 24 hours for 5 days) was added. All participants were also randomised to oral calcifediol (0.532 mg on admission, 0.266 mg on days 3 and 7, then weekly until discharge or ICU admission) at a 2:1 ratio (n=50 in the vitamin D group and n=26 in the control group).

The study found a statistically significant reduction in admission to ICU favouring the vitamin D group (1/50 [2%] versus 13/26 [50%], p value [P] <0.001; univariate regression analysis odds ratio [OR] 0.02, 95% confidence interval [CI] 0.002 to 0.17). Due to statistically significant differences in baseline characteristics for 2 risk factors for unfavourable disease progression (diabetes and hypertension) between the 2 groups, an adjusted multivariate regression analysis was conducted which showed a similar result (OR 0.03, 95% CI 0.003 to 0.25). Mortality data was not assessed statistically: no deaths were reported in the vitamin D group compared with 2 deaths in the control group, for people admitted to ICU.

Several confounding factors were identified for the study. Observation bias may be a major factor in the study. The study is reported to be both open label and double-masked, with blind access to patient data for study data collectors and statisticians: specialists (not further defined) were not blind to allocation and no placebo was used in the control group. It is unclear if care staff and patients were aware of treatment allocation. Objective criteria for comorbidities, functioning, and clinical scores were reportedly used to decide who was admitted to the ICU; however, no data for these is reported. Additionally, a committee of intensivists, pulmonologists, internists and members of an ethics committee decided on who was admitted to ICU. This may bias the main outcome as committee members may have been aware of treatment allocation before a decision to admit to ICU was made. The validity and reliability for the odds ratios from the regression models cannot be assessed as details of, for example, model fit were not reported.

The serum vitamin D (25(OH)D) level of the participants was not assessed at any time during the study. The authors report that residents in the area where the study took place are relatively vitamin D deficient in late winter and early spring; however, the study recruitment period was not reported so it is unclear if any of the study participants were, or were likely to be, vitamin D deficient at time of entry to the study.

Body mass index was not measured by, or adjusted for, in the study. Public Health England (PHE) have reported an increased risk of adverse outcomes from COVID-19 in obese or morbidly obese people. In the UK a report on COVID-19 in critical care found that morbid obesity was present in 7.7% of patients critically unwell in ICU with COVID-19 compared with a rate of 2.9% of the general population.

Some prognostic factors for COVID-19 identified in the PHE report were assessed in the study (age, gender and comorbid illnesses) but some were not (socioeconomic factors, ethnicity, care home residence), or were significantly different (statistically significantly more diabetes and hypertension in the treatment group). However, in the control group there were more males (69%) than females (31%) compared to the vitamin D group which was

balanced (54% and 46%, males to females respectively). Working age males (aged 20 to 64 years) were identified in the PHE report as having twice the risk of death from COVID-19 illness compared with females.

Commentary provided by Professor Neil Gittoes, Consultant, Honorary Professor of Endocrinology and Associate Medical Director, University Hospitals Birmingham NHS Foundation Trust; Chair of NHS England specialised endocrinology Clinical Reference Group

This small, largely unblinded pilot RCT (Castillo et al. 2020) suggests that intensive care admission could be avoided in a cohort receiving a high dose vitamin D supplement. The study was not powered to show a difference in the secondary outcome of mortality. There have been a number of studies published about the links between vitamin D levels and increased rates or severity of COVID-19 illness; however, many of these are ecological studies using correlation, which are of low quality and have many limitations (for example they do not adjust for important factors such as ethnicity or Body Mass Index). A large UK retrospective observational study using UK Biobank data for over 340,000 people (Hastie et al. 2020a) found that, after adjustment for confounders, there was no link between serum vitamin D levels and susceptibility to COVID-19 infection. Similarly, a more recent paper using UK data from over 500,000 people (Hastie et al. 2020b) found no link between vitamin D levels and more severe illness or mortality from COVID-19.

While Castillo and colleagues provide the first RCT evidence for vitamin D supplementation in COVID-19 illness, the study has important limitations and there are large information gaps in what happened in the study. Important information on criteria for admission to ICU are omitted, as are data for length of stay and time to ICU admission, which could support, or not, the study's findings. No data was presented on what additional care was received by the people admitted to ICU or whether some patients were admitted to other settings for additional care (such as medical high dependency units). Occupancy of UK intensive care beds has been very high during the coronavirus pandemic so information on any unmet need for intensive care

during the study is important as the need for ICU admission may be confounded by its availability.

There are a number of ongoing trials of vitamin D supplementation, which will hopefully address the outstanding questions and perhaps provide more compelling evidence for using vitamin D, an appealing low risk potential intervention, to prevent or treat COVID-19 illness. In the meantime, people should be aware of the current government advice around vitamin D supplementation for bone and muscle health to ensure levels are optimal during the pandemic.

Declaration of interests:

Professor Neil Gittoes' declaration of interest in relation to this work can be found in the register of interests for the evidence summary. In addition, he is the task force co-chair of the International Workshop on Hypoparathyroidism and Primary Hyperparathyroidism guideline development group

Study sponsorship

No source of study funding was identified.

References

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