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Commentary on important new evidence from medicines awareness weekly

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Vitamin D levels and severity of COVID-19 illness

A new study (Maghbooli et al. 2020) found that serum vitamin D levels measured at admission to hospital in Iran in 235 adults with COVID-19 may be associated with illness severity. However, the study did not investigate the effect of giving vitamin D supplements and it has several confounding factors so the results should be interpreted with caution. The clinical management of people with COVID-19 should not be changed based on the results of this study and current UK Government advice should continue to be followed. Further studies are underway which will provide further evidence on the place of vitamin D in treating COVID-19 and NICE will review new evidence as it becomes available.

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 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

An observational study using cross-sectional analysis of prospectively collected data from a hospital registry (Maghbooli et al. 2020) included 235 adults (mean age 58.7 years) admitted to hospital in Iran with acute respiratory tract infection symptoms and a diagnosis of SARS-CoV-2 infection (using chest CT scan or RT-PCR). The study investigated the association between serum 25-hydroxyvitamin D (25(OH)D) levels and adverse clinical outcomes, including parameters of immune function and mortality.

A blood test taken at, or shortly after, hospital admission assessed 25(OH)D levels with a level of 30 ng/mL (75 nmols/L) or more, categorised as sufficient (32.8% of participants), 20 to 29 ng/mL (50 to 75 nmols/L) as insufficient and less than 20 ng/mL (50 nmols/L) as deficient. The study also collected data on participants age, sex, body mass index, smoking status, comorbidities, clinical symptoms and signs, radiology, and other laboratory tests. Clinical outcome was assessed by assigning people to three categories of mild-moderate, severe and critical COVID-19 illness severity on admission based on US Centers for Disease Control and Prevention (CDC) criteria. For the analysis, the people in the severe and critical groups were combined in to a single (severe) group (171/235, 72.8%) and compared with people in the mild-moderate group (64/235, 27.2%).

The study found that 122 of 158 (77.2%) people with an insufficient or deficient 25(OH)D level were classed as severe compared with 49 of 77 (63.6%) people who had a sufficient 25(OH)D level (relative risk [RR] 1.59, 95% confidence interval [CI] 1.05 to 2.41, p value [p]=0.02).

Fifteen other clinical outcome comparisons were conducted for sufficient versus insufficient or deficient 25(OH)D levels. Only four other clinical outcomes had statistically significant differences favouring sufficient 25(OH)D levels: unconsciousness (1.3% versus 8.2%, p=0.03), hypoxia in those aged over 40 years (19.4% versus 39.2%, p=0.004), a C-reactive protein (CRP)

greater than 40 mg/L (61.0% versus 77.2%, p=0.01), and lymphocyte percentage <20% (45.5% versus 60.1%, p=0.03).

Thirty-four people died from COVID-19 in the study and all were older than 40 years. The study reports that 9.7% of those with a sufficient 25(OH)D level aged over 40 years died compared with 20% of those who had an insufficient or deficient 25(OH)D level (p=0.04).

The study has several major confounding factors. Firstly, it is at risk of sampling bias because it includes only 235 people out of 611 reported to be on the registry. It is unclear if the other 376 people on the registry had a 25(OH)D level measured and, if not, why this was not done in what is reported to be a prospective registry study. It is also unclear if the 235 people included in the study were recruited consecutively or are representative of the larger number in the registry because no baseline comparison between the 2 groups is presented. The study was conducted in Iran and this population may not be representative of people hospitalised in the UK with COVID-19. The mean age of the study population (58.7 years) was much younger than that in a study (Docherty et al. 2020) reporting the average age of people admitted to hospital with COVID-19 in the UK (median age 73 years).

It is unclear why the authors chose to combine the severe and critical categories of CDC severity for the analysis because these categories are clinically distinct. Combining the categories allows for the logistic regression analyses used but these analyses do not take account of the ordinal nature of the outcomes (mild-moderate, severe and critical). It may have been more appropriate if the analysis had not combined the categories and had used an ordinal logistic regression for ranked categorical outcomes with more than 2 categories.

Although the authors report that they have adjusted the model to take account of some of the prognostic factors for COVID-19 identified by Public Health England (age, sex, smoking, comorbidity and obesity), the study does not report adjustment for other known important prognostic factors, such as concomitant use of immune suppressing treatments, ethnicity, and socioeconomic factors (job, income or place of residence). The validity and

reliability for the relative risks from the regression model cannot be assessed because details of, for example, model fit were not reported.

The study reports using appropriate tests of statistical significance for categorical and continuous data. However, the use of multiple significance tests increases the risk of type I error in the study (a false positive result), particularly at a low level of statistical significance (such as the 0.05 level used) in an observational study.

The mortality analysis raises concerns because it appears to be a post-hoc analysis based on an in study observation that nobody under the age of 40 years died during the study and, subsequently, people under 40 years were excluded from the analysis. This is problematic because many more of those excluded had low levels (insufficient or deficient) of 25(OH)D and survived compared with those with sufficient 25(OH)D levels. This means the subsequent analysis produces a more favourable (and statistically significant), but biased, estimate of the difference in mortality between groups in the study. No analysis of mortality for the full cohort is reported.

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

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. 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. Also, a more recent paper using similar UK data (Hastie et al. 2020b) found no link between vitamin D levels and more severe illness or mortality from COVID-19 after adjustment for confounders.

There is currently no agreed definition of what constitutes vitamin D sufficiency or deficiency in relation to COVID-19 illness. Maghbooli and colleagues use a 30 ng/mL (75 nmols/L) cut off, which is relatively high. The 2016 Scientific Advisory Committee on Nutrition report on vitamin D and health concluded that people with serum or plasma 25(OH)D levels below 25 nmol/L (10 ng/mL) are at increased risk of poor musculoskeletal health outcomes, including rickets and osteomalacia. To protect musculoskeletal health, they recommend that serum or plasma 25(OH)D levels should not fall below 25 nmol/L at any time of the year.

Although Maghbooli and colleagues provide evidence for an association between serum vitamin D levels on admission to hospital and severity of COVID-19 illness, the study has important limitations and there are large information gaps in what happened in the study. Important information on the selection and inclusion of people in the study are omitted. The type of regression analysis used and the way in which data were combined, analysed and reported, particularly for the outcome of mortality, are problematic.

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 UK 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.

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