Vitamin D for Preventive and Adjunct Therapy for Mitigation of Early Stages of Severe Acute Respiratory Syndrome due to COVID-19 (SARS-CoV-2)

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Summary Statement from ASPHER

The use of Vitamin D supplementation by the general population may be useful in the interests of protecting bone health and in increasing resistance to a wide range of infections, especially of the respiratory tract.

The most effective and least costly means by which this can be done is through fortification of milk products, as practiced in Canada, the US, Finland for many decades in total.

Vitamin D supplementation is particularly recommended for populations at increased risk from vitamin D deficiency; risk factors include advanced age, ethnicity, skin colour, poverty, obesity, living at high latitude, lack of exposure to sunlight and being in long term care.

Although conclusive evidence must come from ongoing clinical trials, the fact is that there is growing evidence of a protective effect of Vitamin D for patients with SARS-COV-2 infections, and given that it is a safe and inexpensive prophylactic treatment, we consider it sensible to use it as part of the treatment of COVID-19 symptoms.

We present this report as the first ASPHER statement and for consultation. We invite other learned medical societies to join with us in endorsing this statement, to further develop the consensus, and commit to further research on this important public health issue.

Background

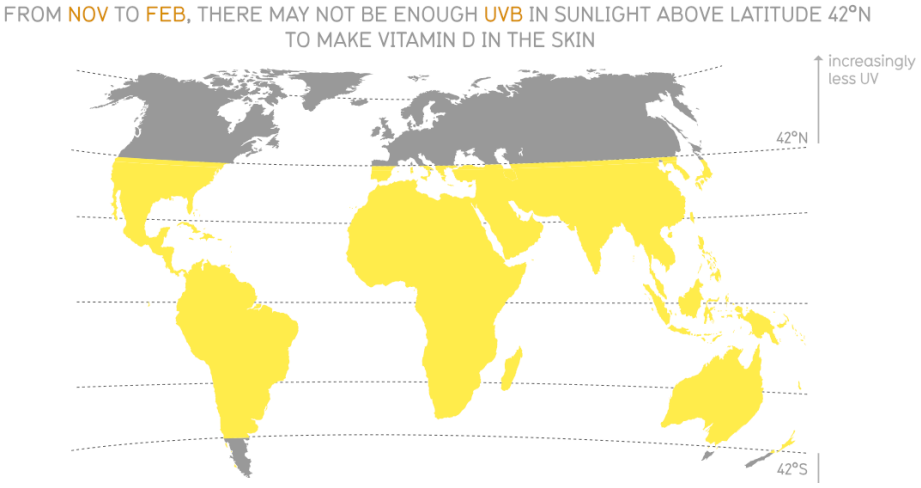
Vitamin D has long been recognized for its benefits to bone health, for prevention of rickets in children, osteoporosis in adults and the elderly[1] and reducing rates of fractures in the elderly.[2] Vitamin D also has proven hormonal activity which may reduce severity of infections particularly by promoting immune responses that lower viral replication rates and increase natural host immunity[3,4] Vitamin D can reduce levels of pro-inflammatory cytokines that cause severe inflammation which may result in severe injury of the lungs, heart and other vital organs, frequently leading to death.[5] Observational studies, metanalysis and clinical trials report that Vitamin D supplementation for patients with deficiency levels of vitamin D reduce the severity of lung disease associated with influenza, viral respiratory infections, rhinosinusitis, chronic rhinitis, asthma, COPD, and TB, and should be considered in the context of COVID-19.[6,7] There is therefore a growing interest in a potential role for Vitamin D as part of prevention and treatment of serious acute respiratory syndrome disease, specifically for COVID-19.[8]

Commentaries and case reports on the role of Vitamin D in COVID-19[9,10,11] support the view expressed by Razdan et al[12] that: "*Dearth of treatment for COVID-19 leaves us*

with no choice but to take precautionary and prophylactic measures to stand a better chance to fight this pandemic. Hence, maintaining adequate Vit D levels is vital to prevent getting infected or to ward off the infection without mortality." Whether Vitamin D supplements can act prophylactically or therapeutically in mitigating the development and outcomes of SARS CoV-2 infections of the COVID-19 pandemic, is raised in a rapidly growing number of publications.

It is noteworthy that the risk factors for vitamin D deficiency and severe COVID-19 markedly overlap, factors such as advanced age, ethnicity, skin colour, poverty, obesity, living at high latitude and lack of exposure to sunlight (Figure 1).[7,13] A study by Spiro et al reports that high percentages of European populations have low vitamin D levels by accepted international definitions, "*especially among: pregnant and breastfeeding women; teenagers and young women; infants and young children under 5 years of age; older people aged 65 years and over; people who have low or no exposure to the sun,* e.g. *those who cover their skin for cultural reason or who are housebound or confined indoors for long periods; people who have darker skin,* e.g. *people of African, African-Caribbean and South Asian origin and living in Europe, because their bodies are not able to make as much vitamin D.*"[14] This has encouraged respected medical organizations such as the French Academy of Medicine to recommend as policy that vitamin D supplementation be used as a preventive and therapeutic supplement for early stages of Severe Acute Respiratory Syndrome due to COVID-19.[15]

Figure 1: Lack of sufficient UVB sunlight to make Vitamin D in the skin across most of Europe in winter months



Source: US National Institutes of Health, PubMed, Harvard Medical School. Figure used with permission from Information is Beautiful. See https://informationisbeautiful.net/visualizations/vitamin-d/ for aditional infographic on sources of Vitamin D and how it may promote health (Accessed 27 November 2020).

Braiman's review of the northern to southern variation in European distribution of COVID-19 mortality indicates higher mortality rates in southern European countries where vitamin D levels are lower, while northern countries where Vitamin D fortification is part of national food standards have lower rates of COVID mortality.[13] A report by Laird extends this study to examine national vitamin D levels in Europe

showing: "*circumstantial and experimental evidence suggests that vitamin D may have an important supportive role for the immune system, particularly in regulating cytokine response to pathogens. Vitamin D levels are low in countries in Europe which have high infection and mortality rates. Optimising vitamin D status to recommendations by national and international public health agencies will certainly have benefits for bone health and potential benefits for Covid19. There is a strong plausible biological hypothesis and evolving epidemiological data supporting a role for vitamin D in Covid-19*"[16]

Nursing home populations have suffered high rates of COVID-19 mortality. In Canada, where over 50% of total COVID mortality was amongst the nursing home and long-term care (LTC) population, a study reported by Lapointe-Shaw et al in JAMA found that mortality rates were many folds greater for the nursing home and LTC aged.as compared to similar age population in community-living situations.[17] This same LTC community is also known to be at much higher risk than the general community for vitamin D deficiency. A recent Swedish study showed 41% of residents of nursing homes had deficient levels of Vitamin D, and a strong association with dementia.[18]

Joliffe reports in a broad review and metanalysis of RCTs on Vitamin D's protective effects for reducing acute respiratory infective conditions and examines the relevance of Vitamin D to COVID-19. The conclusion drawn from 40 accepted RCTs was that: "*Vitamin D supplementation was safe and reduced risk of Acute Respiratory Infections, despite evidence of significant heterogeneity across trials…., The relevance of these findings to COVID-19 is not known and requires investigation*."[19]

Limited, recent preliminary result on Vitamin D effects on COVID-19 severity is now beginning to arrive. An ongoing RCT from Spain by Quesada-Gomez et al reported in mid-September 2020 that high dose of 25-hydroxyvitamin D, significantly reduced the need for ICU treatment of patients requiring hospitalization in comparison with a usual treatment control group, both with proven COVID-19 infection.[20] A further small pilot RCT, by Castillo et al reported in mid-September 2020 that Vitamin D supplements "significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19.[21] Both studies concluded that vitamin D seems to be able to reduce severity of the disease, but larger trials with groups properly matched will be required to show a definitive answer.

Caution must still be advised, as another RCT based in Boston and reported in the New England J Medicine in 2020 showed that large doses of vitamin D supplements failed to reduce length of hospital stay and mortality rates for ventilated severe cases of COVID-19. The study included critically ill patients in ICUs in 44 hospitals in the US recruited from patients with low vitamin D levels divided into treatment and control groups. The treatment group received high dose vitamin D supplements and the control group usual care, with standard vitamin D supplements.[22] However, this study included patients already at a critical clinical stage of the disease, and did not address whether vitamin D is useful in boosting deficiencies in Vitamin D levels before people fall ill and in early stages of disease after infection.

Although the potential for benefits of Vitamin D supplements for COVID-19 patients are not yet proven by randomized clinical trials, a number of such trials are currently underway and recruiting patients including several United States locations,[23,24,25] as well as Angers University in France[26], Grenada University in Spain[27], and Queen Mary University in the UK[28].

Discussion

Without supplementation, several population groups are classically known to have low levels of Vitamin D, including the elderly, refugees and others with dark skin colouring, children, adults at risk of osteomalacia and osteoporosis. This deficit, due to lack of exposure to sunlight, is amplified by lockdowns as well as by geographic and seasonal factors, including in sunny countries. Low Vitamin D levels are common in Europe, and other regions in all age groups. Effects are amplified with seasonal variation, particularly in countries with long and severe winters, reducing sun exposure, migration of dark-skinned people to high latitude countries lacking mandatory food fortification.[29]

Fortification of milk with vitamin D has been standard practice since the 1930s and 1940s in North America.[30,31] The European Calcified Tissue Society reviewed the Vitamin D inadequacy in Europe and the Middle East calling for fortication of milk or flour and routine supplements for the elderly population and other high risk groups.[32] While this review was published in 2019 and thus not aware of the coming storm of the COVID-19 pandemic that struck hard in Europe, their plea is for recognition of the public health of the broad population vitamin D needs, which is also within the mandate for nutritional public health of ASPHER.[33]

A Joint guidance on vitamin D in the era of COVID-19 was issued from the American Society for Bone and Mineral Research (ASBMR), Endocrine Society, American Association of Clinical Endocrinologists (AACE), European Calcified Tissue Society (ECTS), the National Osteoporosis Foundation (NOF), and the International Osteoporosis Foundation (IOF), in July 2020.[34] The following summarizes their views:

> *The current data do not provide any evidence that vitamin D supplementation will help prevent or treat COVID-19 infection; however, our guidance does not preclude further study of the potential effects of vitamin D on COVID-19.*
>
> *Research to date suggests that vitamin D may play a role in enhancing the immune response, and given prior work demonstrating a role for the activated form of vitamin* D *[1,25(OH)2D] in immune responses, further research into vitamin D supplementation in COVID-19 disease is warranted.*
>
> *Vitamin D is very safe when taken at reasonable dosages and is important for musculoskeletal health. Levels are likely to decline as individuals reduce outside activity (and so sun exposure) during the pandemic. Most older and younger adults can safely take 400-1000 IU daily to keep vitamin D levels within the optimal range as recommended by Institute of Medicine guidelines.*

The French Academy of Medicine, mentioned above, recommends vitamin D supplementation of 50,000 to 100,000 IU loading dose in people above 60 and 800 to 1000 IU/day in people below 60, as soon as they are positively diagnosed with COVID-19 in order to limit the respiratory complications.[15]

In view of evidence of low levels of vitamin D in European population groups, Vitamin D supplementation is recommended for European populations especially among the elderly and other high-risk groups[14] exposed to COVID-19 including healthcare workers and other occupational groups, people with chronic medical conditions for general health support and with hope to mitigate COVID-19 disease severity. Low vitamin D levels could be considered a pre-existing health condition adding to other risk factors for severe COVID disease. Addressing this problem will have benefit for infectious disease control including for corona virus pandemics, past present and future.

Public health policies in Europe should consider adoption of mandatory fortification of milk or flour with vitamin D to support general population health needs, along with fortification of flour with iron, vitamin B complex, and Folic Acid (the latter to prevent neural tube defects).

Further studies of micronutrient deficiency conditions are important for public health in the European Region in the in the coming decades, both for the current pandemic and others that may be anticipated.

Summary

Vitamin D levels in the European populations are low by recognized international norms. A growing body of professional opinion believes that vitamin D supplements should be recommended to mitigate illnesses due to severe acute respiratory syndrome (SARS) including COVID-19 and to promote general population health.

SARS CoV-2 (COVID-19) infection can cause serious lung injury in the form of acute respiratory distress in about 30% of severe cases, frequently resulting in death. Significant evidence is available in scientific literature regarding use of Vitamin D for the prophylactic treatment of respiratory illness.

Further efforts are needed in producing scientific evidence on the potential effect of Vitamin-D in the treatment of Covid-19 patients.

Conclusion:

Despite the lack of convincing evidence from Randomised Clinical Trials published to date, there is a persuasive cumulation of individually non-conclusive studies and rationales of the role of Vitamin D in mobilizing bodily defences against infection and severe cytokine response in overwhelming systems failure. The high-risk groups for vitamin D deficiency are also those groups at risk for COVID-19 infection and severe outcomes. There is general agreement that vitamin D supplements and food fortification as practiced for hundreds of millions of people for more than five decades at recommended levels cause no harm.

Thus, ASPHER has reached consensus for a proactive public health response to prepare the public health profession and relevant institutions and the general population for inclusion of vitamin D wellness in response to COVID-19, to be kept in place for any future invasion of a similar catastrophic pandemic.

The vulnerable groups with vitamin D deficiency have a pre-existing risk factor for COVID-19 severity. This recommendation is based on accepting that population groups at special risk in this high mortality pandemic can benefit from accepting Vitamin D as adjunct prophylactic therapy to mitigate severity of COVID-19 cases. Low sun exposure and low vitamin D are common in high risk groups found or deemed vulnerable to COVID-19 in Europe generally, but even more so in people in institutional settings or house-bound. Defecits will only be worsened by quarantine or lock down situations and for hospitalized patients.

Public health policies in Europe should consider mandatory fortification of milk or flour with vitamin D to support general population health needs of bone and immunologic health as well as for resistance to COVD-19 infection and mitigation of severity.

Further studies of micronutrient deficiency conditions are important for public health in the European Region in the coming decades of the 21st century, both for the current pandemic and others that may be anticipated.

Recommendations

ASPHER is in favour of joining with the French Academy of Medicine and other international voices cited above in the following measures:

1. Monitoring of micronutrients including Vitamin D as part of public health's basic responsibility;
2. Public health should define adequate Vitamin D levels in specific population age and gender groups as part of a public health approach to prevention of COVID-19 in high risk groups and the general population;
3. Public Health should strongly support the development of scientific research programmes on the short- and long-term effects of Vitamin-D in Covid-19 prevention and care of Covid-19 patients.
4. Promoting awareness in medical and public media to stress the importance of Vitamin D care especially for COVID-19 high risk groups;
5. Government agencies responsible for supervision of nursing homes and long-term care residential facilities should mandate daily sun exposure, as feasible, and Vitamin D supplements as integral for care of the aged in such facilities;
6. Promoting awareness and pro-active participation by ASPHER member schools of public health in policy formation in their home countries regarding public health nutrition in issues related to supplementation and food fortification in the context of international best practices;
7. Encourage ASPHER member schools to review the curriculum content and faculty awareness of public health nutrition.
8. Work with other learned medical societies, to enhance the scientific consensus n these issues.

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