EDITORIAL

VITAMIN D
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Dear Readers,
I hope this new issue finds you all well.
Once again, we present important contributions on two topics of great relevance in the field of possible extra skeletal effects of vitamin D: an update on the relationship between vitamin D and muscle and another on its connection with asthma and with respiratory infections, which represent one of the major causes of the exacerbation of asthma; indeed, the latter topic could not but elicit references to the theme on everyone's mind today – the COVID-19 infection.
As you can see from the bibliographical selection of this issue, we deemed it correct to devote some space to the many publications on vitamin D and COVID-19. The debate currently in progress concerns two aspects in particular: is it possible that vitamin D status conditions the risk of COVID-19 infection and/or its clinical manifestations?
As you well know, the rational premises for such a connection are in place. Indeed, the state of our current knowledge allows us to summarize the following points, the first of which are general and the latter more specific:

- general:
  - *in vitro* studies have shown that vitamin D improves the innate immune response, such as the macrophage response, and can increase antiviral defense by stimulating the production of antimicrobial peptides such as cathelicidin and β-defensin;
  - observational studies have provided evidence of an association between low serum levels of 25(OH)D and susceptibility to respiratory infections;
  - a recent meta-analysis has shown that daily or weekly vitamin D supplementation significantly reduces the risk of contracting acute infections of the respiratory tracts, and in particular in subjects with vitamin D deficiency (which is not at all surprising);
  - researchers and institutes, including the AIFA, recognize that vitamin D has an "immunomodulatory" effect; in particular, vitamin D has been shown to be able to attenuate adaptive immune response, especially from cytokines (above all IL-6), by reducing the reaction of the acute post-viral phase, which when pronounced contributes to the pathogenesis of the most serious clinical manifestations of the viral infection (so-called "friendly fire" damage);
  - vitamin D supplementation in patients undergoing mechanical ventilation for various causes has been proven to be able to reduce the duration of hospitalization as well as PCR and IL6 levels;
- specific for COVID-19:
  - higher mortality in the countries of southern Europe (Italy and Spain), which are known for a greater prevalence of vitamin D deficiency, compared to those of northern Europe (Germany, Norway, Finland and Iceland) whose dietary intake of vitamin D is greater, thanks in part to the regular practice of fortifying foods;
  - greater prevalence of COVID-19 infections in the regions of northern Italy, with respect to the sunnier ones of the south or to the greater exposure to the sun of populations below the 35th parallel;
  - a particular incidence and seriousness of the infection in the elderly, in whom hypovita-

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minosis D is notoriously and historically endemic, especially in the months of winter and early spring; hypovitaminosis D is dramatically and chronically present during long-term hospitalization;
- obesity, which is often associated with hypovitaminosis D, has been shown to be a significant risk factor for COVID-19 morbidity and mortality;
- an inverse correlation between serum vitamin levels and incidence of and mortality from COVID-19;
- an inverse relationship between 25(OH) D levels and the severity of systemic inflammation and clinical manifestations in patients hospitalized for COVID-19, even if we must admit here that it is known that phlogosis by itself reduces measurable 25(OH)D levels;
- modulation on the part of vitamin D of the renin–angiotensin system and the expression of the ACE2 receptor, recognized as the entry point of the virus into human cells.

As you see, there is biological plausibility for a protective role of vitamin D with regard to the risk and/or seriousness of the clinical manifestations of COVID-19 infections.
Plausibility, however, is not enough.
Hasty and general proclamations about a protective role of vitamin D which are not supported by appropriate and specific scientific evidence have already led Italy's Ministry of Health to characterize this supposed connection as a hoax. And yet I would not immediately rule out the possibility of benefits because, conversely, we have no scientific evidence proving that vitamin D does not have an effect. While we await the results of the specific trials that are currently underway, to actually discourage safe and cost-effective vitamin D supplementation, especially in the elderly or in those forced to remain at home or in hospital, does not seem to me to be opportune during COVID-19 emergency conditions, in particular if we at least consider its recognized skeletal benefits.
Among other things, I worry about the reduction of over 30% of vitamin D supplementation observed in the first months of the year, including in the elderly, in the wake of AIFA's publication of "note 96", which ignores advanced age as a risk factor for hypovitaminosis D, not taking into consideration the progressive reduction of the skin's ability to synthesize vitamin D from the age of 60 (my age!) and the seasonal nadir. Perhaps it is just an unfortunate coincidence that these two factors played a role in the peak of the COVID-19 infection in Italy. In any case, the question presents us with another reason for worrying about the skeletal health of the elderly.
What do you think?
I hope you enjoy reading this issue.