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## Better prepare for the next one. Lifestyle lessons from the COVID-19 pandemic



Scientific journals are being publishing research articles on Severe Acute Respiratory Syndrome Associated Coronavirus (SARS-CoV) since 2003. As an example, Web of Science currently collects almost 3,500 publications, many from 2004, 2005, 2006, then gradually declining with a nadir in 2014. In 2020, we are witnessing a large publication rebound.

It is clear that the scientific knowledge accumulated during these years has not been useful in avoiding the current SARS-CoV-2 (COVID-19) pandemic, either by not providing the necessary solutions or because the rulers, whose responsibility is to protect health and well-being of their people, have not been aware of some useful information likely disseminated among the aforementioned 3,500 publications.

This is the right time to better shape our future health. While societies around the world are fighting the virus and healthcare systems are desperately caring for the sick to try to prevent them from dying, we should think about the future, which will be just as troubling as the present if we don't prepare for similar public health emergencies.

Unfortunately, to date, confinement is the best tool we have to stop the COVID-19 pandemic, a clear indicator of the impotence of modern medicine. Pandemics such as this one are commonplace in human history and we will not avoid future ones.

Confinement profoundly modifies the behavior and, therefore, the habitual lifestyles of individuals and communities, in restrictive terms. The COVID-19 pandemic has caused people to be exposed to adverse environmental conditions, not previously experienced. This brings about relevant stress, whose health consequences are yet to be elucidated [1,2]. Among the main consequences of confinement are noxious conditions such as the lack of positive relationships and interactions; of physiological stimuli; of objectives and goals to be achieved; of creative ideas and opportunities; of changes in chronobiological rhythms and perceptions; of air quality (often for the better); feelings of anxiety and fear; and very importantly, functional and metabolic impairments dictated by a sedentary lifestyle. These effects are slowly evolving and, hence, it is difficult to imagine what their future consequences will be. Changes in the neuroendocrine and immune setting produce adaptive and compensatory responses the effects of which last for months, may be for generations (epigenetics changes generated through major nutritional and lifestyle challenges, such as severe malnutrition or tobacco smoking in women, have been evoked as the cause behind the association with higher incidence of chronic diseases, such as diabetes and cardiovascular diseases, through two or more generations [3]). In other words, these changes in lifestyles occur now, during this phase of Covid-19 pandemics, but their effects are expected to translate into physical and psychological consequences that will last for a long time after the crisis, potentially representing an emergency in the emergency worth considering for its impact on health systems as well as on social and financial policies of the different regions.

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Unlike the seasonal viral infections responsible for influenza epidemics that have accustomed us to consider vaccines as a safe and timely solution, or other infections such as HIV or hepatitis C that we treat with state-of-the-art antiviral agents, COVID-19 and its respiratory aftermaths must be considered as potentially incurable. In fact, during the relatively short evolution of this pandemic, it has not yet been possible to develop a vaccine or identify truly effective drugs against this virus.

Of the epidemiological characteristics of this infection, greater incidents and risks to human health are observed in adults over 65 years of age with concomitant pathologies and in the frail elderly. Frailty can be multifaceted, but we must keenly analyze sub-optimal lifestyles as associated with age [4]. Indeed, it is quite clear that passive protection measures designed to physically reduce exposure to the viral agent are not sufficient to face an emergency scenario like the current one and its "long wave" of health effects. Therefore, proactive measures are necessary based on the definition of protection and prevention strategy that allows counteracting infections with an optimal state of health, from the immunity point of view.

Healthy lifestyles and nutrition are crucial to augment the immune system (immune-fitness) and, therefore, to effectively respond to viral infections; repair the inflammatory and degenerative lesions that they generate in the respiratory tract; and restore homeostasis of the metabolic processes and the immune system itself [5]. In this context, immuno-protection is the cornerstone of medical practice and should not be overlooked in either the presence and the absence of threats like the one we face today. The preservation of the immune system must be a strategic measure of public health and a priority issue of research policies as well as of social and clinical management of lifespan extension worldwide.

Healthy aging policies must aim at reducing chronic diseases, mental health disorders, disability, and frailty. This requires that infrastructures and economic and social determinants of health be implemented, for example, through greater investment in educational programs and social services that lead to the necessary changes of lifestyles. The advent of breakthrough information-communication technologies and artificial intelligence in the last decades facilitates the process also paving the way to other waves of innovations to face this and other societal challenge of the "aging" era.

How can we improve our lifestyles and act proactively to strengthen the immune system and, therefore, prepare for future, unavoidable infections with the best of our immune potential?

We can think of using two tools: classic nutrition and precision nutrition.

Classic nutrition factors include:

### 1 Protein energy malnutrition

- 2 Specific deficiencies of micronutrient vitamins
- 3 Sedentary lifestyle, overweight-obesity and metabolic diseases.
- 4 Exposure to environmental immuno-interfering factors (tobacco smoke, alcohol consumption, substances of abuse and drugs, environmental pollutants, and others)

Precision nutrition is now moving the attention to molecular aspects of the discipline to embody the “P4” concept of modern medicine (predictive, preventative, personalized, participatory). This is a paradigm revolution in human nutrition that will benefit of a new generation of omics techniques that surely will innovate, possibly rewriting, the nutritional approaches to successful aging and immunoprevention strategies.

Some examples of these items include:

- 1 Protein energy malnutrition (PEM). The risk of developing this condition increases with age and becomes particularly high in conditions of severe illness and immobilization or significant reduction in physical activity. The presence of PEM increases the risk of frailty in the elderly and, therefore, of severe comorbidity and death. This picture is generally associated with severe alterations of the immune response that begin with a reduction in the number of white blood cells (leukopenia), which, together with serum albumin levels, is one of the main indicators of PEM; at the somatic level, the main indicator of PEM is a reduction in lean body mass, that is, muscle mass. The latter becomes particularly apparent as a reduction in the musculature of some parts of the body, such as the muscles of the leg and in particular of the thigh or the quadriceps; also, those of the arms and trunk can rapidly suggest an onset of the phenomenon. This process denotes an alteration of the metabolic and energy management processes (metabolic reprogramming) that lead to the use of muscle and other tissue proteins as energy source rather than as functional components (for example, as a support for muscle contraction). This occurs because the physiological processes nutrient (particularly glucose) use for energy – in the presence of altered insulin function – taper off. This energy reprogramming is one of the main endocrine consequences and aging and its sequelae accelerate in case of chronic inflammation (microinflammation) and immunocompromise [6].
- 2 Micronutrient and vitamin deficiency. The importance of nutritional factors and, in particular, of some micronutrients to guarantee an optimal function of the immune system is well known [7]. Specific deficiencies of vitamins and trace elements with a marked immunomodulatory action are observed in Western countries and, in particular, in the elderly. In Spain and Italy, one of the countries that should theoretically follow ideal lifestyles (those part of the Mediterranean Diet), the same deficiencies of other Western countries are now observed, consequent to the globalization of food production and supply systems [8,9]. These unavoidable developments reduce the consumption of nutritional factors with a positive action on the immune system, while providing an excess of caloric intake and, therefore, higher risk of developing overweight, obesity, and metabolic diseases that, in turn, promote secondary immunodeficiency conditions. In summary, the Mediterranean and Western diets are now often high in calories and low in micronutrients, a condition that can lead to malnutrition, similar to that described above for protein [10]. Vitamins such as A, B<sub>6</sub>, B<sub>12</sub>, C, D, E and folic acid and minerals like zinc, iron, selenium, magnesium and copper are factors and cofactors of many enzymes involved in immune processes. In addition, they participate in the production of antimicrobial proteins and in the activity of cells such as neutrophils and macrophages. Fatty acids of the omega 3 series, which are essential, are the precursors of many molecules, e.g. resolvins, proteins and maresins, that accelerate the resolution of inflammatory processes [11].
- 3 Sedentary lifestyle, overweight/obesity, and metabolic diseases.

Sedentary lifestyles and obesity are important risk factors for the development of cardiometabolic diseases and for an accelerated decrease in immunoinflammatory homeostasis in all age groups, particularly in the elderly. The last phenomenon - called immunosenescence - is responsible for the increased susceptibility to infectious diseases seen in those over 65 years of age [12].

- 4 Exposure to environmental immune interference. There are numerous environmental factors responsible for immunosuppression, whose actions add to those of aging, and which might lead to the so-called forms of secondary immunodeficiency [13]. Recently, the importance of epigenetic factors is emerging, in particular, in their relevance to the susceptibility to viral infections.
- 5 Intestinal dysbiosis. A healthy microbiota contributes to the maintenance of the immune system, much of which contributes to the immune response through B and T cells. To corroborate this theory, 2 to 10% of Chinese SARS-Cov patients experienced gastrointestinal symptoms at start [14]. Coronaviruses, including Covid-19, bind to the angiotensin-converting enzyme 2 (ACE2) from the intestinal epithelium and use it as a receptor. The intensity of this link seems to be related to the state of health of the intestinal microbiota. Physicians should be aware that provision of selected probiotics might strengthen the immune response, although full confirmation by human trials is still needed [15,16].
- 6 Parallel to the development of precision therapies in medicine, precision nutrition is an emerging science that is based on well-established factors such as genetic, epigenetic, and microbiome individual variations [17]. Numerous molecular studies are providing mechanistic insight into precision nutrition. As very specific therapeutic objectives must be achieved, precision nutrition must be based on food products with well-established mechanisms of action at the molecular level in terms of gene expression and modulation, and signaling pathways. This includes modulating the response of the immune system through activation of innate immune responses, considering that personal genetic profiles affect immune variables.

We believe it important that future studies include the verification of the nutritional status of the subjects before interventions, via the development of screening tests with reliable protocols and indicators, using omics techniques. These indicators should include both PEM and vitamin status, with complete metabolic and transcriptomic panels dedicated to the expected immune response of the intervention [18]. This approach should also be used for the microbiome and lipidome and for the assessment of genetic profiles.

Paying more attention to the introduction of micronutrients and vitamins is the only immunoprotection strategy we have available and for which there is sufficient evidence available on both the effectiveness and safety of the intervention. The recommended protocol includes optimizing the consumption of these compounds, particularly by the elderly and by pregnant women, in whom the epigenetic effects may be more pronounced. In some cases, the possibility of supplementation, particularly with vitamin D (which is synthesized by sun exposure, often insufficient during the winter season); with long-chain omega 3 fatty acids in subjects who do not usually consume fish; vitamin C to ensure intakes of 200 mg/d (maximum bioavailability); and appropriate probiotics to maintain a state of eubiosis.

Obviously, this strategy must be combined with healthy lifestyles, a balanced diet, regular physical activity and a reduction in exposure to other environmental factors with a negative effect on immunity and, more generally, on human health (described above). The possibility of obtaining a positive synergy in the effects of these interventions is very high and should be considered as an urgent measure that should be taken together with the others identified to date. We hope that this COVID-19 crisis will change the priorities of humanity and society and that we can take this opportunity to foster research aimed at guiding public health policies. Will we be ready next time?

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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