Inmunophysiology and exercise in "times of COVID"

Inmunofisiología y ejercicio en "tiempos de COVID"

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In "times of COVID", the importance of the Immune System has caught everyone's attention. Until now it was the great unknown of the physiological systems, surprisingly even among the medical community. We have understood and assimilated that, in the face of an attack by pathogens, and virus in particular (given that antibiotics are not effective) and most importantly during an initial contact or infection, no longer at an individual level but at a human level, our most effective weapon is the Immune System and the responses that it generates. The correct functioning of this system is also essential in order to generate an effective and correct response to vaccines. Physical exercise that is well-chosen and practised in a selected sports discipline, is the non-pharmacological strategy that has accumulated the greatest scientific evidence with regard to its beneficial effects (and also potential undesired side effects) on the Immune System, particularly in the prevention of infectious diseases. In fact, the *"International Society of Exercise Immunology"* (Padeborn, 1993) and its publication "Exercise Immunology" are of the greatest relevance in the context of Sports Sciences and Sports Medicine.

However, the Immune System also operates physiologically on health conditions, and the concept of Immunophysiology goes beyond the mere functioning of this system. This refers to the bidirectional interactions between the immune, nervous and endocrine systems, which are fundamentally mediated by the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. These are known as immune-neuroendocrine interactions and neuroimmunomodulation. Without forgetting the fact that it also creates a situation of physiological stress, physical exercise regulates the said interactions both homeostatically and homeorhetically. Regulation is therefore different, depending on conditions of health or from an attack by pathogens and/or in the presence of other situations of physical or psychological stress. The dysregulation of these immune-neuroendocrine interactions clearly affects the course and prognosis of infectious, autoimmune and inflammatory diseases, including what is termed "low-grade inflammation"[1-3]. In this context, macrophages, glucocorticoids and catecholamines, together with inflammatory cytokines, are the most relevant immunophysiological players. In the nineties, it had already been demonstrated that the effects of exercise on macrophages were mediated by glucocorticoids and catecholamines[4-6]. It was thus established that the effects of exercise on the innate/inflammatory immune response were regulated by neuroendrocrine stress mediators[7]. More recently, we defined the bioregulatory effects of exercise as "those effects that mitigate or prevent an excessive inflammatory response and stimulate, or do not impair, the innate defences against pathogens, by generating immunophysiological adaptations through an optimal balance between the pro- and the anti-inflamatory responses and optimal transitions between macrophages in the tissues"[1]. Glucocorticoids and catecholamines (particularly noradrenaline) are able to measure the stimulation of the innate defenses against pathogens and, in turn, to regulate and prevent an exacerbation of the inflammatory response of the magrophages, avoiding what is known as "sterile inflammation" or hyperinflammation caused by excess response. Therefore, in an immunophysiological context, good "training of the immune system" through exercise, will make us less prone to infection and allow us to avoide "sterile inflammation" and, where appropriate, exacerbated hyperinflammatory responses. This is far more significant in obese individuals, with underlying low-grade chronic inflammation and a dysregulation of the interactions between the innate/inflammatory and stress responses[8].

What is known as the "cytokine storm" appears to underlie a dysregulated process of the macrophage function, triggering a

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hyperinflammatory condition in severe cases of COVID-19. This uncontrolled systemic (and also local) inflammatory response provokes increased circulating inflammatory cytokines[9] and, in all likelihood, an imbalance in the pro-inflammatory and anti-inflammatory cytokines, observing high levels of IL-6, particularly in obese individuals[10]. Today, we are now able to respond clearly and reliably to the following questions: Has serious COVID-19 been characterised, among other aspects, by hyperinflammation underlying a macrophage activation syndrome with high levels, for example, of IL-6? Yes. Have obese individuals been more prone to COVID-19 and did they have a worse prognosis for the disease? Yes. Do obese individuals have greater baseline levels of inflammatory cykotines such as IL-6 and a dysregulation of the interaction of this cykotine with stress mediators such as noradrenaline and glucocorticoids? Yes. Were the "anti-IL-6" and glucocorticoids among the most effective and most used drugs to prevent a serious or fatal outcome? Yes. And finally, based on scientific evidence, can obese individuals, through a good bioregulation of the innate/inflammatory response, be better protected against being infected by SARS-COV-2 and prevent a serious prognosis of infection by actively performing physical exercise? This is quite clear.... particularly in "COVID times" in which all we have is our Immune System.

And what about athletes? Are they better protected against infection? If infected, can they continue to train? In the same way as usual? It is also known that athletes with continuous high-intensity training sessions may be more prone to inflammation and respiratory viral infections, which are even more likely to occur during the periods referred to as the "open window", whenever the bioregulation of the innate/inflammatory responses is not adequate[1,11,12]. However, the moment when exercise is performed in relation to an infection is also extremely significant. For more than two decades, animal studies have shown that when intense training is performed in the presence of infection, then this is exacerbated and the prognosis is worse. However, training prior to an infection, even at intense levels, can improve the chances of survival[13]. And when should athletes be or not be vaccinated? It seems sensible to avoid the open window period following a training session. In other words, the two to four hours following an intense training session in which the specific or adaptive responses may be weakened, particularly for attenuated viral vaccines (which is not the case for those based on the mRNA technology, the most commonly used one today). However, physical exercise appears to alter the immunological response to the vaccine, modifying the antibody response, primarily or solely in obese individuals and in the sedentary elderly. And, talking about vaccines... Could exercise achieve good immunisation or be a "vaccine"? Although conceptually and in a strict sense, vaccination is focused on the production of specific antibodies and specific memory cells against the pathogen in the context of adaptive response, if we were to broaden the conceptualization of the effects of the immunisation to the prevention of the disease through the alteration of the immune response, then it would be possible to include the stimulatory effects of exercise on the innate response and the adaptations generated to protect the body from infection[1,14]. In fact, the emerging concept of "trained immunity" which describes "the long-term functional reprogramming of the innate immune cells (particularly monocytes and macrophages) induced by exogenous or endogenous stimuli, leading to an altered response towards a second challenge after the return to a nonactivated state"[15], is making it possible to develop vaccines that are based on this innate immunity "training". Therefore, could physical exercise induce trained immunity? Well, some time ago, our investigation group demonstrated that plasma from animals subjected to physical exercise stimulated the innate response of the macrophages of sedentary animals in baseline conditions[4,5], and these effects are mediated by stress hormones or endogenous danger signals[3,7,16]. This seems to be clear.

Unfortunately we have lived through a few months of accelerated reporting and investigation, of doubts and uncertainties. There have even been doubts as to whether the immune response would function as well as it has done up to now against this new coronavirus. Sometimes due to ignorance, and at other times due to the continuous exceptionality of an excess of information in the "alarmist" media, showing the most exceptional cases within a large infected population. And if the Immune System carries on functioning against the virus as expected, then physical exercise will continue to improve the immune responses for the prevention of viral infections... and vaccines work as well! "There's nothing new under the sun".

But let's look to the future. One piece of good news is that the COVID-19 pandemic appears to be coming to an end, which is also my opinion. But what is known as "persistent COVID" is and will still be here, with multiple and varied clinical symptoms that affect almost all the physiological systems. What is more, the title of this Editorial is in "times of COVID" (No. 19) given that this coronavirus will remain endemic and it will be followed by others. Let us hope that experience and the retrieval of information that, on many occasions, is already known, through a greater capacity to transfer basic research to clinical and medical practice, will allow us not to make the same mistakes again. At least the Immune System, and the responses that it generates, are no longer the great unknown.

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