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Sports injury rate and sports performance: role of low-grade chronic inflammation

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Abstract. As known, inflammation is a protective mechanism against pathogens and other triggers driven by biological molecules (neuropeptides, hormones, cytokines, growth factors).
Inflammation is hence a physiological process, but it loses its positive connotation when the anti-inflammatory signal molecules are not able to "suppress" naturally the signs and symptoms of inflammation.
In athletes, among the neuro-immuno-endocrine factors controlling homeostasis, one represents the watershed between physiology and pathology, i.e. inflammation, and in particular Low-Grade Chronic Inflammation (LGCI).
Starting from this perspective, it is interesting to note how physical exercise induces biphasic responses on many endocrines, and above all, immunological mechanisms, among which the main one is inflammation. Sedentary people are more likely to develop a state of LGCI (with consequent increase in the incidence of related diseases) compared to those who perform a moderate physical activity; the latter will show reduced levels of numerous inflammatory markers, including Interleukin 1-beta (IL-1β), Tumor Necrosis Factor-Alpha (TNF-α) and Interleukin 6 (IL-6), and an increase, at the same time, in anti-inflammatory cytokines and other signal molecules such as Interleukin-10 (IL-10) (6-8). This status and the related cytokine movement has been defined as a "physiological controlled state of inflammation"

Key words: inflammation, overtraining, sport, arnica

A spark neglected makes a mighty fire
Robert Herrick (1591-1674)

Introduction

Practicing a sports activity appropriately, both at amateur and professional levels, is based on a delicate balance between the need to maintain the general state of health and the aspiration to improve one's performance.

In athletes, among the neuro-immuno-endocrine factors controlling homeostasis, one represents the watershed between physiology and pathology, i.e. inflammation, and in particular Low-Grade Chronic Inflammation (LGCI). This concept was well described by Maffetone and Laursen (1) who pointed out that "in shape" and "healthy" are not necessarily synonymous and that the second state does not necessarily derive from the latter: the main discriminating factor between these two conditions is inflammation or, as explained in this article, the "level" of inflammation.

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able to "suppress" naturally the signs and symptoms of inflammation. The non-resolution of the inflammatory process causes the establishment of a deceitful, hidden and invisible chronic inflammatory state which is both the cause and the effect of many widespread chronic diseases, even with sometimes a fatal outcome such as cardiovascular ones (2, 3). Therefore, it has been named, with full rights, the "silent killer" (4, 5). Paradoxically, athletes can, in their paradigmatic image of healthy people, be among the main unaware victims of this killer.

Starting from this perspective, it is interesting to note how physical exercise induces biphasic responses on many endocrines, and above all, immunological mechanisms, among which the main one is inflammation. Sedentary people are more likely to develop a state of LGCI (with consequent increase in the incidence of related diseases) compared to those who perform a moderate physical activity; the latter will show reduced levels of numerous inflammatory markers, including Interleukin 1-beta (IL-1β), Tumor Necrosis Factor-Alpha (TNF-α) and Interleukin 6 (IL-6), and an increase, at the same time, in anti-inflammatory cytokines and other signal molecules such as Interleukin-10 (IL-10) (6-8). This status and the related cytokine movement has been defined as a "physiological controlled state of inflammation" (9).

The non-linearity of the immune system's response to physical activity is shown in its biphasic trend when the effort becomes particularly heavy and continuous; at this point, the effort stimulates the immune system in a much more constant and intense way, causing the markers of inflammation to go up to supra-physiological levels, in the typical range of LGCI (Figure 1).

In athletes, this means a greater susceptibility to infections (10, 11) and, in the most serious situations, it involves a decline in performance (12), an increase in injuries involving long recovery (13) and the possibility of suffering from cardiovascular (14) and degenerative diseases (15).

Unfortunately, therapeutic options with conventional medicines aimed at managing chronic inflammatory phenomena don't exist. Moreover, the stringent regulations on anti-doping prevention discourage the use of many anti-inflammatory drugs for a prolonged time.

This article aims at outlining the mechanisms that correlate inflammation, immune system, metabolism, Overtraining Syndrome (OTS) and Overreaching (OVR) to new therapeutic opportunities, both pharmacological and nutraceutical, for the management of LGCI in the athletes.

Overreaching-Overtraining and the loss of health / performance homeostasis

The search for the performance limit and exceeding the limit itself is expressed in the phrase "no-pain, no-gain", that is "if no state of suffering is achieved, physical work is not sufficient to achieve the objective". At this point, the phenomenon of Overreaching (OVR) is triggered or, in the most extreme cases, that of Overtraining (OTS - Overtraining Syndrome) (1, 10, 11, 16-21).

Overreaching is described as an accumulation of training (or non-training stress) resulting in short-term decrement in physical performance, with or without physiological and psychological implications. The restoration of performance capacity may take from days to weeks (22).

Overtraining syndrome is depicted as an accumulation of training (or non-training stress) resulting in long-term decrement in physical performance, with or without physiological and psychological implications. The restoration of performance capacity may take from weeks to months (22).

The psychophysical stress that derives from the abovementioned improper training practice (OVR/OTS) has important physiological repercussions: it

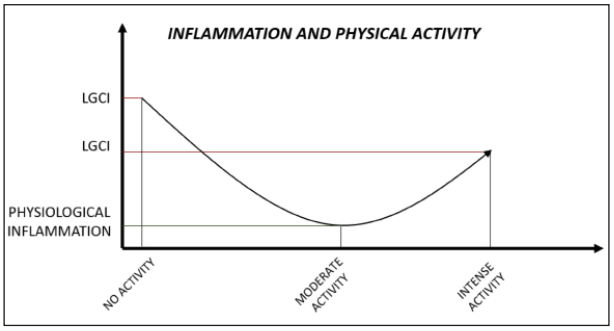

Figure 1. Biphasic trend of inflammation according to the intensity of the physical activity.

could stimulate to an increase in sub-acute inflammatory phenomena that leads, in the medium-long term, to Low-Grade Chronic Inflammation (LGCI). In a LGCI there is a persistent altered immunological condition, in which a latent inflammation, unperceived by the person him/herself, and a non-efficient inflammation resolution phase coexist.

Training, when not appropriately planned, and practiced without adequate nutrition, may lead to such paradoxical situation: the athlete is in a state of apparently good "athletic shape" to obtain the desired performance but, in fact, he/she is not in an optimal general state of health, although not yet evident. Maffettone and Laursen highlight this concept very well in the title of their article *Athlete: Fit and Unhealthy?* (1).

Such prolonged imbalanced situation may lead to a performance decline and to an increase of physical injuries' risk, combined with biochemical and psycho-emotional problems. This condition is known as OVR, a typical Psycho-Neuro-Endocrine-Immunological (P.N.E.I.) disorder, involving the nervous system, the neuroendocrine system and the immune system. OVR and OTS are among the causes of hyperactivation and imbalance of the hypothalamic-pituitary-adrenal axis (HPA) (17, 18, 21).

The chronic activation syndrome of the HPA axis is known as "chronic stress" and involves the progressive reduction of the body's ability to synthesize the neuro-hormonal mediators appointed to control the axis, with consequent loss of the ability to modulate the neuro-endocrine axis (desynchronization of the HPA axis) (23) (Figure 2). This state of severe stress causes well-known physio-pathological reactions such as:

- alteration of the perception of fatigue, which leads the athlete to face training and / or competitions above his/her physiological, constitutional, organ-anthropometric possibilities and to mismanage his/her recovery times (24);
- change of eating habits, preferential choices of hyperglycaemic and high-calorie foods in response to the increased energy needs (24);
- alteration of the immune response with increased levels of IL-6 (LGCI marker) and activation of the chronic inflammatory process, onset of aging mechanisms and alteration of some metabolic pathways including the one involving Serotonin and Kinurenina connected with latent depressive states (19).
- increase in oxidative stress, with a reduction of redox balancing capabilities (excessive intracellular ROS accumulation induce acidosis due to rapid exhaustion of the pH buffering systems) (25).

The reduction of the body's adaptive capacity leads to a significant increase in the risk of physical injuries, metabolic damages (related to the cellular metabolism, with reduction of the mitochondrial energetic capacity due to the progressive blockade of electron transport chains), and psychological and cognitive alterations (1, 17).

The role of chronic inflammation in sports injury and in performance decline

Inflammation is one of the physiological functions with homeostatic control; therefore, there is a level of inflammation within the parameters of "normality" called physiological inflammation, character-

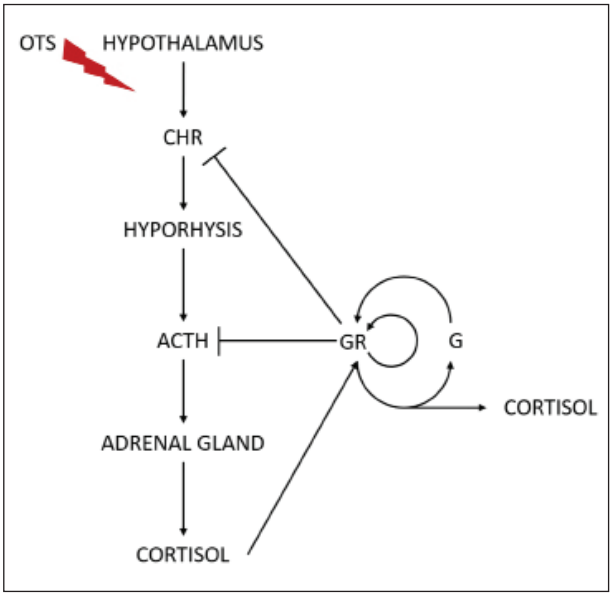

Figure 2. Chronic activation of the HPA axis. Chronic stress stimulates the synthesis of Corticotropin-releasing Hormone (CHR) by the hypothalamus; it spreads in the hypophysis, and activates ACTH (Adrenocorticotropic Hormone); ACTH induces cortisol synthesis in the adrenal gland; cortisol binds to the glucocorticoid receptor (G) inducing its own down-regulation through the formation of the GR complex that binds both CHR and ACTH to form a negative feedback loop.

ized by the fluctuation of the inflammatory cytokines within physiological levels and temporally scanned in three phases: onset, progression and resolution (Figure 3A). The acute inflammatory phenomenon has almost the same characteristics and the same time trend as the physiological inflammation, but the homeostatic threshold of the cytokine values is exceeded causing the signs and symptoms of the phlogistic phenomenon (Figure 3B).

The LGCI, on the other hand, is characterized by an altered sequence of the inflammation phases and by a different cytokines profile, with the persistence of moderate levels of pro-inflammatory cytokines and low levels of the anti-inflammatory ones; hence the sub-acute chronicity of the inflammatory process (Figure 3C) (20).

Apart from the LGCI, a second element contributes in the alteration of the homeostatic control mechanisms in the athlete: the condition of prevalent and persistent acidosis (26). Both LGCI and metabolic acidosis affect negatively sports performance and athlete's physiological homeostasis.

The physiological condition of homeostasis is tied to the maintenance of many fundamental vital parameters (pH, body temperature, glycaemia and oxygen partial pressure) each within a precise range; the deviation of these parameters from these limits coincides with a state that can be defined as pathological. In the sports domain, especially when high performance is required, the immune system and the metabolism in general are already intensely stressed. An example is the major susceptibility to upper respiratory tract infections (URTI) by athletes such as marathon runners and triathletes (10, 11).

In sports, the physiological inflammation that results from physical exertion constitutes a fundamental mechanism for the implementation of the reparative processes of the tissues stressed by exercise itself.

Intense physical exercise means that the threshold of an athlete's physiological inflammation is higher compared to sedentary people but, in the case of OVS, there is also a higher risk of falling back into the condition of LGCI, with deterioration of the immune response and increase in circulating levels of pro-inflammatory cytokines (IL-1; IL-6; TNF-α) (8, 9). As excellently described by McInnes et collaborators (21), the inflammatory phenomenon is not limited to the onset area but can spread systemically an attack each tissue and organ thanks to the spread of the mentioned cytokines.

From the musculoskeletal point of view, the persistence of the low-grade inflammatory phenomenon

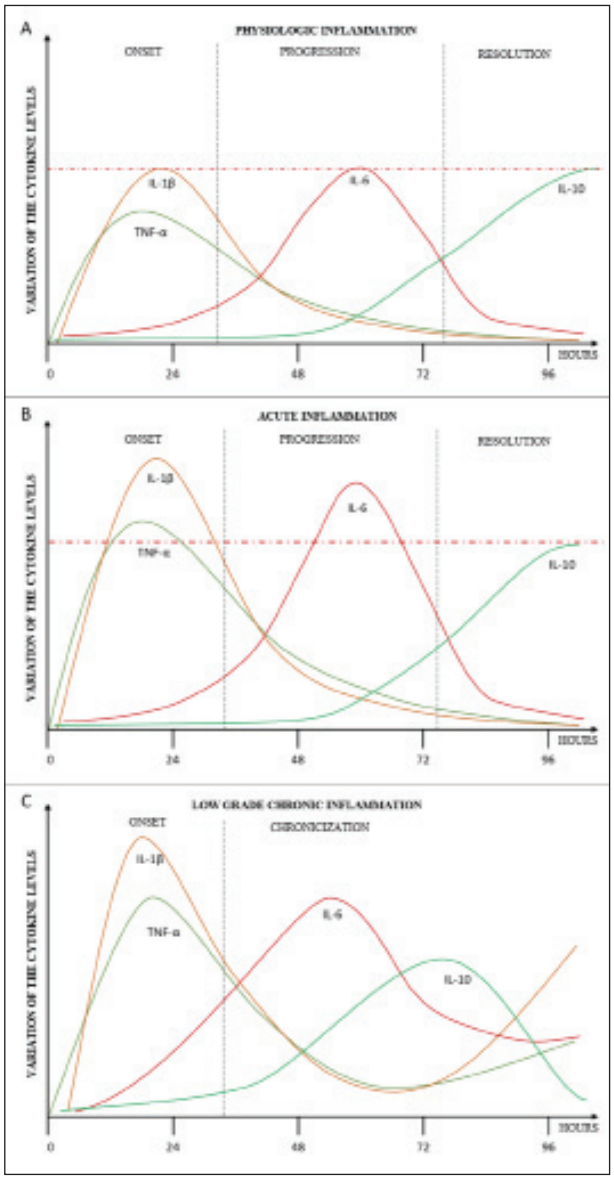

Figure 3. **A**) Chronobiology of the cytokine levels progression controlling the physiological inflammatory phenomenon. **B**) Chronobiology of the cytokine levels progression that control the acute inflammatory phenomenon. **C**) alteration of the cytokine profile in LGCI (*images taken from and elaborated by: Milani L, Perra A, Cardani D. Arnica comp. -Heel A 60 year-long history. From homeopathic materiae medicae to molecular biology and genomics Adv Ther. 2017; 12: 17-33*).

means that all microtraumas and microlesions that are created physiologically during physical exercise cannot be effectively repaired because the normal chronobiology of inflammation is threatened by LGCI, which delays or prevents completely the repair phase (17).

The accumulation of "unsolved" microtraumas and microlesions can lead the athlete to a greater risk of injury; the reduced ability to repair tissues can lengthen the recovery time, thus triggering a negative vicious circle both for the performance and for the athlete's morale (1, 17, 18).

Similarly, this happens also to the cardiovascular system (1, 27) and to the cardiac muscle, which is exposed to the same kind of dynamics. Also, the heart, during exercise, undergoes the same stress phenomena as the other muscles. As previously described, the status of LGCI affects negatively the function and recovery of heart after exercise. Moreover, in some cardiovascular system diseases, IL-1, TNF-α and IL-6 are involved, thus could increase the risk of an impaired cardiac function.

A state of acidosis often accompanies LGCI, increasing its effects (inflammatory phenomena are more intense and less manageable in a predominantly acidic extracellular environment) (28) and compromising cellular functionality (alteration of mitochondrial functions) (29). The increase muscle protein breakdown caused by EIMD (Exercise-Induced Muscle Damage) (17) contributes to the progressive exhaustion of the redox control capacities of the biological buffer systems (carbonates, phosphates, citrates) with consequent deposit of H^+ ions in the extra-cellular matrix and decrease of pH.

In athletes these phenomena cause, not only in a decline in performance accompanied by higher injury risk, but also an obvious impairment of the general state of health.

These observations highlight even more the need to preserve the balance between the two "fit" and "healthy" states as much as possible. Planning correctly training programs and competitive activities, accurate diet and psychological support, when necessary, are certainly the cornerstones of a proper sports activity, both amateur, with due limits, and professional, in which everything will be related to the requested performance.

Low dose pharmacological therapy and dietary supplementation for the treatment of LGCI and metabolic acidosis in athletes

More than in anyone else, in athletes it is essential to take into consideration the opportunity to act both preventively and therapeutically on LGCI and acidosis through the use of medicines and food supplements (fully compliant with the anti-drug regulations drawn up by WADA - World Anti-Doping Agency[1, 2]).

Recent developments in the field of pharmacology of low doses or Low Dose Medicine (branch of pharmacology that studies the possibilities of using many bioactive molecules at very low concentrations and therefore free from the most adverse events given to high-dose conventional use) have contributed to the understanding of the mechanisms of inflammation allowing to formulate a strategy for the modulation of inflammation, respecting its biology. It is a new pharmacological paradigm based on the use of low doses of natural principles and biological molecules able to act on targets in specific aspects of inflammatory mechanisms (30). At the same time, the development of nutritional supplements in the domain of Physiological Nutraceuticals now offers to sports people, and to everybody, a series of tools able to support the most articulated nutritional and nutraceutical programs (31).

As mentioned, it should be noted that, to date, a protocol for the treatment of chronic low-grade inflammation (LGCI) based on the use of conventional anti-inflammatory drugs is not available. Generally, drugs designed for acute use (e.g. NSAIDs) are used for a long time, with severe consequences, especially cardiovascular- and immune-related adverse events (32, 33).

In recent years, basic and clinical research have helped to clarify the mechanism of the biological action of low doses signaling molecules highlighting the efficacy and safety of this pharmacological approach for the modulation of the inflammatory response, especially in LGCI (34-42).

1 http://www.wada-ama.orglen/World-Anti-Doping-Program/Sportsand-Anti-Doping-Organizations/InternationalStandards/Prohibited-List/

2 http://www.nada-bonn.de/fileadmin/user upload/nada/Medizin/101221_ Beispielliste 2011.pdf.

Understanding the mechanisms of the regulation of immune-inflammation through the in-depth study of the underlying immunological aspects, has allowed to hypothesize the possibility to intervene effectively on the LGCI also through long-term treatments. To reach this goal, a low dose medicinal would be ideal (because of its intrinsic highest tolerability).

Arnica comp. -Heel (Biologische Heilmittel Heel GmbH, Baden-Baden, Germany), the "progenitor" of low-dose drugs with anti-inflammatory action, is highly recommended by virtue of its composition based on natural active compounds with marked anti-inflammatory properties or, more correctly, with modulatory activity on inflammation.

In summary, Arnica comp. -Heel (available in tablets, oral drops, injectable vials, ointment) induces the resolution of chronic inflammation by acting on the persisting onset phase, normalizing it by reducing the expression of IL-1β, TNF-α and IL-6 and stimulating the resolution phase by increasing the synthesis of IL-10, which identifies, in the chronobiology of inflammation, the phase of resolution (Figure 4).

Extensive literature supports the validity of Arnica comp. -Heel as anti-inflammatory medicine (43-54) also in sports, with appreciable results and in compliance with the WADA / NADA standards (55-58) on the use of anti-inflammatory drugs at competitive levels.

In addition to the reduction of the LGCI, it is fundamental to sustain acid-base buffer systems, for example, through food or supplementation with substances able to control pH in the extracellular environment, favouring the physiological alkalization. The basification of the extracellular environment is needed to reduce the phenomena of oxidative stress, which is responsible not only for its pro-inflammatory action, but also for lower energy efficiency in the cell.

GunaBasic, food supplement distributed by Guna S.p.a. (Milan, Italy), through the supplementation of organic compounds of calcium (carbonate / lactate),

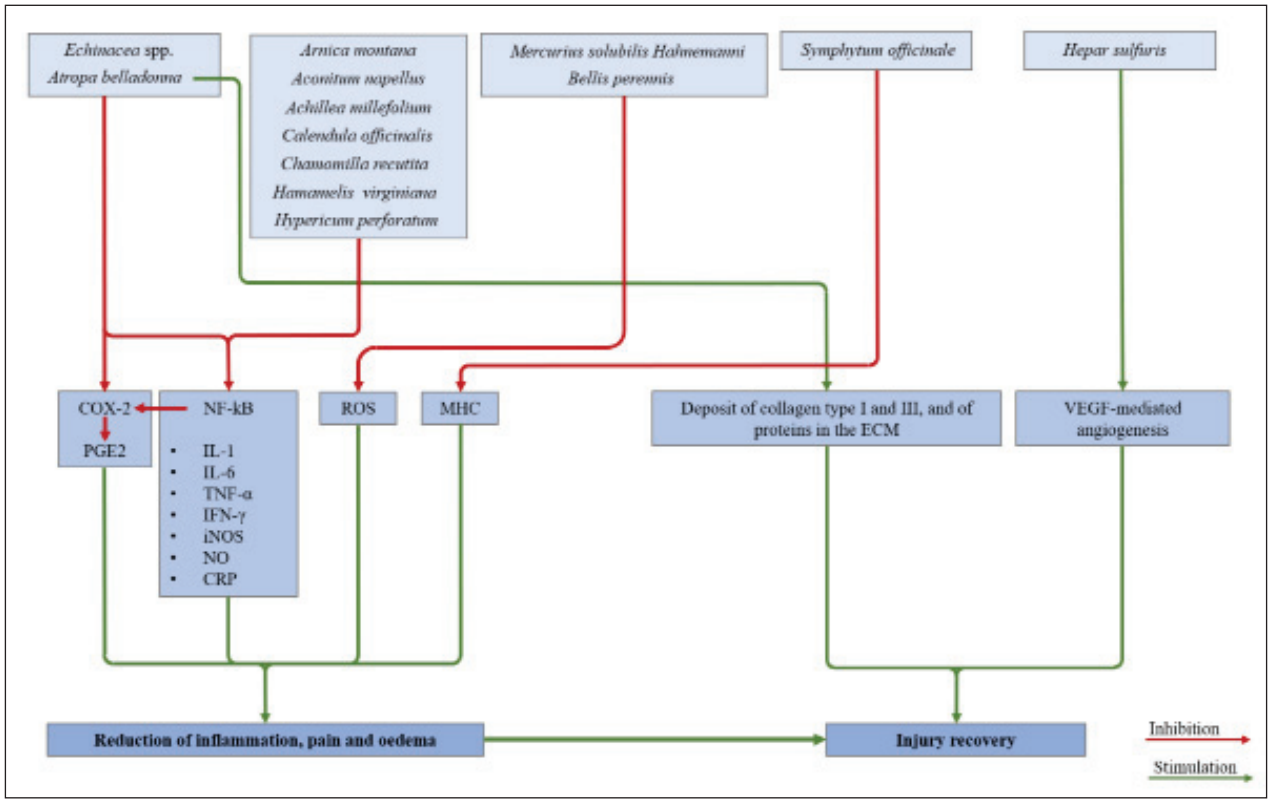

Figure 4. Synoptic table of the main biological actions carried out by the components of Arnica comp. -Heel. (*image taken from and elaborated by: Milani L, Perra A, Cardani D. Arnica comp. -Heel. A 60 year-long history. From homeopathic Materiae Medicae to molecular biology and genomics Adv Ther. 2017; 12: 17-33*).

potassium (citrate) and magnesium (carbonate / citrate) can restore, physiologically, the complex system of biologically active tampons (Figure 5) thus recovering the normal cyclicity of acidosis / alkalosis altered by OTS (59).

Counteracting tissue acidosis through acid-base rebalancing, providing substrates such as trace elements and minerals useful for mineral and metabolic rebalancing, antagonizing chronic inflammatory and degenerative processes, means putting the athlete's organism in the ideal conditions to maintain its homeostatic equilibrium, therefore for a good condition of health and for an optimal performance.

Conclusions

The distinction between good and bad, opportune and harmful, physiological and pathological, in Nature is often blurred and sometimes imperceptible. And not always what is right is also appropriate, especially for the human body, and even more for that of the athlete.

"How much" therefore becomes a crucial factor: many natural phenomena show a biphasic pattern, related to quantity or intensity (... or dose); in Medicine this delicate trend often underlies the shift from physiological to pathological.

Among the many physio-pathological phenomena with a "double and conflicting" behaviour, inflammation and pH appear paradigmatic and crucial; so that sports activity may be "fit" without becoming "unhealthy" and an athlete may reach his/her maximum performing capacity with no short-, medium- or long-term health risk.

Inflammation, and in particular low-grade chronic inflammation (LGCI), together with the conditions of oxidative stress and acidosis induced by over-training, threaten the athletic performance and increase the risk of injury, slowing down psycho-physical recovery.

The control of the LGCI, regardless of the reasons that cause it, and maintaining the buffer systems in good efficiency, thanks to appropriate pharmacological and nutritional interventions too, are key elements in the life of an athlete, both amateur and professional, helping to keep the right balance between good health and high sports performance.

The low dose pharmacological and physiological nutraceutical approach proposed in this article can not only reduce the incidence of injuries and increase the performance threshold, but also constitute the best example of effective preventive therapy of chronic-degenerative diseases that, in the presence of LGCI, more easily affect the athlete.

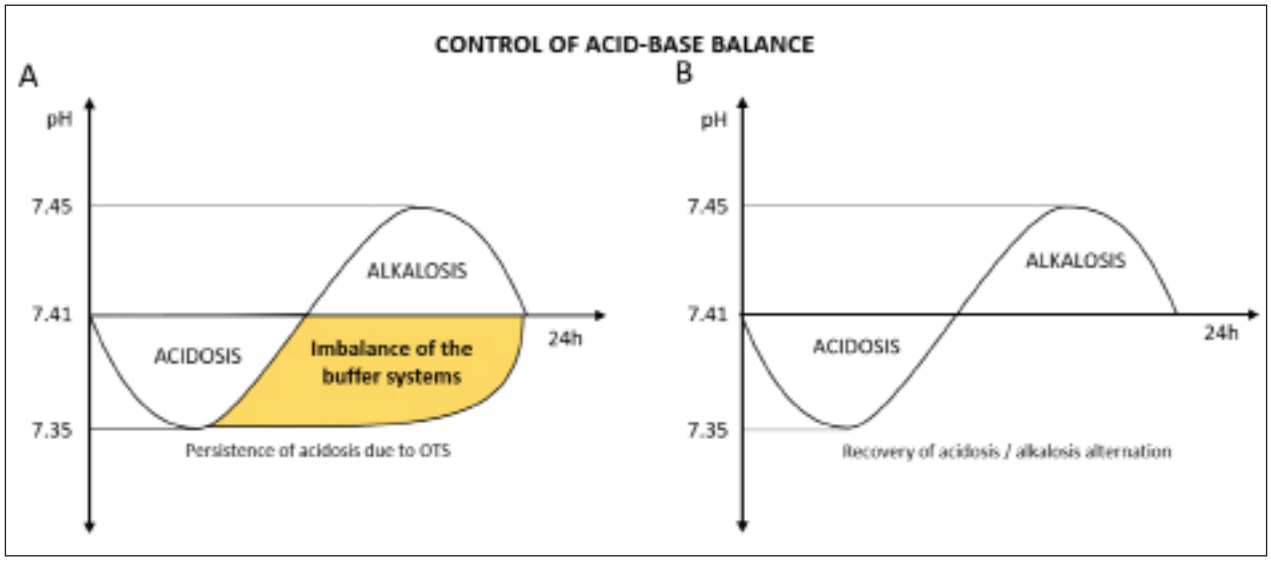

Figure 5. **A**) OTS is associated with the expansion of the tissue acidosis phase caused by the exhaustion of the buffer systems that regulate acid-base homeostasis. **B**) Supplementation with complete buffer systems contributes to the restoration of the correct acidosis / alkalosis alternation.

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