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EDITORIAL

The benefits of physical activity (and the serious damage caused by neglecting physical exercise)

I'd say that by now we know enough, actually a lot, about this genre of human activity - motor activity, linked to movement - in particular, we know its beneficial effects and the very limited side effects (which can be expressed as "the less you do, the worse it is!"). Fortunately, not a day goes by that science, I repeat science, not just idle chatter, fails to show us more extraordinary marvels of the human body's adaptation processes and responses to this vital stimulus that is movement.

Italian research is regularly subject to criticism, yet it was here that a new hormone with extraordinary functional capabilities was discovered. It is called Irisin and takes its name from Iris, messenger of the gods and personification of the rainbow, a mythical Greek figure with wings to indicate the speed with which she executed the orders of Zeus and Hera.

It's not a random name - this (new) hormone also has messenger functions.

The discovery, which could lead to an authentic revolution in the fight against osteoporosis, bears the signature of an all-Italian research group, as I pointed out, born from the collaboration between the University of Bari and the Marche Polytechnic University of Ancona, and supported by SIOMMMS (Italian Society of Osteoporosis, Mineral Metabolism and Skeletal Diseases), and is published in the official journal of the American National Academy of Sciences (PNAS).

The main feature of this hormone, already known for some years but for other attributes, is that it is produced only as a result of intense physical activity, and even in very low doses it has the ability to "manufacture" new bone: a recently discovered activity because, as previously mentioned, its initial physiological role discovered in 2015 was that of a "fat burner". Extraordinarily lipolytic activity was observed, so much so that the scientific world is considering its transformation into a drug for the treatment of obesity and, from today, it will also be employed in the fight against osteoporosis. Individuals suffering from advanced stages of both diseases are inhibited from carrying out a significant amount of physical activity.

For normal individuals, moving regularly and with a certain intensity is enough for the drug to be automatically produced by our muscles. Muscles are therefore no longer to be thought of as the sole performers of contractions and decontractions, but now even as endocrine organs. Although exercise is a well known and powerful stimulus

for new bone formation and the absence of gravity or loss of muscle mass causes bone loss, it was still unclear how muscles could communicate with bones. Today we have finally understood the mechanism related to how Irisin performs this extraordinary task of connectivity between muscle and bone, so much so that it is being considered a therapy for sarcopenia and osteoporosis, which occur in tandem in elderly bedridden patients or those unable to move, and as an endogenous resource (medication?) for those who, on the other hand, can physically exercise and sweat.

Irisin has been shown to have marked anabolic actions on the bone structure. This anabolic action is mediated mainly through the stimulation of bone synthesis, but with significant parallel reductions in the number of osteoclasts. Higher amounts of Irisin (3,500 $g \cdot kg^{-1}$ per week) cause browning of the adipose tissue; a fact that was not observed with low doses of Irisin. Presumably, low-doses of Irisin modulates skeletal genes, but not white adipose tissue. It was also noted that although the precursor of the Irisin, Fndc5 was abundantly expressed in skeletal muscle, other sites, such as bone and the brain, also expressed Fndc5, albeit at low levels. Furthermore, the muscle fibres of mice injected with Irisin showed a higher positivity of Fndc5 and the expression of Irisin-induced Fdnc5 mRNA in cultured myoblasts. The research data thus highlight a previously unknown action of Irisin, which could be the molecular entity responsible for muscle-bone connectivity.

Physical exercise has widely recognised benefits on metabolic and skeletal health and is routinely used as a non-pharmacological intervention in therapeutic protocols for a variety of diseases. Reducing the level of physical activity, for example in former athletes, can lead to a progressive loss of bone. Likewise, lack of activity and weightlessness invariably cause acute, rapid and severe bone loss, with a profound increase in the risk of fracture. For example, astronauts lose bone mass 10 times faster than women in early menopause, while patients in a vegetative state or with spinal cord injury present a high risk of fragility fractures, even at low bone mineral density (BMD).

Although there is a clear link between physical activity and bone acquisition and maintenance, the question of whether and how muscle function regulates bone mass has remained largely unresolved. Several lines of evidence point towards direct muscle-bone connectivity. First of all, increased muscle mass appears to be closely related to increased bone mineral density and, consequently, to a reduced risk of fracture in postmenopausal women. In contrast, age-related sarcopenia has been linked to senile osteoporosis. Secondly, excess glucocorticoids and vitamin D deficiency are catabolic, whereas androgens are anabolic for both bone and muscle. Thirdly, it has been observed how in rats with experimental spinal injury, electrical stimulation of the muscle saves the high bone resorption and osteoclastogenesis in vivo, basically providing direct evidence of muscle-bone communication, probably through a soluble molecule. The newly identified Irisin myokine, produced by skeletal muscle in response to exercise, has attracted attention as a potential target for the treatment of metabolic disorders.

The study previously showed that the myokine-enriched medium from myoblast cultures was capable of improving the differentiation of bone marrow stromal cells in mature bone osteoblasts in vitro. Here, we demonstrate that recombinant Irisin (r-Irisin), when injected into mice, increases cortical bone mass and strength. We find that this action results from a direct effect of Irisin on the formation of osteoblastic bone, which is mainly exerted through the suppression of sclerostin (Sost), a Wnt signal inhibitor. It was therefore believed that Irisin could act as the main molecule for the future development of new therapies that could simultaneously target bone, muscle and metabolic disorders.

So what is the purpose of this intervention? As if it were necessary, it is further proof that movement undeniably improves the quality of human life. Movement creates the conditions for structuring a more functional muscular bone system, both in terms of quality and quantity. Weight, as research highlights, favours these aspects in particular. So as of tomorrow, whoever you are, remember that 20 minutes of weight training can take you (but not just you, everyone the world over) with the goddess Iris to the Olympus of well-being. For your body and your mind.

Antonio Urso
EWF President

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