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REVIEW ARTICLE

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The interplay between bone, muscle and adipose tissue — is there a role for potential new metabolic biomarker?

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ABSTRACT

Recent studies in mice and humans have shown the tight connection between bone and muscle tissues. Physical activity affects the function of osteocytes, mature bone cells, stimulating the synthesis of several hormone-like myokines in skeletal muscles. Anabolic action of physical exercise on bone is mediated by a myokine called irisin. This protein was initially assigned to regulate glucose homeostasis in humans but recently the influence of irisin on bone and adipose tissue metabolism was also demonstrated. In the human blood, irisin occurs in different forms, free or complexed, glycosylated and non-glycosylated which makes a reliable and reproducible measurement of this protein a crucial issue for the clinical interpretation of experimental findings. In humans, irisin was shown to inversely correlate with the prevalence of bone fractures. Data obtained so far suggest that irisin could be a potential target for the treatment of osteoporosis and play an important role in the bone healing process.

Key words: bone, muscle, adipose tissue, myokines, irisin, bone fractures

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Structural integrity of bone is preserved by three types of cells: osteoblasts (bone forming cells), osteocytes (mature osteoblasts) and osteoclasts (bone resorbing cells). Cell to cell crosstalk in bone tissue involves not only biochemical interactions but also mechanical and electrical signaling. Bone is a metabolically active endocrine organ [1]. Metabolism of bone tissue is regulated by several factors, above all, physical exercise and hormones acting directly or indirectly on bone. Osteoblasts produce a wide range of factors involved in the proliferation and development of bone resorbing cells (RANK-ligand, osteoprotegerin). Moreover, osteoblasts and osteocytes release other signaling proteins periostin, sclerostin and Dickkopf (DKK) regulating osteoblastogenesis and bone formation. Bone forming cells possess membrane receptors for parathyroid hormone (PTH) and nuclear receptors for estrogens and 1,25 (OH)2D whereas osteoclasts present receptors for RANK, calcitonin and estrogens but not for PTH and vitamin D.

Bone and muscle influence each other by releasing a range of directly or indirectly acting factors. Physical activity affects osteocyte function and stimulates synthesis of several hormone-like myokines in skeletal muscle cells. Recent studies in mice and humans proved tight communication between bone and muscle tissues. Anabolic action of physical exercise on bone is mediated by a myokine called irisin [2]. Small protein molecule- irisin, the cleavage product of fibronectin type III domain-containing protein 5 (FNDC5) is secreted by skeletal muscle mainly after exercise. Irisin is also expressed in other organs containing muscle and, to lesser extent, in adipose and brain tissue. The existence of irisin in humans was questioned until its detection in the circulation was proven by Jedrychowski et al with the use of gas chromatography/mass spectrometry technique [3]. In the human blood irisin occurs in different forms: free or complexed, glycosylated and non-glycosylated that makes reliable and reproducible measurement of this protein, a crucial issue for the clinical interpretation of experimental findings [4]. In adult healthy individuals irisin concentration in the blood was found to be in the range of 3–5 ng/mL and increased after physical exercise [4, 5]. Little is known about the circulating irisin in children, however, it seems that its levels are much higher and increase after heavy exercise [6, 7].

Irisin was initially assigned to regulate glucose homeostasis in humans, in particular in individuals with type 2 diabetes [8–10]. Recently, an influence of irisin on bone and adipose tissue metabolism was also reported [11]. Although, serum level of irisin was related to a wide range of clinical disorders the studies in humans reported inconclusive and sometimes discrepant results [12, 13]. It is clear that further well designed studies are necessary for clarification of effects of irisin on different tissues.

So far, most human studies reported a weak but positive association of irisin with body mass and markers of insulin resistance [4]. Interestingly, a direct correlation was observed between blood irisin levels, fasting insulin and glucose in healthy and obese subjects, children and women with polycystic ovary syndrome, but not in diabetics. It is worth to note that secretion of irisin was not affected by food intake [14]. Unexpectedly, in most previous studies carried on in patients with prediabetes or type 2 diabetes lower irisin levels, compared to normoglycemic subjects, were observed. The mechanism behind this phenomenon has not been elucidated yet. Similarly, the uniform data are lacking regarding the possible role of irisin in metabolic syndrome, liver and cardiovascular diseases [4].

It was postulated that physiological function of irisin in different tissues may depend on its effective concentration and type of cellular receptors [5]. Studies in mice bring discrepant results demonstrating positive or negative effects of irisin on bone. Kim et al. reported on irisin functional receptors on osteocytes and adipocytes in mice. These irisin receptors belong to alpha-V class of integrins through which irisin promotes bone remodelling by stimulating sclerostin expression. Direct induction of sclerostin, an osteocyte-derived signalling molecule inhibiting bone formation, by irisin was shown *in vitro* and *in vivo*. Based on this observation the authors suggested that irisin could be a potential target for treatment of osteoporosis [5].

Recent findings from animal experiments demonstrated the anabolic action of irisin on bone tissue [2, 15, 16]. Zhang et al showed that exercise-induced secretion of irisin increases osteoblastogenesis and decrease osteoclastogenesis in experimental mice [16]. Colaianni et al reported that irisin may increase cortical bone mass [2, 15]. In addition they observed that treatment with recombinant irisin prevented bone loss and protected against muscle atrophy in animals subjected to immobilization which may be an important step forward on the way to search for novel therapies for elderly and physically disable patients [17].

Irisin was shown to inversely correlate with the prevalence of bone fractures in postmenopausal women with low bone mass [18]. Irisin levels were lower than normal in diabetics with increased risk of osteoporosis and bone fractures suggesting its role in prevention of fractures [19]. It is likely that irisin may also play a role in bone healing process.

The first study performed in adult patients with hip fractures in which irisin concentration was measured in the serum and irisin presence was showed immunohistochemically in bone tissues samples, taken during arthroplasty, revealed that concentration of this myokine increases during the bone union process [21]. Patients included in this study were carefully selected based on the exclusion criteria like bone metabolic diseases, malignancy, diabetes, kidney disease and hormonal disorders. All study patients underwent hip arthroplasty within 24 hours after admission to the hospital. Interestingly, the mean value of serum irisin was found to be significantly higher 60 days after operation, compared to the concentrations at baseline, 1 day and at 15 days after operation. These findings led authors to conclusion that irisin may positively affect bone healing which is of importance in the light of constant search for factors affecting bone healing process.

It is not surprising that the relationship between irisin and estradiol level in elderly individuals was also investigated. It was reported that the synthesis of sclerostin and irisin may be influenced by estradiol in postmenopausal overweight women with osteoporosis [5, 22]. In obese subjects a direct relationship of irisin with estradiol level, muscle mass and insulin sensitivity was observed [20, 22]. On the contrary, older age and body fat was negatively correlated with irisin and sclerostin in adults with prediabetes [20]. A possible link of metabolic impairment biomarkers with bone metabolism in children has not been extensively investigated however, recently a negative effect of inflammation and insulin resistance on bone development in young girls was postulated [23]. Moreover, in children with diabetes mellitus type 1 the detrimental impact of increased sclerostin on bone formation has been shown [24]. Taken together these data provide insight into the complex regulatory interplay of bone, muscle and adipose tissues.

Continuous bone remodelling essential for longitudinal growth of skeleton in children, motion, maintaining of bone mass, repairing damages and fracture healing is an energy consuming process, therefore, must be linked to energy metabolism, in particular to glucose metabolism [25, 26]. The utilization of glucose by bone tissues is approximately half of that by adipose tissue and much lower than by muscles [1]. It is extremely interesting that the anabolic action of parathyroid hormone on bone, as demonstrated by Esen et al, was through increase of aerobic glycolysis (glucose consumption and production of lactate) via IGF-1 signalling and the same is true for irisin as anabolic agent [27, 28]. The anabolic effect of irisin on bone is particularly dependent on glucose metabolism, moreover irisin plays

an important role in the regulation of energy expenditure in different metabolic conditions [1, 28].

Whether irisin, a novel hormone-like myokine, plays a unique role linking bone, muscle and adipose tissue metabolism in humans remains to be investigated. Further studies are necessary to clarify the interplay between irisin and potential other exercise-induced mediators released by bone, adipose and muscle cells.

Abbreviations: RANK-receptor activator of nuclear factor kappaβ

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