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Review

Muscle and bone, two interconnected tissues

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ABSTRACT

As bones are levers for skeletal muscle to exert forces, both are complementary and essential for locomotion and individual autonomy. In the past decades, the idea of a bone–muscle unit has emerged. Numerous studies have confirmed this hypothesis from *in utero* to aging works. Space flight, bed rest as well as osteoporosis and sarcopenia experimentations have allowed to accumulate considerable evidence. Mechanical loading is a key mechanism linking both tissues with a central promoting role of physical activity. Moreover, the skeletal muscle secretome accounts various molecules that affect bone including insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (FGF-2), interleukin-6 (IL-6), IL-15, myostatin, osteoglycin (OGN), FAM5C, Tmem119 and osteoactivin. Even though studies on the potential effects of bone on muscle metabolism are sparse, few osteokines have been identified. Prostaglandin E2 (PGE2) and Wnt3a, which are secreted by osteocytes, osteocalcin (OCN) and IGF-1, which are produced by osteoblasts and sclerostin which is secreted by both cell types, might impact skeletal muscle cells. Cartilage and adipose tissue are also likely to participate to this control loop and should not be set aside. Indeed, chondrocytes are known to secrete Dickkopf-1 (DKK-1) and Indian hedgehog (Ihh) and adipocytes produce leptin, adiponectin and IL-6, which potentially modulate bone and muscle metabolisms. The understanding of this system will enable to define new levers to prevent/treat sarcopenia and osteoporosis at the same time. These strategies might include nutritional interventions and physical exercise.

Contents

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1. Introduction

Evidence from numerous studies has revealed for decades, that a close functional and developmental relationship exists between muscle and bone mass. According to the concept of the bone–muscle unit, a very strong relationship should exist between maximum muscle force and bone mass/geometry, and both tissues fulfil a common function, locomotion. "Indeed, if skeletal muscle was initially considered as a tissue whose primary function is to move objects against the force of gravity" (Vandenburgh et al., 1999), the sliding filament theory described the fact that contraction of myofilaments is at the heart of movements (Huxley and Niedergerke, 1954; Huxley and Hanson, 1954). Huxley (1975) then developed a 2 or 3 steps model and Cooke (2004) gathered information on the historical improvement of the muscle contraction model from 1972 to 2004. If muscle contraction is essential for motion, the skeleton (levers) is needed to exert forces (Campbell and Reece, 2004; Marieb, 1999). Regarding phylogeny, if arthropods are frequently described as the first land animals (MacNaughton et al., 2002; Schaefer et al., 2010), the emergence of land life and the diversification of organisms are believed to be partly due to the appearance of the skeleton (Volkmann and Baluska, 2006). The primary mechanical function of bones is to provide rigid levers (thanks to mineralization) for muscles to pull against, and to remain as light as possible to allow efficient locomotion (Turner, 1998), the mechanisms underlying such a relationship are still poorly understood and most of the biochemical interactions among the tissues and cells remain mostly unknown (Abreu et al., 2012). In recent years, a great number of scientific papers considered bone as a target of skeletal muscle secretory pattern but surprisingly, only a few mentioned the potential effects of bone on muscle metabolism. The objective of this review is thus to provide an update on the development of knowledge about the locomotor system.

2. Methodology

Computer-assisted searches of publications and reviews were conducted on PubMed database to identify pertinent papers published until 2014. Database was interrogated with the following keywords: locomotor system/function, musculoskeletal system, bone–muscle crosstalk, bone, skeleton, osteoporosis, cartilage, muscle, skeletal muscle, sarcopenia, osteoblast, osteoclast, osteocyte, osteokines, bone-secreted factors, myoblast, chondrocyte, tendon, tenocytes, tendon secreted factors, metabolism, formation, resorption, loss, atrophy, humoral factor, myokines, myostatin, endocrinology, secretory organ, bed rest, space flight/travel, mechanosensation, mechanical loading.

Moreover, relevant references mentioned in the previously identified papers were analyzed as well.

3. Is there a link between muscle and bone?

An essential component of the musculoskeletal system is the anchoring of the force-generating muscles to the solid support of the organism: the skeleton. Most of the available data provide evidence that muscle and bone closely interact. These observations led to the concept of the "Bone–muscle unit", this was evidenced phenotypically by the lifelong linear association between total body bone mineral content (BMC) and lean body mass. This was the case in the study carried out on 1450 persons from 2 to 87 years by Ferretti et al. (1998). In the same way, in the Finnish Twin Cohort Study, lean mass was a better predictor of whole body bone mineral density (BMD) than fat mass ($p < 0.01$) (Bogl et al., 2011). In addition, a clinical study performed in boys and girls during pubertal development showed that the increase in bone strength was preceded by the increase in muscle strength (Rauch et al., 2004). Jackowski et al. (2014) have shown that lean tissue mass accrual impacts adult bone strength.

Preclinical data strengthen the lessons from such clinical trials. Muscle bone crosstalk appears to manifest even before birth in mammals. Long bone shape and the joint is dependent on muscle contraction. In the absence of mechanical loads, the stereotypical circumferential outline of each bone is lost, leading to the development of mechanically inferior bones (Bren-Mattison et al., 2011; Sharir et al., 2011). Indeed, MyoD−/−/Myf5−/− (dd/ff) mice lack skeletal muscle, so they develop without any active movement *in utero* and die soon after birth. In the fetuses, long bones were found to be less mineralized and had altered morphological features. They also presented many more osteoclasts in the newly layed bone (Gomez et al., 2007). In a study were mice limb muscle were removed and replaced by implants of either minced skeletal muscle, nonlimb skeletal muscle, cardiac muscle, liver or nothing, nodules of cartilage and bone were only induced by the three first ones (Zacks and Sheff, 1982). Finally, fracture healing was impaired by excision of a large muscle segment, while the diffusion of high molecular weight molecule from muscle appeared to enhance bone synthesis (Kaufman et al., 2008; Utvag et al., 2003). Liu et al. (2010) reviewed the potential role of muscle in bone repair and suggested that osteo-inducible cellular populations from muscle may directly be implicated in bone formation and healing.

In summary, various situations such as ageing or pathological states, as well as environmental factors (nutrition, physical activity/mechanical stress) may influence muscle and bone simultaneously. These observations lead to the concept of possible interactions between muscle and bone, which might be very important for understanding the physiology and pathophysiology of sarcopenia and osteoporosis. As a matter of fact, muscle/bone relationships include different levels of cross-talk: through systemic humoral pathways, but also at the cellular and molecular levels. The crosstalk can be bidirectional, i.e., from muscle to bone and