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Muscle-bone interactions: From experimental models to the clinic? A critical update

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ABSTRACT

Bone is a biomechanical tissue shaped by forces from muscles and gravitation. Simultaneous bone and muscle decay and dysfunction (osteosarcopenia or sarco-osteoporosis) is seen in ageing, numerous clinical situations including after stroke or paralysis, in neuromuscular dystrophies, glucocorticoid excess, or in association with vitamin D, growth hormone/insulin like growth factor or sex steroid deficiency, as well as in spaceflight. Physical exercise may be beneficial in these situations, but further work is still needed to translate acceptable and effective biomechanical interventions like vibration therapy from animal models to humans. Novel antiresorptive and anabolic therapies are emerging for osteoporosis as well as drugs for sarcopenia, cancer cachexia or muscle wasting disorders, including antibodies against myostatin or activin receptor type IIA and IIB (e.g. bimagrumab). Ideally, increasing muscle mass would increase muscle strength and restore bone loss from disuse. However, the classical view that muscle is unidirectionally dominant over bone via mechanical loading is overly simplistic. Indeed, recent studies indicate a role for neuronal regulation of not only muscle but also bone metabolism, bone signaling pathways like receptor activator of nuclear factor kappa-B ligand (RANKL) implicated in muscle biology, myokines affecting bone and possible bone-to-muscle communication. Moreover, pharmacological strategies inducing isolated myocyte hypertrophy may not translate into increased muscle power because tendons, connective tissue, neurons and energy metabolism need to adapt as well. We aim here to critically review key musculoskeletal molecular pathways involved in mechanoregulation and their effect on the bone-muscle unit as a whole, as well as preclinical and emerging clinical evidence regarding the effects of sarcopenia therapies on osteoporosis and vice versa.

1. Introduction: the clinical background

Bone and muscle are integrated organs with shared functions e.g. in locomotion and growth, and both may act as endocrine organs (Karsenty and Ferron, 2012; Pedersen and Febbraio, 2012). It is therefore not unexpected that development and maintenance of bone and muscle go hand in hand most of the time. Indeed, physical exercise can increase the strength and mass of muscle and bone, while both are compromised by ageing and situations of disuse like immobilization, stroke, paralysis, bed rest or spaceflight.

Disuse osteoporosis however has no clear definition. In fact, diminished physical activity and/or neuromuscular dysfunction probably contributes to bone loss in most elderly as well as in most forms of so-called secondary osteoporosis. Indeed, bone loss, muscle wasting and low physical activity are recognized in e.g. chronic obstructive pulmonary disease (COPD), heart failure, stroke, critical illness, cancer, Parkinson's disease or glucocorticoid treatment, to name just a few. The term *sarcopenia* (from Greek *sarx*, flesh and *penia*, poverty) is usually reserved for loss of muscle mass and strength related to ageing. Several alternative terms for sarcopenia have been suggested with greater emphasis on the loss of muscle power or locomotor function, i.e. *dynapenia* (Clark and Manini,

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2008) or *dysmobility syndrome* (Binkley et al., 2013), respectively. The muscle deficit and dysfunction secondary to diseases like cancer, HIV or COPD are usually termed *cachexia* (from Greek *kakos*, bad and *hexis*, condition). This term is not specific for muscle because it refers to weight loss in general, although weight loss is more readily assessed and usually accompanied by muscle loss. Notably, unintentional weight loss was part of the first developed *frailty* criteria (Fried et al., 2001), underscoring the intimate relation between sarcopenia and frailty (Gielen et al., 2012). *Muscle wasting diseases* has been proposed as the umbrella term for cachexia, sarcopenia and neuromuscular diseases (Anker et al., 2014). In recent years there is also increasing awareness that osteoporosis not only often coexists with sarcopenia and falls risk (Huo et al., 2015; Verschueren et al., 2013) but that both are part of the same disease i.e. that bone and muscle loss share common causes, may reinforce eachother via muscle-bone interactions, and require a concerted treatment approach. This integrated view is underlined by use of the terms *osteosarcopenia*, *sarco-osteoporosis*, or *musculoskeletal frailty* (Gielen et al., 2012; Huo et al., 2015).

Effective drugs for cachexia, sarcopenia or most neuromuscular diseases are currently lacking, but several promising candidates are now under development. Whether such treatments could be useful for osteoporosis too will be examined in this review. It is important to realize that age-related declines in bone structure and strength are only moderate compared to the exponential rise in fracture risk in the elderly, pointing to the importance of additional fracture risk factors, especially falls (Riggs et al., 2006). Indeed, fractures are not completely prevented by currently available powerful anti-resorptive drugs (bisphosphonates or denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa B ligand, RANKL) or even osteoanabolic treatments like intermittent parathyroid hormone (PTH) therapy (with e.g. teriparatide). Presumably, these strategies still do not sufficiently increase bone strength and obviously, they do not reduce concurrent falls risk or resolve underlying sarcopenia and frailty. Conversely, physical exercise or mechanical interventions like vibration therapy may improve balance and muscle power, but effects on bone appear modest at best (see Section 3.1.3). Thus, in order to 'cure' osteoporosis, we need more potent anabolic -pharmacological or biomechanical- therapies which preferentially strengthen the musculoskeletal unit as a whole, and simultaneously address coexisting sarcopenia, frailty and falls risk, especially in the oldest old.

The aim of this review is to update our understanding of the molecular and cellular basis of muscle-bone interactions and mechanobiology. In the final chapter, we will critically examine the effects of muscle-anabolic stimuli on bone and vice versa. Indeed, with the recognition of typical 'bone' signaling pathways also affecting muscle and anecdotal evidence that bone metabolism influences muscle outcomes, the reverse possibility of bone-to-muscle effects is also gaining ground. We will do so with a focus on preclinical animal models, as in vivo experimental models for sarcopenia and frailty are high on the research agenda (Seldeen et al., 2015).

2. Preclinical models to study mechanical loading and disuse

Before discussing the results of studies on musculoskeletal mechanobiology in further detail, we provide here an overview of preclinical models. It is important to understand the strengths and limitations as well as caveats of different models before we discuss the lessons learned from these models.

2.1. In vitro models of skeletal mechanoregulation

Osteoblasts and especially osteocytes (either as primary cultures or osteoblast-/osteocyte-like cell lines) are most often used to study the effects of mechanical loading on bone in vitro. However, many often-used cell lines such as MLO-Y4 cells only partially display osteocyte-like features, e.g. showing stellate morphology and lacking certain osteoblast markers, but still showing proliferation and lacking expression of key osteocyte markers like sclerostin or fibroblast growth factor 23 (FGF-23). Primary osteocyte culture techniques may circumvent some of these limitations but remain an imperfect reflection of the in vivo situation (Kalajzic et al., 2013).

Paracrine effects of muscle-derived cytokines (so-called myokines, see Section 3.4) or growth factors on bone have been studied using osteoblast/osteocyte cultures in conditioned media from muscle cell lines like C2C12 or primary myotubes (Colaianni et al., 2014; Johnson et al., 2014). Conversely, muscle cells can be co-cultured with osteoclasts, osteoblasts or osteocytes to study to role of soluble, cell-derived factors or direct intercellular communication on bone cells in trans-well or mixed culture setups, respectively (Jähn et al., 2012; Juffer et al., 2014).

In the current paradigm of skeletal mechanoregulation, osteocytes are believed to constitute the main cell type which senses mechanical loads through shear stress from fluid flow in their extensive lacunocanalicular network and subsequently orchestrate osteoblast and osteoclast activity (Klein-Nulend et al., 2013). In vitro, osteoblasts and osteocytes respond to pulsed fluid flow or centrifugation-induced hypergravity by opening of connexin 43 hemichannels (Burra et al., 2010), altering transcription of genes like cyclo-oxygenase 2 (COX-2, the rate-limiting enzyme in prostaglandin synthesis) and producing factors like nitric oxide (NO), which are known to be important regulators of bone turnover (Klein-Nulend et al., 2014; Lau et al., 2010; Tan et al., 2007). The osteocyte primary cilia is thought to be an important mechanosensor and mechanotransduction signaling hub, in conjunction with the thin, viscous pericellular matrix which surrounds osteocytes and connects to their cytoskeleton (Klein-Nulend et al., 2012; Malone et al., 2007). Mechanical loading has also been studied in explants or 3D tissue culture systems (Barron et al., 2010; Klein-Nulend et al., 1986; Vazquez et al., 2014). With regards to unloading or microgravity, studies have also examined cellular responses to spaceflight or parabolic flights, or attempted to mimic these conditions, e.g. using the random positioning machine or rotating wall vessels (Ulbrich et al., 2014).

In summary, several in vitro models exist to study musculoskeletal mechanoregulation, although in vivo models may be more physiologically relevant.

2.2. Role of different cell types in skeletal mechanoregulation in vivo

Several studies in animals have tried to delineate a role for osteoblasts and osteocytes in skeletal mechanoregulation in vivo. In one study, the diphtheria toxin receptor was expressed under the dentin matrix protein 1 (Dmp1) promoter, allowing preferential ablation of 70–80% of osteocytes but reportedly no osteoblasts. These mice became resistant to *unloading*-induced bone loss, but loading responses were unaffected (Tatsumi et al., 2007). Similarly, downregulation of the Wnt inhibitor sclerostin in osteocytes is believed to be an essential component of osteocyte mechanoregulation, but loading was shown to produce sclerostin-independent osteogenic responses in Sost−/− mice (Morse et al., 2014). Still, osteocytes are believed to be involved in skeletal loading responsiveness by sensing fluid flow produced by mechanical stimuli (Wang et al., 2013; Wang et al., 2014). A role for the osteocyte primary cilia as a mechanotransductor is supported by impaired loading responsiveness in mice with osteoblast and osteocyte-specific deletion of primary cilia components like kinesin

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family member 3A (*Kif3A*) or polycystic kidney disease 1 homolog (*Pkd1*) (Qiu et al., 2012; Temiyasathit et al., 2012; Xiao et al., 2011). Connexin 43 on the other hand forms mechanoresponsive hemichannels which are involved in gap junction communication within the osteocyte network (Batra et al., 2012; Cheng et al., 2001). Conditional Cx43-KO mice have indeed been suggested to have altered skeletal responses to loading and disuse, although both increases and decreases have been observed (which may be due to differences in Cre mice used for genetic recombination, or technical aspects of strain-gauging; see Section 2.3) (Bivi et al., 2013; Grimston et al., 2008, 2011, 2012; Lloyd et al., 2012; Lloyd et al., 2013; Zhang et al., 2011).

In summary, although osteocytes have now become generally accepted as chief regulators of skeletal mechanobiology, a critical review of the evidence learns that this remains based on indirect evidence, justifying further investigation. Because in vivo models remain the golden standard in this regard, we will discuss available animal models of loading and disuse in the next section.

2.3. Animal models of mechanical loading

A primary distinction can be made as to whether animal models of musculoskeletal loading require voluntary physical exercise, forced physical exercise, or passive mechanostimulation of bone and/or muscle (Table 1). In general, voluntary physical exercise models (e.g. spontaneous wheel running) bare greatest relevance to the clinical situation and require the least investigator effort, allowing long-term studies. However, they do not establish a causal link between the mechanical stimulus and the observed musculoskeletal effects because exercise affects a myriad of other systems e.g. cardiovascular, immune function, endocrine etc. Forced physical exercise interventions have the same pitfalls as voluntary activity models with an additional caveat of being more stressful. Yet the intensity of the exercise can be tightly controlled and the effect of behavior e.g. lack of motivation is excluded. Electrical neural stimulation models (e.g. Lau et al., 2015) allow greater control over stimulus amplitude, timing etc. and allow muscle-bone interactions, but are more invasive and do not prove that the effect on bone is purely via motorneurons or skeletal strains from muscle contractions. Direct bone loading models (radius/ulna, tibia/fibula) dissociate bone from muscle stimulation and allow calibration of loads on bone with strain gauges (Meakin et al., 2014a, b); however this may have limited clinical relevance because such an intervention is not easily applied in humans. Moreover, strain gauging is technically challenging and limited to just one cortical bone site.

Other passive mechanical stimuli that have been tested in animal models can be more readily envisioned as potential interventions for musculoskeletal disuse. For example, electromyostimulation (triggering muscle contractions by locally applied electrical currents over certain muscle groups) prevents bone loss in the hindlimb-unloaded rat model (Lam and Qin, 2008) as well as in experimental spinal cord injury, suggesting that muscle contractions can restore bone loss independently from neural input (Qin et al., 2013). Electromyostimulation is attractive because it is already commonly used by athletes and in a recent pilot randomized trial, it increased muscle mass (although not bone mass) in spinal cord injury patients (Arija-Blazquez et al., 2014).

Whole-body vibration platform studies have been performed in mice and rats, whereby these rodents undergo high-frequency (45–150 Hz) vertical oscillations which trigger muscle contractions as well as producing direct impact on bone. These studies have found evidence of increased bone volume, which was however evident at certain distal sites but not others, and associated with magnitude across the low-level range in a non-linear fashion (0.1 or 1.0 g but not 0.3 g) (Christiansen and Silva, 2006; Hatori et al., 2015). Studies in sheep, turkeys and humans further suggest that bone responses may be frequency-dependent, possibly related to lower resonance frequencies in larger species (Christiansen and Silva, 2006; Rubin et al., 2001).

Although low-intensity pulsed ultrasound (LIPUS) has been extensively studied in relation to fracture healing (Griffin et al., 2014), studies in osteoporosis models have been disappointing (Warden et al., 2001a, b; Yang et al., 2005). However, other recent pulsed focused ultrasound regimens did prevent bone loss in animal models (Ferreri et al., 2011; Poliachik et al., 2014; Uddin and Qin, 2015). Further investigation using these animal models is required to determine optimal mechanical stimulation protocols.

2.4. Animals models of disuse

Animal models to investigate disuse are generally more invasive compared to loading models. They differ in the extent to which they

Table 1
Animal models of mechanical loading.

In vivo models	Clinical relevance	Caveats	Examples
Voluntary physical exercise			
Wheel running	Endurance exercise	Confounding of environmental enrichment	
Jumping	Gravitational loading	Initially forced during operant conditioning	(Honda et al., 2001)
Tower climbing	Resistance exercise	Requires considerable housing space	(Notomi et al., 2001)
Forced physical exercise			
Running, jumping, …	Same as above	Stressful	(Ophoff et al., 2009)
Weightlifting	Resistance exercise	Can also be voluntary	(Wirth et al., 2003)
Bipedal stance exercise (raised cages)	Limited	Requires animal adaptation	(Yao et al., 2000)
Increased cage space, …	Public health, role of public space/ crowding	Possible behavioral changes, role of environmental enrichment	
Passive stimulation			
3 or 4-point bending	Limited	Unphysiological direction of skeletal loads	(Reijnders et al., 2007)
Ulna loading	Limited	Mainly cortical bone	
Tibia loading	Limited	Still requires sedation; risk of joint overloading	(De Souza et al., 2005)
Free-fall impact	Impact loading	No direct strain control	(Welch et al., 2004)
Electroneurostimulation	Use as intervention	Highly invasive; non-selective mechanism e.g. of skeletal innervation (see Section 3.3.)	(Lam and Qin, 2008)
Electromyostimulation	Use as intervention		
Pulsed focused ultrasound	Use as intervention	Mixed findings in different studies; required confirmation	(Poliachik et al., 2014)
Whole-body vibration	Use as intervention		(Camargos et al., 2015)
Hydraulic stimulation	Use as intervention		(Hu et al., 2012)

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are reversible and allow the study of reloading/rehabilitation (Table 2). In the most widely used model originally developed for NASA studies (Morey-Holton and Globus, 2002), rodents are hindlimb-suspended by their tails. The head-down tilt also reproduces fluid shifts experienced by astronauts. This is also the only model in which ground reaction forces of the hindlimbs are completely abolished. In a recent variant of this model, partial weight suspension allows for a tunable percentage of bodyweight which can be delivered by a two-point harness, with bone loss starting already from a 30% reduction in weight bearing (Ellman et al., 2013). Some models disrupt nervous transmission (neurectomy, spinal cord injury), which probably has pleiotropic effects on bone (see Section 3.3) beyond the sole loss of muscle contractions. Another popular and accessible model involves botulinum toxin injection, which interferes with presynaptic release of the vesicle-bound neurotransmitter acetylcholine. This produces rapid bone loss as demonstrated in rats, mice and zebrafish (Chappard et al., 2001; Poliachik et al., 2010; Recidoro et al., 2014; Warner et al., 2006). This effect of neuromuscular blockade ultimately depends on osteoclast activity (Aliprantis et al., 2012), although the initial molecular events triggering paralysis-induced bone loss remain to be determined. Caveats of this model include its systemic component (bone loss is also evident in internal control limbs) and the potential concern of blocking not only motor efferents but also other neurotransmission relying on acetylcholine release e.g. in parasympathetic fibers (see also Section 3.3).

The most fascinating, natural disuse model is undoubtedly mammalian hibernation, e.g. in marmots and squirrels. Bears, the most advanced hibernators, avoid significant bone loss despite sometimes >6 months of relative immobility (Lennox and Goodship, 2008; McGee-Lawrence et al., 2009; McGee et al., 2008; Vestergaard et al., 2011; Wojda et al., 2013). This is accompanied by decreased bone turnover with balanced resorption and formation, possibly due to autonomous nervous system effects or circulating anabolic hormones (Donahue et al., 2006; Seger et al., 2011).

In summary, various animal models of loading and disuse exist. Each model differs in terms of its generalizability to clinical situations or its possible use as a clinical intervention. No model is perfect and all models have specific caveats and technical challenges which need to be taken into consideration when interpreting results of research studies reported below.

3. The integrated physiology of bone and muscle

The mass and strength of bone and muscle need to be matched, both during development and maintenance. Their concerted regulation is probably determined by both genetic and environmental (e.g. nutritional) factors, either via shared control mechanisms (e.g. endocrine, nervous system regulation) or by muscle-bone crosstalk at the organ level (biomechanical signals from physical activity), cellular level (intercellular communication) or molecular level (myokines, cytokines or growth factors) (Fig. 1).

Bone and muscle mass and functions are integrated at several levels: (i) biomechanical signals acting both directly on bone and muscle as well as indirectly via muscle contractions on bone, (ii) shared nutritional signals as well as endocrine regulation e.g. growth hormone/insulin like growth factors and binding proteins (GH/IGFs/IGFBPs), glucocorticoids, sex steroids and vitamin D, (iii) central nervous system control of muscle and bone metabolism, (iv) local hormones, growth factors and cytokines acting in both tissues as well as possibly via reciprocal muscle-bone paracrine actions, (v) putative intercellular communication between bone and muscle cells.

3.1. Biomechanical signals

Bone is a biomechanical tissue which adapts its structure to withstand varying forces acting upon it in the most efficient way, i.e. able to withstand habitual strains with the least possible material (because building, maintaining and carrying around bone mass requires considerable energy). According to the mechanostat theory (Frost, 2003), bone strength is matched to the mechanical strains it experiences, and when more or less stress is applied, bone adapts until a new strain equilibrium is reached. However, not only the magnitude of strains determines the subsequent osteogenic response; loads/strains are also more effective when they are acute/dynamic (as opposed to static loads, e.g. jumping vs. standing) and have an unusual frequency/distribution, with periods of rest between them (Avin et al., 2015; Lam et al., 2011; Meakin et al., 2014a, b).

3.1.1. Importance of local strains vs. other biomechanical signals

Apart from the stress-strain theory, other biomechanical signals have been proposed to trigger osteogenic responses (Avin et al., 2015). Price's group has shown that osteogenic gains and

Table 2
Animal models of musculoskeletal unloading.

In vivo models	Clinical relevance	Reversible	Caveats	E.g.
Casting	Casting, immobilization	Readily	Difficult to be effective; rodents chew at cast	(Yarrow et al., 2014)
Hindlimb suspension, partial weight suspension	Spaceflight	Readily	Reproduces body fluid shifts; may provoke herniation of testes into inguinal canal in rodents	(Morey-Holton and Globus, 2002)
Botulinum toxin injection	Botulinum toxin injection, neuro-muscular disorders	Yes, predictable	Possible local autonomous nervous system effects; considerable systemic effects	(Chappard et al., 2001)
Tenectomy, tendon clipping	Tendon rupture e.g. Achilles heel	Little		
Sciatic neurectomy	Nerve injury	Little	Neural component	(Sugiyama et al., 2012)
Spinal cord injury (contusion, transsection)	Spinal cord injury	Very little	Multisystem derangments	(Yarrow et al., 2014)
Genetic models e.g. Duchenne muscular dystrophy	Neuromuscular diseases	None, progressive	Multisystem derangments	(Rufo et al., 2011)
Hibernating mammals	Limited	Not applicable		(Seger et al., 2011)

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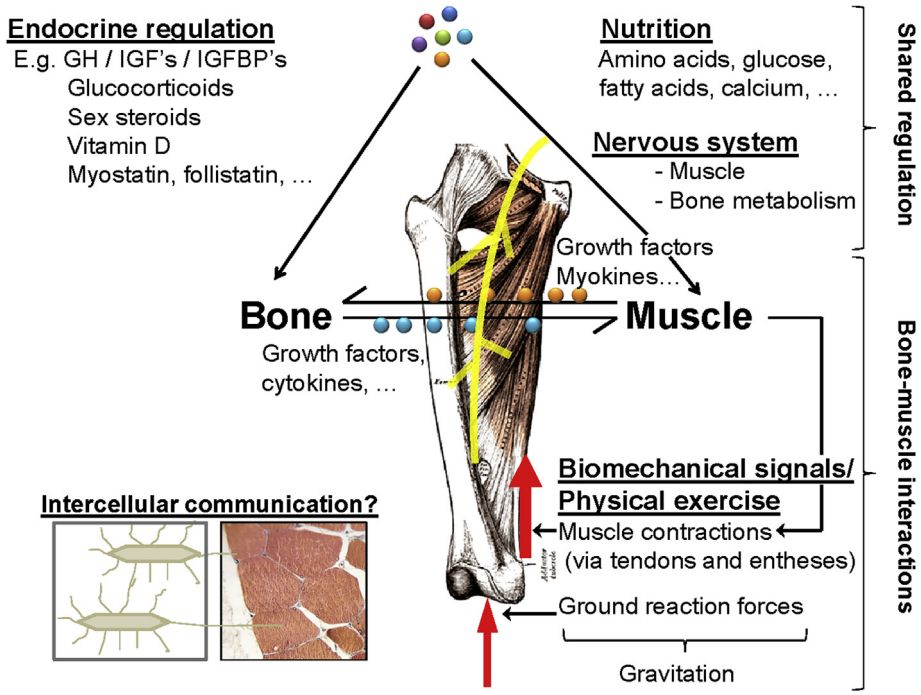

Fig. 1. Schematic overview of mechanisms involved in muscle-bone interactions.

downregulation of osteocytic expression of sclerostin (a crucial Wnt signaling inhibitor) are not necessarily related to peak strains elicited during mechanical loading (Moustafa et al., 2012). This could be due to inaccuracies in measuring/modeling peak surface strains, because the true stimulus is not the absolute strain but its deviation from habitual strain patters (the comfort zone or "lazy zone" theory (Frost, 2003; Turner et al., 1994)), or because alternative biomechanical inputs are at play. However, experimental studies in mice and recently for the first time in humans suggest that the relationship between bone strength and the loads imposed on it is essentially linear with no evidence of an "adapted window" or lazy zone where bone mass remains constant over a range of loads (Fig. 2) (Christen et al., 2014; Sugiyama et al., 2012). Thus, this element of the mechanostat theory does not seem to uphold experimentally, although the central tenet (bone adapts its strength to habitual strains) remains valid.

If osteocytes would sense mechanical stimuli not directly via strain but via fluid flow and shear stress, vibration could increase bone mass independent from any produced strains. Rubin et al. have shown that high-frequency, low-magnitude vibration (producing only 5 microstrain) increased trabecular bone volume in a sheep hindlimb model (Rubin et al., 2002). Clinical studies also suggested benefit in children and postmenopausal women (Gilsanz et al., 2006; Rubin et al., 2004; Ward et al., 2004). However, no effect was seen on cortical bone (Castillo et al., 2006; Rubin et al., 2002). Vibrating the leg (low-level accelerations) without loading/deformation was also suggested to produce osteoanabolic effects by Rubin's group, although independent investigators could not confirm this (Christiansen et al., 2009; Garman et al., 2007). An intriguing recent study suggests that resonance phenomena might partly explain the highly location- and frequency-specific effects of in vivo tibia loading (Zhao et al., 2014). This intriguing possibility requires further study.

A non-invasive hydraulic stimulation model (see Table 1) was

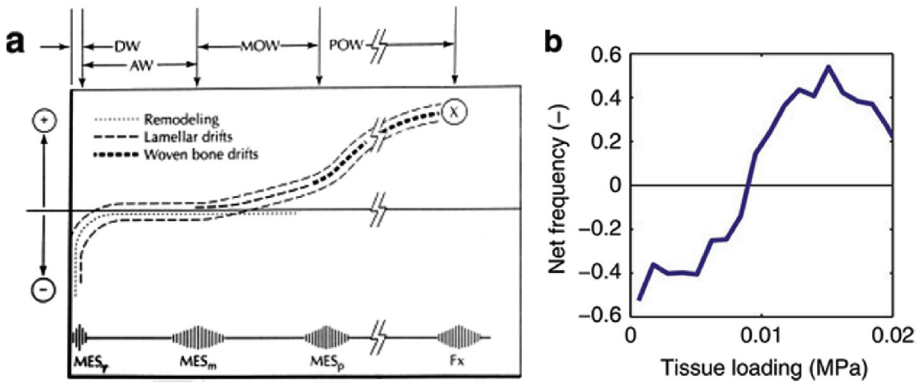

Fig. 2. (a) Theoretical model of the relationship between bone gain or loss (Y-axis) and peak bone strains (X-axis) proposed by Frost, including an "adapted window" (AW), parallel to the horizontal line, in which no net gain or loss occurs (Frost, 2003). (b) Results from Christen et al. showing the net difference between bone formation and resorption frequencies (Y-axis) according to strain energy density (a measure of tissue loading; on the X-axis), showing the opposite pattern i.e. a sigmoidal dose–response curve which is steep around the x = 0 line and plateaus at its extremes, but with no evidence of a steady-state "lazy zone" (Christen et al., 2014).

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recently developed in which a blood pressure cuff is intermittently inflated around the tibia, mimicking the muscle pump. This increased intramedullary pressure and cortical bone volume as well as mitigating trabecular bone loss in a disuse rat model (Hu et al., 2012; Hu et al., 2014; Hu and Qin, 2014). However, whether the underlying mechanism truly involves bone interstitial fluid flow, vascular ischemia-reperfusion signaling or release of myokines requires further investigation.

Finally, a series of rodent studies suggested that loading one bone may induce adaptive responses in distant bones via sensory neuron afferent signals (Sample et al., 2008; Sample et al., 2010, 2012). However, these findings of osteogenic responses in distant bones have been contradicted by other investigators and thus remain highly controversial (Sugiyama et al., 2010).

All in all, we can conclude that mechanotransduction is still a largely local phenomenon (McBride and Silva, 2012).

3.1.2. Importance of muscle contractions vs. other forces

The loads on the skeleton can be classified as muscle contraction forces acting via tendon attachment sites on the one hand, and ground reaction forces (impacts) or gravitational loads on the other hand (Fig. 1). Theoretically, the largest forces on bone arise from muscle contractions, and these may even be amplified further by the effect of short lever arms. During a one-legged jump for example, the calf muscles exert a force on the foot bones three times greater than the ground reaction forces, resulting in a combined load of about 14 times our bodyweight (Rittweger et al., 1999). Similarly, between walking 3 km/h and running 12 km/h, peak hip contact forces increase from 4.4 to 10× bodyweight, while ground reaction forces increase from only about 1–2.5× bodyweight (Giarmatzis et al.). In contrast, cyclists and swimmers also have great muscle mass and strength but bone mass appears not to be increased, suggesting that muscle activity amplifies mainly the effect of ground reaction forces but is dramatically less effective in a low-gravity environment (Gomez-Bruton et al., 2013; Olmedillas et al., 2012).

Using various animal models described in Section 2, several studies have examined whether muscle forces or gravitational loading are most important for bone homeostasis. Botulinum toxin injection has been reported to disrupt gait only transiently, while muscle atrophy and bone loss persist (Manske et al., 2011). Combined hindlimb suspension and botulinum toxin injection has additive effects, with greatest effect of the latter (Ellman et al., 2014; Warden et al., 2013a, b). Still, the importance of muscle contractions vs. gravitational and ground reaction forces has not been answered definitively by these studies and has proven challenging to address, showing again the need for a holistic view on musculoskeletal interactions.

3.1.3. Whole-body vibration: bone, muscle and balance stimulation?

Whole-body vibration has generated much clinical interest because it could be a safe, low-demanding type of exercise to stimulate bone accrual, trigger muscle contractions and improve balance (Wysocki et al., 2011). Several human trials have indeed shown improvements in muscle strength and balance parameters (Bautmans et al., 2005; Bogaerts et al., 2007, 2011; Bruyère et al., 2005; Gusi et al., 2006; Roelants et al., 2004; Rogan et al., 2011; Verschueren et al., 2004). One trial also reported reduced falls risk (von Stengel et al., 2011). However, randomized trials in elderly human subjects have generally failed to demonstrate bone mineral density (BMD) increases (Buckinx et al., 2014; Slatkovska et al., 2011, 2014; Tankisheva et al., 2015; Verschueren et al., 2011; Wysocki et al., 2011), with notable exceptions (Gusi et al., 2006; Verschueren et al., 2004). Still, BMD gains were demonstrated in some studies in children and young adults (Gilsanz et al., 2006; Lam et al., 2013; Reyes et al., 2011; Ward et al., 2004). The lack of effect on BMD may have several reasons. First, the effect of vibration appears to be highly localized (Coughlin and Niebur, 2012) and may not be adequately captured by conventional dual energy X-ray absorptiometry (DXA). Secondly, the osteogenic response to vibration may become blunted with ageing (Lynch et al., 2010) (see Section 3.1.4.). Thirdly, because the vibratory stimulus may not have been sufficiently intense in some trials or may not have been transmitted sufficiently far (Pel et al., 2009; Tankisheva et al., 2013). Fourthly, because of technical differences between vibration platform designs (Pel et al., 2009). Or fifthly, because the optimal vibration characteristics remain to be determined (see Section 3.1.). Other mechanical stimuli have proven effective in rodent models (e.g. dynamic hydraulic stimulation or electromyostimulation, see Section 2.2) and require further investigation in humans.

Overall, we can conclude that whole-body vibration remains an attractive therapeutic candidate for musculoskeletal strengthening and balance improvement, but more research on this and other biomechanical therapies for osteoporosis as well as sarcopenia and falls is warranted to define the most effective and convenient strategy.

3.1.4. Musculoskeletal mechanoresponsivity in senescence

In this section, we will examine the influence of ageing on musculoskeletal mechanoresponsivity. For skeletal muscle, evidence in animal models and humans shows that hypertrophy and protein synthesis in response to exercise may be blunted. However, this is not confirmed in all studies, and training can certainly still be effective in the elderly (Harber et al., 2012; Leenders et al., 2013). In studies which did show impaired responses, this was accompanied by diminished responsiveness of crucial myocyte signaling pathways such as Akt/mammalian target of rapamycin (mTOR), extracellular signaling regulated kinase (ERK) 1/2, insulin-like growth factor-1 (IGF-1) and microRNAs (see also Hackl et al. elsewhere in this Special Issue) (Fry et al., 2011; Rivas et al., 2014). Increased oxidative stress as well as Notch signaling may also play a role (Kovacheva et al., 2010). Lower satellite cell number and density is a hallmark of senescent muscle (Ballak et al., 2015) and has been shown in mouse parabiosis experiments to be involved in impaired muscle regeneration via systemic factors in the aged milieu interne (Conboy et al., 2005). However, there is consistent evidence that these muscle progenitor cells are not necessarily to blame for sarcopenia or diminished hypertrophy in ageing (Fry et al., 2015; Lee et al., 2012). Moreover, muscle protein breakdown, autophagy and ubiquitination do not appear to be affected by ageing either, so therapeutics targeting these pathways may retain efficacy in elderly sarcopenic subjects (Fry et al., 2013; Stefanetti et al., 2014). All in all, the underlying cause of age-related blunting of skeletal muscle responsivity remains unclear.

Regarding bone, studies in aged animals have also reported diminished mechanical loading responses (Lynch et al., 2011; Meakin et al., 2014a, b, 2015; Srinivasan et al., 2010; Turner et al., 1994, 1995; Willie et al., 2013), although other studies have suggested unaltered or paradoxically increased mechanoresponsivity (Brodt and Silva, 2010; Jarvinen et al., 2003; Leppanen et al., 2008; Silva et al., 2012). These seemingly contradictory findings may depend on technical aspects of strain gauges (see Section 2.2), the animal's gender and fighting behavior in group vs. single-housed males (Meakin et al., 2013), loading/exercise protocols used (inducing lamellar or woven bone formation), endpoints examined (bone formation, structure or strength) and reporting of absolute vs. relative changes. Additionally, ageing bones feature overall better geometric adaptation, producing lower strains for the same loads (Willie et al., 2013). Finally, ageing may also produce more

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pronounced alterations in bone mineral and matrix (collagen) properties in response to loading, rather than structural adaptations (Aido et al., 2015). In any case, ageing certainly does not completely prohibit even woven bone formation, although strain threshold may be higher (Holguin et al., 2014; Turner et al., 1995). Whether the senescent skeleton also becomes less sensitive to mechanical stimulation in humans is even less clear, but preliminary studies suggest that this may be the case (Saarto et al., 2012; Winters-Stone et al., 2012).

Even if the mechanostat is assumed to suffer from senescence (i.e., bone formation not responding appropriately to mechanical stimulation), the underlying mechanisms are incompletely resolved. An important distinction has to be made between mechanoresponsivity and mechanosensitivity, i.e. whether the deficit lies in sensor vs. effector mechanisms. Most studies are only able to assess the final response; mechanosensitivity is much more challenging to address because it is difficult to quantify in vivo. Ageing mice have decreased load-induced osteoblast proliferation but unaltered sclerostin downregulation, which may suggest that impaired mechanosensitivity is not the culprit (Meakin et al., 2014a, b). However, despite diminished osteoblast function in senescence, skeletal responses to other stimuli like intermittent PTH are not diminished or even increased with ageing (Jilka et al., 2010; Knopp et al., 2005), suggesting a mechanical stimulus-specific deficit. An interesting recent study using serial in vivo microcomputed tomography (microCT) suggested that ageing blunts mainly the recruitment of novel mineralizing surfaces (i.e. *modeling*-based bone formation), with a lesser effect on formation thickness or eroded surface (which are *remodeling* parameters) (Birkhold et al., 2014). Most previous studies have examined only bone resorption and formation, but not whether bone formation occurred adjacent to previous resorption sites (=remodeling) or on novel surfaces (=modeling). Although considerable expertise is required to make this distinction and modeling has been considered irrelevant in the adult skeleton, emerging evidence suggests that this may not be the case (Ominsky et al., 2015).

At the cellular level, it is known that osteocyte apoptosis is an important hallmark of ageing (Jilka et al., 2007), but the role of osteocyte senescence in faulty mechanotransduction remains to be investigated. At the molecular level, one of the possible mechanisms involves endoplasmatic reticulum stress. Indeed, aged osteocytes show increased endoplasmatic reticulum stress, and both ageing and endoplasmatic reticulum stress diminish COX-2 responses of primary osteocytes to pulsative fluid flow stimulation (Chalil et al., 2015). Although mechanical loading in vivo or pulsed fluid flow in vitro rapidly upregulates COX-2 (Bakker et al., 2003; Klein-Nulend et al., 2013), the importance of prostaglandin signaling for skeletal loading responses requires further confirmation in vivo. Indeed, COX-2 knockout mice show a normal loading response, which may however be due in part to compensatory COX-1 regulation (Alam et al., 2005). Other investigators showed that low-dose cyclosporin (which modulates intracellular calcium signaling) restores load-induced bone formation in ageing animals, although the exact target cells of this effect remain unclear (Srinivasan et al., 2010; Srinivasan et al., 2014; Worton et al., 2014).

In summary, it appears that the threshold for anabolic responses of both aged muscle and bone are somewhat raised, although potent biomechanical stimulation can still be effective. Further research is needed to define the underlying cellular and molecular mechanisms, with particular attention for remodeling-vs. modeling-based bone formation (i.e. bone formation refilling previous excavations vs. de novo bone formation on previously quiescent surfaces).

3.1.5. Can physical activity during growth prevent osteosarcopenia?

Another critical question is whether the musculoskeletal benefits of physical activity during peak bone and muscle mass acquisition are sustained into old age, or whether bone and muscle strength inevitably converge to an inherent set-point (Gafni and Baron, 2007). Low peak bone mass (PBM) is evident in both daughters and sons of women and men with osteoporosis (Lapauw et al., 2009; Nagy et al., 2013), suggesting that osteoporosis risk is partly due to diminished PBM acquisition. Theoretical models have suggested that even small increases in PBM may postpone the onset of osteoporosis substantially (Hernandez et al., 2003). The circumpubertal growth spurt constitutes an attractive window for exercise interventions because of the great relative contribution to ultimate bone mass acquisition during these few years (Baxter-Jones et al., 2011), as well as increasing sedentarism in children around this age.

Several randomized trials have shown that impact exercise (e.g. jumping) in children may increase their bone density as well as cortical area and thickness (Gunter et al., 2008; Tan et al., 2014). The accrued benefits diminished but remained significant during post-intervention follow-up in several studies, although strictly speaking these children had not yet reached adulthood (Gunter et al., 2008; Meyer et al., 2013). Formally demonstrating that interventions increase not only PBM in children but also prevent osteoporosis in the elderly in a randomized trial may prove extremely difficult. Interestingly, part of the post-intervention benefits may be due to sustained spontaneous physical exercise, which may stimulate long-term effectiveness (Meyer et al., 2013).

In preclinical models, increased bone density or cortical thickness following e.g. running exercise at young age have been reported to be evanescent (Pajamaki et al., 2003). However, structural adaptations like increased cortical bone cross-sectional area from passive external (tibia or ulna) loading provide a larger biomechanical advantage which may also be intrinsically more difficult to erode with ageing or experimentally-induced estrogen deficiency (Warden et al., 2007; Warden et al., 2013a, b, 2014). After all, periosteal expansion is considered irreversible and confers quadratic increases in bone strength. Along the same lines, a recent quantitative CT study in former baseball players demonstrated superior cortical bone geometry, which declined after throwing activities ceased but were still partially maintained even long after retirement (Warden et al., 2014a, b). These results suggest that interventions which sufficiently enhance especially cortical bone around the age of PBM acquisition may translate into increased bone strength in old age, although the effects of less intense stimuli may be offset with time.

3.2. Shared endocrine regulators in bone-muscle interactions

Muscle and bone share many endocrine, paracrine and autocrine signaling pathways. Here we will focus on growth hormone/insulin-like growth factor (GH/IGF), vitamin D receptor (VDR), glucocorticoid receptor (GR) and sex steroid signaling. Myostatin, follistatin and related proteins may also have endocrine signaling (see Section 4). Importantly, all these endocrine regulators are affected by ageing and associated with osteoporosis and sarcopenia (Gielen et al., 2012).

3.2.1. Growth hormone/insulin-like growth factor signaling

Both human cases of growth hormone insensitivity (Laron syndrome) as well as mice with genetically disrupted GH/IGF signaling display concordantly impaired bone and muscle mass acquisition (Venken et al., 2007). Contrary to elderly humans however, normal ageing rodents do not have decreased IGF-1. Recently however, an inducible liver IGF-1 deficient model

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demonstrated increased muscle oxidative stress and accelerated bone loss in ageing mice (Gong et al., 2014). Also in adult men and women, relative appendicular skeletal muscle mass has been associated with cortical thickness and trabecular bone volume, and both correlate inversely with circulating concentrations of IGF-binding protein 2 (IGFBP-2, which restricts IGF-1 bioactivity) (Amin et al., 2004; Lebrasseur et al., 2012). Conditional deletion studies in mice suggest that while direct skeletal effects may result from both GH and IGF-1-receptor signaling in the osteoblast lineage (see Mohan et al. in this Special Issue), the effects on muscle are mediated by the IGF-1 and insulin receptor and do not require GH (Heron-Milhavet et al., 2010; Kim et al., 2005; Mavalli et al., 2010; Vijayakumar et al., 2013). However, whether muscle-specific IGF-1-resistance affects bone remains to be determined.

Regarding mechanoresponsivity, studies in conditional knock-out mice found that a functional IGF-1-receptor is not required for exercise-induced muscle hypertrophy (Spangenburg et al., 2008). Contrary to the situation in muscle however, IGF-1 may be required for skeletal mechanoresponsiveness, while IGF-1-resistance may be involved in disuse osteoporosis. Using the noninvasive tibia loading model, Gross et al. showed that IGF-1 expression in osteoblasts increased periosteal bone formation in response to a low-magnitude loading regimen (Gross et al., 2002). Conversely, conditional deletion of IGF-1 in osteoblasts or osteocytes blocks osteogenic loading responses (Kesavan et al., 2011; Kubota et al., 2013; Lau et al., 2013). This is in line with earlier studies showing load-induced IGF-1 and IGFBP-2 expression in osteocytes (Reijnders et al., 2007a, b). Unloaded rats on the other hand are resistant to increased bone formation following IGF-1 administration (Sakata et al., 2003; Sakata et al., 2004; Sunters et al., 2010). Along the same lines, IGF-1 treatment in young male rats increased periosteal bone formation but exacerbated cancellous bone *loss* during unloading, although it did promote recovery during reloading (Boudignon et al., 2007). Similarly, IGF-1 therapy in mice had no effect on disuse osteopenia nor IGF-1-receptor phosphorylation in botulinum toxin-injected muscle (Niehoff et al., 2014). On the other hand, local IGF-1 overexpression in muscle conferred resistance to bone and muscle loss in disuse (Alzghoul et al., 2004). In another rat disuse model, GH treatment increased IGF-1 and mitigated loss of muscle mass and periosteal bone formation, but not trabecular bone volume or bone strength (Grubbe et al., 2014). Whether GH plays a role in mechanoregulation independently of IGF-1 remains to be investigated.

Decreased IGF-1 levels have been reported in several clinical situations of acute severe disuse (Aberg et al., 2011; Bondanelli et al., 2006; Boonen et al., 1999). A placebo-controlled trial in women with hip fractures showed that recombinant human IGF-1/IGFBP-3 enhanced bone density, grip strength and functional recovery (Boonen et al., 2002). Another small randomized study in elderly cast-immobilized men recently showed that GH therapy enhanced tendon and muscle cross-sectional area during rehabilitation (Boesen et al., 2014).

Collectively, these studies suggest that GH/IGF-1 deficiency and resistance is involved in reduced skeletal mechanoresponsitivity as well as muscle atrophy and bone loss in situations of disuse. IGF therapy may be useful to stimulate muscle mass and periosteal bone formation during rehabilitation, although combination with other therapies may be required to prevent trabecular bone loss in the acute phase.

3.2.2. Calciotropic axis regulation of muscle and bone

Vitamin D signaling is beneficial for bone health via its effects on intestinal calcium absorption, although it exerts osteolytic actions at higher concentrations (Lieben et al., 2012; Lieben and Carmeliet, 2013). Emerging evidence also points to possible neuromuscular effects of vitamin D (Bouillon et al., 2013; Girgis et al., 2013). Importantly, the presence of VDR in muscle has not been without controversy until recent studies which suggest that $1,25(OH)_2$-vitamin D stimulates muscle VDR expression (Bouillon et al., 2014; Girgis et al., 2014a, b; Pike, 2014; Pojednic et al., 2015). In VDR-knock-out mice, a recent study showed diminished locomotive ability accompanied by alterations at the neuromuscular junction (Sakai et al., 2015). Vestibular dysfunction in VDR-KO mice has also been suggested (Minasyan et al., 2009). Whether calcium, VDR or PTH signaling are involved in mechanoregulation remains however unknown but at least in vitro, $1,25(OH)_2$-vitamin D has been suggested to regulate NO synthesis in osteoblasts in response to pulsed fluid flow (Willems et al., 2012).

Numerous observational studies have demonstrated an association between vitamin D deficiency, osteoporosis and sarcopenia. A classical though underappreciated finding in rickets and/or osteomalacia can be profound muscle weakness; however, this could be due to either vitamin D, calcium deficiency, or increased PTH levels. Indeed, neuromuscular impairment is a classical symptom of hyperparathyroidism, and PTH replacement has been associated with *impaired* muscle function in hypoparathyroidism (Sikjaer et al., 2014). Other recent studies show that high PTH and 1,25-(OH)2-vitamin D (but not 25-OH-vitamin D) are associated with accelerated muscle loss in ageing men (Gielen et al., 2015; Renoud et al., 2014). Recent meta-analyses of randomized trials suggest that calcium and vitamin D supplementation in general do not increase bone density (Reid et al., 2014) nor decrease fracture risk (Bolland et al., 2014a, b), except possibly in elderly or institutionalized subjects (Chung et al., 2011). Another meta-analysis showed that vitamin D increases muscle strength but not mass or power, mainly in older adults (Beaudart et al., 2014). However, vitamin D with or without calcium does not reduce the risk of any fall (Bolland et al., 2014a, b; Gillespie et al., 2012), although it did reduce the *rate* of falls in institutionalized elderly (Cameron et al., 2012). Another recent 2×2 factorial trial in community-dwelling elderly women showed that exercise and balance training reduced the rate of injurious falls, while vitamin D had no effect (Uusi-Rasi et al., 2015). On the contrary, annual high-dose vitamin D has even been associated with *increased* falls risk in randomized trials (Sanders et al., 2010; Smith et al., 2007). The underlying mechanisms remain unclear but may be related to beneficial effects on mobility or a catabolic effect of vitamin D in the absence of calcium supplements.

We can conclude that avoiding vitamin D deficiency may have musculoskeletal benefits, although we expect no *anabolic* actions of high-dose vitamin D or calcium. The effects observed in knock-out mice may translate only to the most severely affected population, i.e. institutionalized but not community-dwelling elderly. More research into the neuromuscular targets of VDR actions, the independent contributions of calcium and PTH and the mechanisms for the increased falls risk in randomized trials with high-dose vitamin D is warranted.

3.2.3. Glucocorticoid receptor signaling

Ageing is associated with endogenous hyperglucocorticoidism as well as increased musculoskeletal sensitivity to the effects of glucocorticoids (Manolagas, 2010), which may contribute to muscle atrophy as well as bone loss. Glucocorticoids tend to act as a double-edged sword: both excess in Cushing syndrome as well as deficiency in Addison's syndrome are associated with bone resorption and muscle weakness (Hosoyama et al., 2005; Muls et al., 1982). The mechanisms underlying glucocorticoid-induced bone and muscle decay are manifold and include both direct effects on osteoblasts, osteocytes, osteoclasts and myocytes, as well as indirect deleterious effects on intestinal calcium absorption and sex steroid production (Jia et al., 2006; Manolagas, 2010; Plotkin

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et al., 2007).

Muscle-specific glucocorticoid receptor (GR) knock-out (GRKO) mouse models display increased muscle mass as well as favorable metabolic alterations (Shimizu et al., 2015). A similar model showed protection against cancer cachexia (Braun et al., 2013; Braun et al., 2014). Such mice are protected against muscle atrophy induced by exogenous and possibly also endogenous glucocorticoid excess (Hu et al., 2009) but not muscle atrophy from other stimuli (Watson et al., 2012). However, it remains to be determined whether these muscle-specific GRKO mice are also protected from glucocorticoid-induced osteoporosis via muscle-bone interactions.

3.2.4. Androgen and estrogen receptor signaling

Androgens not only exert anabolic effects on muscle, but also regulate bone metabolism via the androgen receptor (AR) as well as aromatization of androgens into estrogens and stimulation of estrogen receptors (ERα and ERβ) (Vanderschueren et al., 2014). Surprisingly however, the target cells and underlying mechanisms of these effects on muscle and bone are not entirely clear (Dubois et al., 2012).

Androgen receptor knock-out (ARKO) mice have reduced muscle mass, but physical activity is also reduced (Callewaert et al., 2009; MacLean et al., 2008; Ophoff et al., 2009a, b; Rana et al., 2011). However, in three different myoblast or satellite cell-specific ARKO models, this muscle mass deficit was far less pronounced and consistent only in partially decreased weights of the most androgen sensitive muscles (bulbocarvernosus and levator ani) (Chambon et al., 2010; Dubois et al., 2014; Ophoff et al., 2009a, b). This points to a possible role for non-myocytic AR; indeed, AR ablation in mesenchymal, probably stromal cells prevents bulbocarvenosus development (Ipulan et al., 2014). Importantly, deletion of the AR in muscle did not influence peak bone mass acquisition (Dubois et al., 2014; Ophoff et al., 2009a, b) (and unpublished data), demonstrating that at least in conditional genetic mouse models, the effects of androgens on bone are not entirely attributable to the (notably weak) effects on peripheral muscle mass.

Male double ARKO-ERαKO mice have additional muscle loss compared to ARKO alone (Callewaert et al., 2009). Other animal studies also support a possible role of estrogens on skeletal muscle, although there are conflicting findings whether this occurs via ERα or ERβ (Brown et al., 2009; Velders et al., 2012). Whether estrogens play any role in human muscle physiology is even less conclusive (Velders and Diel, 2013).

Several groups have shown that global ERαKO mice have a diminished skeletal mechanoresponsiveness (Lee et al., 2003; Windahl et al., 2013a, b). This effect however is ligand-independent via the activation function 1 (AF-1) interaction surface of ERα (Windahl et al., 2013a, b) and either not reproduced or even the opposite in ovariectomized rodents (Vanderschueren et al., 2014). Evidence from cell-specific ERαKO models has however been confusing. In a recent osteoblast- and osteocyte-specific (osteocalcin-Cre) ERαKO model, female mice displayed *enhanced* loading responsiveness (Melville et al., 2015). Windahl et al. on the other hand found unaffected osteogenic responses in loaded osteocyte-specific (Dmp1-Cre) ERαKO male mice (Windahl et al., 2013a, b). Conversely, Dmp1-Cre ERαKO *female* mice show increased sensitivity to trabecular bone loss, but protection from cortical BMD loss during hindlimb suspension (Kondoh et al., 2014). Further clarification of these findings is required.

Regarding androgens and muscle, it is well known that testosterone increases lean body mass as well as strength in young men or those with muscle wasting diseases, both in combination with or independently from physical training (Bhasin et al., 1996; Casaburi et al., 2004; Giorgi et al., 1999; Kvorning et al., 2006). Still, this may be an additive rather than a synergistic effect (Grinspoon et al., 2000; Sullivan et al., 2005). Studies in high-functioning elderly however have suggested no benefit of adding testosterone to physical training (Hildreth et al., 2013; Kvorning et al., 2013), and cardiovascular safety concerns have emerged in a trial in frail elderly men (Basaria et al., 2010).

Regarding skeletal mechanoresponsiveness however, the situation is quite the opposite. Both ARKO and orchidectomized mice display increased loading responsiveness, which was associated with downregulation of the Wnt inhibitor sclerostin in androgen deficient states (Callewaert et al., 2010; Sinnesael et al., 2015). The target cell for this effect remains however unclear since osteocyte-specific ARKO mice showed unaltered loading responses (Sinnesael et al., 2012). How sex steroid receptors interact with mechanical signaling remains a mystery, but altered phosphorylation of connexin 43 hemichannels via Akt is one possibility (Batra et al., 2014; Ren et al., 2013). Alternatively, secondary changes in bone turnover (low in ERαKO, high in gonadectomized and ARKO mice) and number of osteoblasts available potentially explain the observed phenotypes. On the other hand, a recent study in ovariectomized rats suggested that the addition of a bisphosphonate to whole-body vibration increased cortical thickness more than either intervention alone (Camargos et al., 2015). This may suggest that high bone turnover is not necessarily beneficial for mechanoresponsiveness, although vibration is also a less potent stimulus than external tibia loading.

In summary, AR and ERs appear to exert independent actions on muscle and bone, as well as on the skeletal response to mechanical loading. ERα has ligand-independent effects on skeletal loading responses, but sex steroid deficiency (contrary to ageing or IGF-I deficiency) rather seems to increase skeletal mechanoresponsiveness. Even though androgen deficiency may blunt the training response of muscle (Kvorning et al., 2006), studies in ARKO mice suggest that exercise remains an attractive strategy to mitigate musculoskeletal involution regardless of sex steroid deficiency (Ophoff et al., 2009a, b). The effects of androgens on muscle may also, via muscle-bone interactions, be partly responsible for skeletal sexual dimorphism in humans, although this is not the case in muscle-specific AR knock-out mouse models.

In general, we conclude that the tight covariation of bone and muscle in health and disease likely relies in part on shared regulatory mechanisms including GH/IGF-, vitamin D, glucocorticoid and sex steroid signaling. Tissue-specific genetic mouse models have provided unique insights into the direct effects of these pathways in target tissues. More work is needed to establish their indirect role via muscle-bone communication. Systemic perturbations in these endocrine systems in humans may exacerbate muscle and bone loss from unloading, but unloading certainly has direct effects independent of these endocrine systems. Exercise or mechanical stimuli likely remain effective even in elderly subjects with low GH/IGF-1, vitamin D or sex steroid levels.

3.3. Neural regulation of the muscle-bone unit

The dependency of proper muscle function on neuromotor input is well established. Denervation, spinal cord injury, neuromuscular diseases (incl. stroke, Parkinson's disease etc.) or loss of muscle contractions invariably results in profound muscle and bone loss. Some studies in disuse models suggest that the ensuing bone and muscle loss is at least partially reversible by electromyostimulation (Lam and Qin, 2008). Other anabolic stimuli e.g. androgens may still retain some efficacy as well (Cardozo et al., 2010; Libouban et al., 2008; Qin et al., 2015; Wu et al., 2012; Yarrow et al., 2014a, b). However, this might also be due to secondary hypogonadism in situations of disuse (Wimalawansa et al.,

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1999).

Direct neural regulation of bone metabolism is a more recently established concept. Apart from effects mediated by various hypothalamic and pituitary-derived peptide hormones (e.g. leptin (Takeda et al., 2002), neuropeptide Y, etc.), the periosteum as well as trabecular bone and adjacent bone marrow (and to a lesser extent cortical bone and the growth plate) are innervated directly by autonomic efferent and sensory afferent fibers (Gajda et al., 2005; Gajda et al., 2010; Mach et al., 2002). Furthermore, neurectomy enhances skeletal mechanoresponsiveness (de Souza et al., 2005), but this could have many reasons including reduced habitual strain patterns (see Section 3.1.1.) (Meakin et al., 2013), neuronal inhibition of bone remodeling or alternatively, a general permissive effect of increased bone turnover.

Sympathetic nervous system activity has been proposed to decrease bone mass by decreasing bone formation and increasing bone resorption via β2 adrenergic receptors (Adrb2) in osteoblasts, although β1 and α adrenergic receptors may also regulate bone mass indirectly (Bouxsein et al., 2009; Fonseca et al., 2011; Pierroz et al., 2012; Takeda et al., 2002). Sympathetic control of bone mass in turn has been suggested to be inhibited by parasympathetic signaling via M3 muscarinic receptors in the nervous system, at least in mice (Shi et al., 2010). Notably, skeletal muscle hypertrophy is a well known effect of the Adrb2 agonist clenbuterol, leading to its abuse in sports doping and the meat industry. However, it has an opposite, deleterious effects on bone (Bonnet et al., 2005; Cavalie et al., 2002). Part of this effect may be due to decreased fat mass in clenbuterol-treated animals and concomitantly reduced levels of leptin (peripheral leptin signaling being anabolic for bone) (Bonnet et al., 2005). Interestingly, Adrb2-KO mice show increased while Adrb1-KO mice show decreased bone mass and lack of response to mechanical loading (Pierroz et al., 2012). Others however showed using pharmacological strategies that the sympathetic nervous system does not mediate loading responses (de Souza et al., 2005; Marenzana et al., 2007). Elefteriou's group recently showed that sympathetic outflow may be responsible for the low bone mass associated with bilateral vestibular lesions in mice (Vignaux et al., 2013; Vignaux et al., 2015). Vestibular dysfunction and osteoporosis are common and may be relevant to ageing as well as spaceflight conditions. However, epidemiological studies in humans are conflicting as to whether β-blockers increase bone density or reduce fracture risk as they do in animal models, and a randomized trial found that propranolol *decreased* rather than increased bone formation markers (Reid et al., 2005).

Inhibition of sensory nerves leads to trabecular bone loss in mouse models, but whether this is due to altered loading patters or local mediators like substance P or calcitonin-gene-related peptide (CGRP) remains unclear (Ding et al., 2010; Heffner et al., 2014; Offley et al., 2005; Wang et al., 2009, 2010). More recently, neuron-specific deletion of semaphorin 3A was found to explain low bone formation and accrual via sensory innervation (Fukuda et al., 2013) (see also Verlinden et al. in this Special Issue). Whether sensory nerves are involved in the adaptive response to skeletal loading requires confirmation (Sample et al., 2008) (see Section 3.1.1.).

Thus, we can conclude that the concerted regulation of the bone-muscle unit may partly depend on common central nervous system regulation. To what extent disuse osteoporosis as well as muscle atrophy involves motoneurons, sensory, sympathetic or parasympathetic fibers requires further investigation in preclinical models. Validation of these concepts in humans is more challenging but necessary because of initial negative findings in a randomized trial with propranolol (Reid et al., 2005).

3.4. Myokines and intercellular communication

Possible paracrine muscle-to-bone communication requires close contact between these tissues; the periosteum constitutes such an interface. A long-standing clinical observation is the fact that fracture healing is accelerated not only when the periosteum is intact, but even more so when covered by functioning adjacent muscle (Stein et al., 2002). Similarly, investigation in rodent models has revealed that muscle flaps or even minced muscle (Utvag et al., 2002; Zacks and Sheff, 1982) are more beneficial than other tissues (Harry et al., 2008) in fracture healing, an effect that can be blocked by small-pore filters (Kaufman et al., 2008). Nevertheless, this may also represent an effect of muscle-derived blood vessels and/or stem cells in fracture healing.

Perdersen et al. coined to the term myokines for skeletal muscle-derived cytokines and chemoattract cytokines (chemokines) (Pedersen et al., 2003). Not only cytokines but in fact several proteins known to positively or negatively regulate bone mass are expressed in muscle (Table 3). Additionally, muscle tissue —as the biggest internal organ in our body-may contribute to endocrine regulation via these factors at more distant skeletal sites (Fig. 1). Myokines cannot easily be classified as positive or negative regulators since many have demonstrated both stimulatory and inhibitory musculoskeletal effects, depending on their concentration and experimental setting.

Research on myokines was headed by interleukin 6 (IL-6) (Pedersen et al., 2003), of which the release from contracting muscle is believed to promote glucose uptake and contribute to the favorable effects of exercise on energy metabolism (Pedersen and Febbraio, 2012). However, release of IL-6 from mechanically activated myotubes promotes osteoclastogenesis in vitro (Juffer et al., 2014). These and other studies suggest that exercise under nutrient (especially glucose) deprivation may stimulate bone resorption via elevated IL-6 levels (Pedersen and Febbraio, 2012). IL-6 is chronically elevated in Duchenne muscular dystrophy which may play a role in the systemic bone loss in this disorder (Rufo et al., 2011). On the other hand, IL-6 also has a direct role in osteoblast differentiation (Bellido et al., 1997), which may be positive at low levels since IL6-KO mice have *decreased* bone mass and tissue density (Yang et al., 2007). Similarly, IL-6 is required for muscle hypertrophy and recovery from muscle atrophy (Serrano et al., 2008; Washington et al., 2011), but chronic direct IL-6 administration *induces* muscle atrophy (Haddad et al., 2005). Other members of the IL-6 family include IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM) and ciliary neurotrophic factor (CNTF) (Bellido et al., 1996; Walker et al., 2010). LIF has myokine properties, and its receptor regulates bone formation (Walker et al., 2010). Recently, Sims' group showed that conditioned media from C2C12 myotubes reduced osteoblast differentiation in vitro, partially via CTNF (Johnson et al., 2014). Whether other members of this family can act as myokines remains to be seen.

IL-7 is another myokine (Haugen et al., 2010) with a known double-edged role in osteoclastogenesis and bone formation (Aguila et al., 2012; Weitzmann et al., 2002). IL-15 overexpression in muscle reduced body fat and increased bone mass in transgenic mice, although only when systemic IL-15 levels were increased as well (Quinn et al., 2009). Therefore, muscle-derived IL-15 is one of the few myokines with confirmed regulation of bone as well as fat mass, although this constitutes an endocrine rather than a paracrine mechanism.

Cyclically strained myotubes also increase expression of chemoattractant cytokines (chemokines) like IL-8, CXC ligand 1 (CXCL1) and CCL7 (Juffer et al., 2014), which are known to attract osteoclast precursors and other inflammatory cells into bone (Onan et al., 2009). Importantly, muscle cells express RANKL and its decoy

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Table 3
Example proteins secreted by muscle with known effects on bone: possible paracrine and/or endocrine mediators of muscle-bone interactions (non-exhaustive list).

	Ref.
Cytokines and chemokines (myokines)	
IL-6	(Pedersen et al., 2003)
IL-7	(Haugen et al., 2010)
IL-8	(Onan et al., 2009)
IL-15	(Quinn et al., 2009)
Leukemia inhibitory factor (LIF)	(Walker et al., 2010)
Ciliary neurotrophic factor (CNTF)	(Johnson et al., 2014)
Receptor activator of nuclear factor-kB signaling ligand (RANKL)	(Juffer et al., 2014)
Myostatin	See Section 4.
Semaphorins	(Henningsen et al., 2010)
Growth factors	
Insulin-like growth factor 1 (IGF-1)	(Hamrick et al., 2010; Henningsen et al., 2010)
IGF-2	(Henningsen et al., 2010)
Fibroblast growth factor 2 (FGF-2)	(Hamrick et al., 2010)
FGF-21	(Henningsen et al., 2010)
Transforming growth factor β (TGF-β) isoforms	(Henningsen et al., 2010)
Platelet-derived growth factor (PDGF)	(Henningsen et al., 2010)
Connective tissue growth factor (CTGF)	(Henningsen et al., 2010)
Bone morphogenetic protein 1 (BMP-1)	(Henningsen et al., 2010)
Matrix-related proteins	
Osteonectin (secreted protein acidic and rich in cysteine, SPARC)	(Chan et al., 2007; Henningsen et al., 2010)
Matrix metalloproteinase 2 (MMP-2)	(Chan et al., 2007; Henningsen et al., 2010)
Cathepsins	(Henningsen et al., 2010)
Coagulation factors (tPA, uPA, TFPI, …)	(Henningsen et al., 2010)

receptor osteoprotegerin (OPG), which are considered primordial regulators of bone resorption (Xiong et al., 2011). Moreover, loading acutely decreases the RANKL/OPG mRNA ratio in C2C12 myotubes (Juffer et al., 2014). This may have therapeutic implications for the use of anti-RANKL therapy with denosumab in disuse osteoporosis. The role of RANKL as a myokine and its relation to skeletal muscle atrophy is a topic of ongoing research.

Finally, irisin received much attention as an exercise-induced myokine which stimulates development of brown rather than white adipose tissue and regulates energy expenditure (Bostrom et al., 2012). Although mouse irisin also regulated osteoblast differentiation in vitro in one study (Colaianni et al., 2014), other studies have questioned the existence of irisin in humans (Albrecht et al., 2015; Raschke et al., 2013).

Muscle is not only a source of myokines (cytokines and chemokines) but also of growth factors. Hamwrick et al. provided the example of IGF-1 (see Section 3.2.1.) and fibroblast growth factor-2 (FGF-2) as two muscle-derived growth factors which localize to the muscle-bone interface and exhibit receptors in bone (Hamrick et al., 2010). Although IGFs and FGFs are probably among the most abundant muscle-derived growth factors, the list of candidate paracrine regulators in muscle-bone communication is extensive. Proteomic studies have identified muscle-derived peptides with known effects on bone metabolism including IGF-1, IGF-2 and several IGF binding proteins, TGF-β as well as other growth factors (Henningsen et al., 2010). Several matrix proteins identified (osteonectin, decorin, collagens, dentin matrix proteins, cadherins etc. (Chan et al., 2007; Henningsen et al., 2010)) may just represent common expression in muscle and bone.

Although all of these myokines are regulated by loading/disuse and *potentially* influence bone metabolism, direct confirmation in vivo that any of these muscle-derived cytokines affect bone metabolism via a paracrine mechanism remains lacking. Moreover, a recent study combining voluntary wheel running and in vivo tibia loading concluded that non-osteogenic physical exercise, sufficient to raise circulating IGF-1 levels and induce muscle hypertrophy, did not increase the effect of bone loading in elderly mice (Meakin et al., 2015). Therefore, until proven otherwise, the role of myokines in muscle-bone interactions remains speculative.

3.5. Bone talks back: bone-to-muscle communication

Recent work suggests that bone could also act as an endocrine organ affecting myogenesis. Genetic disruption in mice or knockdown in chicken of Indian hedgehog ($Ihh^{-/-}$), a member of the hedgehog family expressed at the perichondrium and involved in chondrocyte differentiation and long bone development, dramatically affects muscle development (Bren-Mattison et al., 2011). This occurred independently of bone length and at embryonic development stages when other hedgehogs are unlikely to compensate, suggesting that long-range, perichondrium-derived *Ihh* signaling could be involved. A recent study identified impaired skeletal muscle development in osteoblast/osteocyte-specific (Col2.3-driven) connexin43-KO mice (see Section 2.2) and implicated undercarboxylated osteocalcin as an endocrine factor involved in bone-to-muscle communication (Shen et al., 2015). Regarding clinical evidence, a pilot randomized trial suggested that bisphosphonate treatment prevented muscle atrophy in children with severe burn injuries (Borsheim et al., 2014).

In vitro studies have suggested that the osteocyte-like cell lines such as MLO-Y4 express muscle-anabolic as well as catabolic factors such as IL-6, PGE_2, vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), IGF-1 and mechano growth factor (MGF) (Bakker et al., 2014; Bakker and Jaspers, 2015; Juffer et al., 2012; Mo et al., 2012). Further in vivo studies regarding the roles of these molecules in reciprocal muscle-bone communication are eagerly awaited.

4. Muscle anabolic drug targets and their effect on bone

4.1. Myostatin, activin A, their receptors, and follistatin

One of the most promising pathways for the treatment of muscle wasting disorders is inhibition of myostatin/follistatin and activin receptors. Before going into the details of how myostatin and activin A signaling induce muscle wasting and bone loss, we

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will first introduce this pathway and its signaling components.

Myostatin (gene MSTN, also known as growth and differentiation factor-8, GDF-8), as well as activin A and GDF-11 are members of the bone morphogenetic protein (BMP)/transforming growth factor-β (TGF-β) ligand superfamily. *Myostatin* is a secreted protein predominantly expressed in muscle, and stored extracellularly in an inactive complex with its propeptide (Fig. 3) (Lee and McPherron, 2001). *Activin A* as well as follistatin are produced by osteoblasts and are abundant within the bone matrix. Activin and inhibin were originally discovered as ovarian-derived hormones with opposite actions in hypothalamic-pituary feedback regulation of follicle-stimulating hormone (FSH) (see Section 4.3). *Follistatin*, GDF-associated serum protein 1 (GASP-1), GASP-2, follistatin-like 3 and other binding proteins inhibit myostatin, activins, GDF-11, TGF-β and other members of this family (Lee and Lee, 2013). Myostatin levels as well as the myostatin:follistatin ratio increase with age in slow-twitch muscles and bone marrow in mice, which may contribute to muscle atrophy and age-related bone loss (Bowser et al., 2013; Han et al., 2013). GDF-11 levels also increase with age (Egerman et al., 2015). GDF-11 is more widely expressed, with roles in skeletal patterning and myostatin-like effects on skeletal muscle mass and regeneration. However, muscle-specific GDF-11-KO has no additional effect in Mstn−/− mice (McPherron et al., 2009).

Myostatin and activin A signal mostly through activin receptors IIB and IIA (ActRIIB and ActRIIA, genes ACVR2B and ACVR2) respectively, although some functional overlap exists. Depending on the ligand, type II activin receptors phosphorylate and heterodimerize with different type I activin receptors or activin receptor-like kinases: myostatin and activin A preferentially trigger heterodimerization and signaling via ALK4. These receptor complexes phosphorylate Smad2 and 3 leading to Smad2/3/4 complex formation, ultimately influencing transcription and changes in protein synthesis etc. (Fig. 3) (Han et al., 2013). Thus, activin receptors share regulation at the ligand, inhibitor, co-receptor and downstream signaling level with TGF-β and BMP-receptors, with generally inhibitory musculoskeletal effects of the former and stimulatory effects of the latter two types of receptors.

Upon secretion by muscle cells, pre-promyostatin is cleaved, the active C-terminal fragment dimerizes and is stored as an inactive complex with the N-terminal fragment. Follistatin, follistatin-like 3 (FSTL-3), GDF-associated serum protein 1 (GASP-1), GASP-2 and other binding proteins inhibit myostatin, activin A as well as other bone morphogenetic protein (BMP)/transforming growth factor β (TGF-β) ligands. Activin receptors type II B and A (ActRIIB, ActRIIA) preferentially bind myostatin and activin A respectively, with lower affinity for the other ligand or other TGF-β/BMP ligands. Ligand binding triggers recruitment and phosphorylation of a type I activin co-receptor, mostly the serine–threonine kinase ALK4 (activin receptor-like kinase 4, encoded by ACVR1B). This complex stimulates phosphorylation of Smad2 and 3, resulting in Smad 2/3/4 complex formation and nuclear translocation to Smad binding elements. Additionally, Akt phosphorylation and activity are inhibited which decreases inhibition of FoxO and other transcription factors. Pharmacologically, this pathway can be inhibited by monoclonal anti-myostatin antibodies or ActRIIA/B-IgG-Fc fusion proteins (ligand trap strategy).

4.2. Myostatin inhibition

Genetic myostatin deficiency results in marked muscle hypertrophy in mutant ("mighty") mice, rats (Mendias et al., 2015) as well as in natural genetic models in cattle (Belgian blue), dogs, sheep and rare human cases (Schuelke et al., 2004). Myostatin is downregulated both locally and in circulating form by physical exercise,

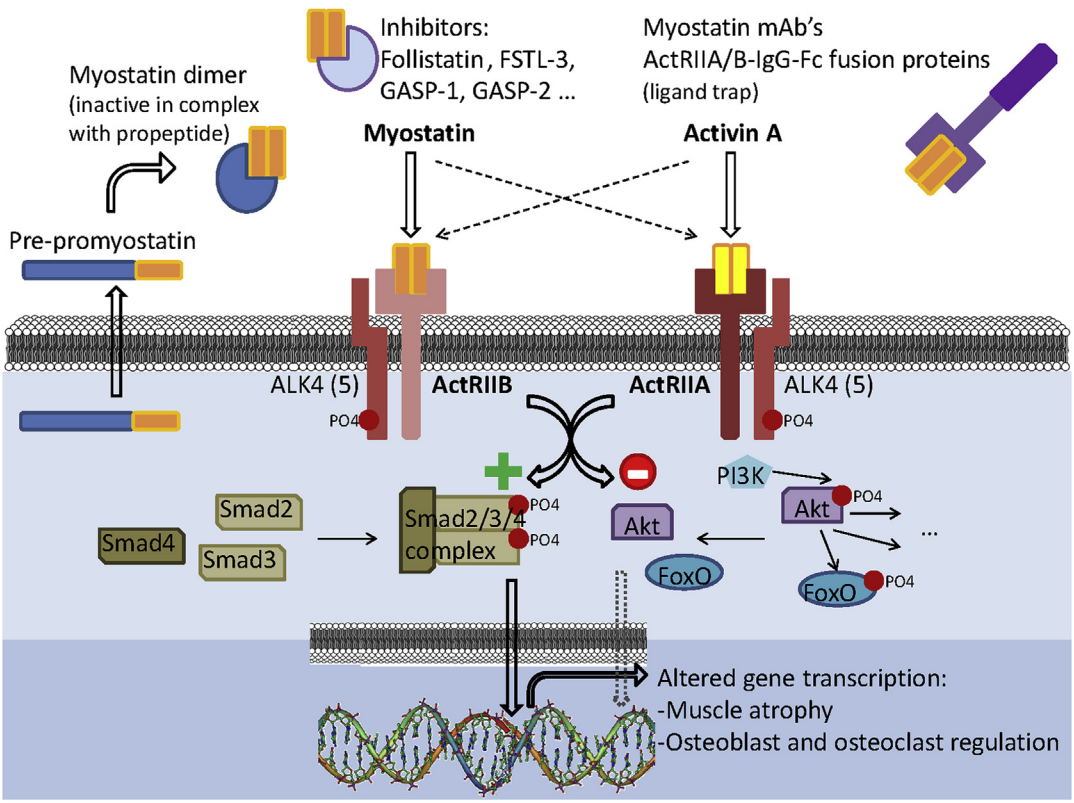

Fig. 3. Schematic overview of myostatin and activin A signaling via activin receptors.

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which may thus account for some of the resultant muscle hypertrophy. Inducible Mstn-KO at adult age is sufficient to explain subsequent muscle fiber hypertrophy, showing that the effect is not purely developmental (Welle et al., 2007). Pharmacological myostatin inhibition reproduces this muscle hypertrophy while myostatin infusion has the opposite effect. Satellite cells are not required for this pathway to act, making it attractive even in conditions with impaired muscle regeneration (Lee et al., 2012; Wang and McPherron, 2012).

However, myostatin-deficient muscles have been found *relatively* weaker or not even stronger in absolute terms compared to controls, despite considerable increases in muscle mass (Amthor et al., 2007; Mendias et al., 2011; Personius et al., 2010). This is reminiscent of early muscle hypertrophy in Duchenne's disease; indeed, intermyocytic connective tissue deficits as well as tendon weakness may partly explain this mass/strength paradox in Mstn−/− mice (Elashry et al., 2012; Mendias et al., 2008, 2015). Cortical bone area is increased in certain bones like the radius and at tendon insertion sites like the third femoral trochanter or deltoid crest, but not at more conventional skeletal sites like the femoral diaphysis (Hamrick et al., 2000; Hamrick et al., 2002, 2006). Moreover, exercise *decreases* muscle mass in Mstn-KO but increases it in control littermates, and restores skeletal muscle function (Hamrick et al., 2006; Matsakas et al., 2012). Thus, myostatin inhibition dramatically increases muscle mass but this may be a partially dystrophic phenotype requiring concomitant physical training. On the other hand, Mstn−/− mice can be viewed as more sensitive to the beneficial effects of exercise on muscle as well as skeletal loading (Hamrick et al., 2007), which translates into greater bone strength gains with exercise (Hamrick et al., 2006). Myostatin is a glucocorticoid-responsive gene and Mstn-KO mice are protected against glucocorticoid-induced muscle atrophy (Gilson et al., 2007) but unfortunately equally susceptible to bone and muscle decay from hindlimb suspension (Hamrick et al., 2007). We recently reported that Mstn−/− mice are equally susceptible to muscle atrophy from androgen deficiency, but more sensitive to the anabolic effects of androgens on muscle (Dubois et al., 2014).

Apart from its role in muscle hypertrophy, myostatin seems to regulate other functions too. It is expressed during fracture repair and acts as a negative regulator of callus size, and may thus have therapeutic potential in delayed or non-union (Kellum et al., 2009). Recently, myostatin was found to be highly expressed in synovium of rheumatoid arthritis patients, and Mstn-KO or inhibition was shown to inhibit osteoclast differentiation and bone destruction in both tumor necrosis factor alpha (TNF-α)-transgenic as well as serum-induced arthritis models (Dankbar et al., 2015). Moreover, muscle-specific myostatin knock-out decreases adiposity and improves insulin sensitivity in mice, pointing to the positive indirect role of muscle in systemic energy metabolism (Guo et al., 2009).

Human monoclonal anti-myostatin antibodies are under development for muscle wasting disorders (LY2495655, Eli Lilly and Company; PF-06252616, Pfizer). Reports in abstract suggest positive effects of LY2495655 on muscle mass and strength in healthy volunteers and cancer subjects. One previous trial with MYO-029 (formerly Wyeth) in Becker muscular dystrophy, facioscapulohumeral dystrophy, and limb-girdle muscular dystrophy found a trend in increased muscle size but not strength (Wagner et al., 2008).

In summary, myostatin inhibition remains an attractive pharmacological target, although in both experimental and clinical studies it seems that the resultant muscle hypertrophy does not necessarily translate into greater strength or power. Whether pharmacological myostatin inhibition also influences bone health in humans remains to be determined.

4.3. Activin receptor IIA inhibition

Like myostatin, activin A has been assumed to induce muscle atrophy whereas its inhibition at the ligand or receptor level promotes muscle hypertrophy. Still, only recently have experimental studies provided direct evidence for a role of activin A in muscle wasting and regeneration (Chen et al., 2014; Chen et al., 2015; Yaden et al., 2014), and surprisingly, a direct role for the ActRIIA in muscle remains to be examined.

Regarding bone, conflicting effects of activin have been described in vitro, where activin A either inhibits mineralization or increases osteoblastogenesis, and increases or decreases osteoclastogenesis (Alves et al., 2013; Eijken et al., 2007; Fowler et al., 2015; Gaddy-Kurten et al., 2002). A soluble ActRIIA-IgG1-Fc fusion protein (ACE-011, sotatercept) has been developed as a means to prevent activin A and similar ligands from binding to this receptor (ligand trap strategy). ActRIIA inhibition increased bone volume by a dual anabolic and antiresorptive mechanism in mice (Pearsall et al., 2008) as well as monkeys (Fajardo et al., 2010; Lotinun et al., 2010). This strategy also prevented cancer-induced bone destruction in murine breast cancer and multiple myeloma models (Chantry et al., 2010; Vallet et al., 2010). Trials in postmenopausal women also showed increased bone formation and decreased resorption markers and increased bone density despite an expected suppression of FSH (Ruckle et al., 2009; Sherman et al., 2013). The findings were opposite to an earlier study showing that activin A increases bone mass in rats (Sakai et al., 2000), possibly because the effects of activin A are dose-dependent, or because other ligands are at play.

In phase I human trials designed for osteoporosis, sotatercept was found to robustly increase haematocrit levels (Sherman et al., 2013). Subsequent investigation revealed that both ActRIIA and ActRIIB antagonism stimulate erythropoiesis in an EPO-independent manner by attenuating stromal cell inhibition in the bone microenvironment (Iancu-Rubin et al., 2013; Suragani et al., 2014a, b). Consequently, development of this pharmacological strategy has shifted from osteoporosis to anemia, which might be useful in conditions were the two coincide like multiple myeloma, thalassemia (Dussiot et al., 2014; Suragani et al., 2014a, b) or even in the frail elderly.

4.4. Activin receptor IIB inhibition

Pharmacological inhibition of activin signaling by a soluble ActRIIB/Fc fusion protein results in greater muscle hypertrophy compared to earlier studies with monoclonal antibodies against myostatin, and the former also remain effective in Mstn−/− mice (Lee et al., 2005; Lee, 2007). ActRIIB/Fc not only induced hypertrophy of fast-twitch fibers, but also decreased adiposity and increased BMD and serum markers of bone formation. ActRIIB/Fc also proved effective for simian immunodeficiency virus-associated cachexia (O'Connell et al., 2015). Treatment was similarly effective in aged or orchidectomized rodent models, and increased trabecular, periosteal as well as endocortical bone volume (Chiu et al., 2013; Koncarevic et al., 2010). Thus, unlike myostatin inhibition which increases bone mass indirectly at enthesial sites, ActRIIB directly increases trabecular and cortical bone volume throughout the skeleton, even in Mstn−/− mice (Bialek et al., 2014). Likewise, ActRIIB inhibition improved bone and muscle weakness in murine type III osteogenesis imperfecta (DiGirolamo et al., 2015). Moreover, this strategy mitigated cancer cachexia and prolonged survival without influencing tumor growth in preclinical models, whereas myostatin inhibition did not prevent muscle loss (Benny Klimek et al., 2010; Zhou et al., 2010). These differences suggest that myostatin is certainly not the only ligand for ActRIIB. Bone

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morphogenetic protein 3 (BMP-3) is another known ActRIIB ligand with known inhibitory effects on bone, but ActRIIB-Fc fusion protein was equally effective in increasing bone formation in BMP-3 deficient mice (Bialek et al., 2014).

A human anti-ActrRIIB antibody (BYM388, bimagrumab) is currently being investigated for muscle wasting disorders. In preclinical models, this strategy prevented myostatin- and activin A-induced as well as glucocorticoid-induced muscle atrophy, beyond the effects of sole myostatin inhibition by genetic or pharmacological means (Lach-Trifilieff et al., 2014). Bimagrumab was found effective in a randomized trial subjects with inclusion body myositis (Amato et al., 2014), and was recently granted FDA orphan drug approval based on this trial.

However, ActRIIB not only inhibits muscle hypertrophy but also couples muscle mass to metabolism. Hence, the ActRIIB/Fc fusion protein induced muscle fatiguability and metabolic myopathy in the mdx (Duchenne muscular dystrophy) mouse model, elevating lactate levels due to defective oxidative phosphorylation in mitochondria (Relizani et al., 2014). It remains to be seen whether this side-effect is specific to muscular dystrophies or, as in Mstn−/− mice, represents a general dystrophic feature of anti-ActRIIB-mediated muscle hypertrophy. In normal mice, ActRIIB inhibition activated brown adipogenesis and non-shivering thermogenesis, enhancing mitochondrial function but also uncoupling oxidation (Fournier et al., 2012).

In summary, pharmacological inhibition of myostatin signaling, especially by targeting ActRIIB, is a promising strategy to increase muscle mass in sarcopenia. Studies in Mstn-KO mice have also revealed sensitization to the benefits from exercise or androgen therapy as well as protection against muscle and/or bone loss or regeneration from certain insults (e.g. glucocorticoid excess, inflammatory arthritis, fracture repair). On a cautionary note however, myostatin inhibition led to relative muscle strength deficits and appeared ineffective to prevent muscle atrophy from disuse, androgen deficiency or cancer cachexia. Stimulatory effects on bone mass and muscle strength have been shown in early trials with ActRIIA and ActRIIB inhibition respectively, but the reciprocal effects on muscle or bone as well as other tissues like the hematopoietic system and mitochondrial function require investigation in ongoing clinical trials.

5. General conclusions

Bone and muscle have been described as “neighbors with close ties” (DiGirolamo et al., 2013), but given their inseparable function, regulation and crosstalk, we believe a metaphor of Siamese twins connected by tendons and periosteum may be more appropriate.

A third partner in this relationship, which goes beyond the scope of this review, is adipose tissue (both in fat pads as well as within bone and muscle). There is increasing awareness that obesity is not a stimulatory for bone and muscle mass, but rather leads to relative deficits (i.e. bone and muscle mass not increasing as much as may be expected for body size) termed (osteo-)sarcopenic obesity (Nielson et al., 2012). Since bone, muscle and fat cells are all mesenchymal lineage-derived, it is possible that sarcopenia and osteoporosis partly result from a cellular mechanism involving excess adipogenic and insufficient myogenic and osteogenic differentiation. Such a mechanism may be involved in the effects of testosterone, which increases bone and muscle mass and reduces fat mass (Borst et al., 2014; Vanderschueren et al., 2014; Yarrow et al., 2014a, b). Interestingly, a recent study showed that lipocalin 2 (LCN2) has a dual role not only as an adipokine but also as a strongly mechanoresponsive factor in bone linked to impaired osteoblastogenesis and osteoblast-derived release of osteoclastogenic factors (Rucci et al., 2015). Further work is needed to delineate the role of fat in muscle-bone interactions.Following almost two decades of research (McPherron et al., 1997), bimagrumab recently became the first approved specific drug for muscle wasting disorders. As a result, hope is rising that treatment strategies for sarcopenia will also have secondary positive effects on osteoporosis and falls risk. Nevertheless, critical review of preclinical studies indicates that the effects myotrophic therapies on bone may be limited to tendon attachment sites, and concomitant physical exercise may be needed to match muscle hypertrophy with tendon and connective tissue strength as well as mitochondrial function and possibly also neural determinants of muscle power and function.

For osteoporosis too, several new therapies are also underway which simultaneously increase bone formation and decrease bone resorption, either via combinations of existing drugs or novel strategies like inhibition of the Wnt inhibitor sclerostin (McClung et al., 2014). Studies in mice suggest that bone-derived factors may also influence muscle function (Bren-Mattison et al., 2011; Shen et al., 2015) (Section 3.5). In addition, a pilot randomized trial has suggested that bisphosphonates improved protein synthesis as well muscle characteristics following pediatric burn injuries (Borsheim et al., 2014). RANKL is also a myokine (Juffer et al., 2014) and preclinical data presented in conference abstracts suggests that muscle-derived RANKL as well as sclerostin inhibition may also influence muscle function. Thus, future preclinical and clinical studies in osteoporosis should simultaneously evaluate secondary effects on muscle power and falls risk, which may have important consequences on fracture outcomes.

This review focused on biomechanical loading, endocrine pathways and activin receptor signaling as potential therapies for osteo-sarcopenia, but these are certainly not the only interesting strategies. For example, the ghrelin-receptor agonist anamorelin has appetite-enhancing and robust effects on lean body mass in cancer cachexia (Garcia et al., 2015), but effects on bone have not been reported. Ultimately, it remains to be seen whether a single strategy, either pharmacological or biomechanical, can emerge as a holistic treatment for osteosarcopenia in the growing frail elderly population (Girgis et al., 2014a, b), or whether combination or sequential therapy with several drugs is most effective and safe (Boonen et al., 2011). In any case, exciting times are ahead for both clinicians and researchers; but paying more attention to sarcopenia and fall risk factors in osteoporosis, as well as bone health in neuromuscular disorders and other situations of disuse can start as of now.

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