



Published in final edited form as:

*J Bone Miner Res.* 2013 September ; 28(9): 1857–1865. doi:10.1002/jbmr.1980.

## Forum on Bone and Skeletal Muscle Interactions: Summary of the Proceedings of an ASBMR Workshop

L. F. Bonewald, Ph.D.<sup>1</sup>, D. Kiel, M.D., M.P.H.<sup>2</sup>, T. Clemens, Ph.D.<sup>3</sup>, K. Esser, Ph.D.<sup>4</sup>, E. Orwoll, M.D.<sup>5</sup>, R. O’Keefe, M.D.<sup>6</sup>, and R. Fielding, Ph.D.<sup>7</sup>

<sup>1</sup>Department of Oral and Craniofacial Science, School of Dentistry, University of Missouri-Kansas City <sup>2</sup>Institute for Aging Research, Hebrew SeniorLife and Harvard Medical School, Boston, Massachusetts <sup>3</sup>Johns Hopkins University, Baltimore, Maryland <sup>4</sup>University of Kentucky, Lexington, Kentucky <sup>5</sup>Oregon Health and Science University, Portland, Oregon <sup>6</sup>University of Rochester Medical Center, Rochester, New York <sup>7</sup>Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts

### Abstract

Annual costs are enormous for musculoskeletal diseases such as osteoporosis and sarcopenia and for bone and muscle injuries, costing billions annually in health care. While it is clear that muscle and bone development, growth and function are connected, and that muscle loads bone, little is known regarding cellular and molecular interactions between these two tissues. A conference supported by the National Institutes of Health, NIH, and the American Society for Bone and Mineral Research, ASBMR, was held in July 2012 to address the enormous burden of musculoskeletal disease. National and international experts in either bone or muscle presented their findings and their novel hypotheses regarding muscle-bone interactions in order to stimulate the exchange of ideas between these two fields. The immediate goal of the conference was to identify critical research themes that would lead to collaborative research interactions and grant applications focusing on interactions between muscle and bone. The ultimate goal of the meeting was to generate a better understanding of how these two tissues integrate and crosstalk in both health and disease in order to stimulate new therapeutic strategies to enhance and maintain musculoskeletal health.

### Keywords

muscle; bone; musculoskeletal; osteoporosis; sarcopenia; aging

### Introduction

The musculoskeletal system enables us to stand and move and protects our vital organs. Musculoskeletal diseases are the most common cause of chronic disabilities worldwide(1, 2). The cost of musculoskeletal injury or disease is greater than breast cancer, stroke, and cardiovascular disease combined and results in greater disability. Annual total costs for bone and joint health in the U.S. alone are estimated at \$849 billion (7.7% of the GDP) and 1 in 2 adults age 18 and older report suffering from a musculoskeletal condition that lasted more than 3 months. Of the 57.9 million Americans injured annually, more than one-half incur

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Corresponding author: Lynda F Bonewald, Ph.D., Department of Oral and Craniofacial Science, School of Dentistry, University of Missouri-Kansas City, 650 East 25<sup>th</sup> Street, Kansas City Missouri, USA, 64108, **Tel:** 816 235-2068, **Fax:** 816 235-5524, Bonewaldl@umkc.edu.

injuries to the musculoskeletal system. Hip fractures account for 300,000 hospitalizations per year; 24% of those patients die within a year and 25% are relegated to long-term care facilities (See the website [http://www.boneandjointburden.org/pdfs/bmus\\_executive\\_summary\\_low.pdf](http://www.boneandjointburden.org/pdfs/bmus_executive_summary_low.pdf)).

The loss of bone (osteoporosis) and muscle (sarcopenia) is a tremendous and growing, public health issue(3, 4). Sarcopenia can be thought of as the muscular equivalent of osteoporosis as it results in poor balance, reduced walking speed, falls, and fractures. In 2000, sarcopenia cost \$18.5 billion or 1.5% of total health care expenditures(5, 6). The combination of osteoporosis and sarcopenia is a major contributor to frailty in the elderly population(7, 8). Given the scope of the problem, it is critical to obtain a better understanding of how to provide more effective management of bone and muscle disorders and to identify new therapeutics to prevent the loss of muscle and bone with disuse, aging and disease.

Throughout life, the tissue mass of bone and muscle are tightly correlated. During organogenesis, muscle and bone develop in close association from common mesodermal precursors to determine adult muscle and bone mass. In addition, changes in muscle and bone mass brought about by exercise or disuse are also closely coupled. With age, loss of muscle mass is associated with loss of bone mass. Despite these obvious examples suggesting coupling of bone and muscle mass, the precise mechanisms responsible for synchronizing bone and skeletal mass remain unclear. Although this coupling clearly exists in both health and disease, little is known about responsible mechanisms other than loading. Therefore a conference was convened to bring together leading muscle and bone researchers to identify critical research areas that would lead to collaborations to address musculoskeletal disease.

The long term goals of this meeting were to initiate and promote understanding of the close association between muscle and bone during development and growth, support studies to determine how nutrition and physical activity affect general health, to dissect the association between sarcopenia and osteoporosis and determine what role aging plays in these processes, to begin to identify molecular and cellular mechanisms responsible for the close association between muscle and bone, to define defective mechanotransduction in both muscle and bone, to determine if muscle communicates with bone independent of mechanical loading, to identify means to prevent, treat, and reverse or regenerate muscle and bone loss, and to assess the feasibility of establishing a combined research field that integrates both muscle and bone physiology. It was hoped that this topical meeting would build upon previous meetings and open new avenues with regards to muscle-bone crosstalk(9). This review covers session highlights and summarizes the outcomes of this meeting.

## **Bone and Muscle Interactions during Development**

An intimate functional relationship between muscle and bone is observed throughout development, growth, and aging(10). This close relationship has provided a foundation for highly influential models of bone adaptation. While muscle has long been recognized as the primary source of anabolic mechanical stimuli for bone tissue(11, 12), very little is currently known about the potential anabolic stimuli of bone on muscle and its potential contribution to normal muscle function. Therefore, research on this emerging area of muscle-bone interactions is needed, particularly when considering the number of musculoskeletal diseases during development that have a significant impact on both bones and muscles.

Muscle bone cross talk appears to manifest even before birth in mammals. Using a mouse model in which paralysis can be induced in the developing embryo, it was demonstrated that

long bone shape and the joint is dependent on muscle contraction (11) In the absence of mechanical loads, the stereotypical circumferential outline of each bone is lost, leading to the development of mechanically inferior bones. These findings suggest a common mechanism that permits the formation of different circumferential outlines in different bones.

It is not clear how bone and muscle crosstalk biochemically during childhood and adolescence and whether or how this interaction is perturbed in disease. The Indian Hedgehog pathway appears to play a crucial role in bone signaling to muscle during development(13). There are data that suggests that not only is an intact extracellular niche required for engraftment of transplanted muscle stem cells into an injured host muscle, but that this effect requires the graft to be exposed to physiological levels of FGF2 prior to injection into the host. These findings begin to identify signaling pathways important in muscle and bone crosstalk during development.

Normal and pathological bone and muscle development in children and adolescents are increasing areas of interest. Chronic inflammatory diseases during childhood are associated with muscle deficits, low cancellous bone density, and smaller periosteal circumference, consistent with the effects of inflammatory cytokines on bone. In longitudinal studies, a given increase in muscle was associated with a lesser increase in bone in children with chronic disease, compared with healthy controls(14). Additional studies are needed to determine if glucocorticoids and cytokines impair the osteocyte response to biomechanical loading in childhood diseases, and if physical activity interventions will be effective in this high-risk population.

After adolescence, additional determinants of bone and muscle mass are at work. During growth, the peak velocity for lean body mass precedes that of bone mineral content, consistent with the “mechanostat” theory that increasing muscle mass during growth creates the stimulus for the increase in bone mass(11). Furthermore, during puberty, circulating IGF-I may promote bone periosteal apposition and mass accrual indirectly, through stimulating muscle growth; conversely, during senescence, rising levels of the inhibitory IGF binding protein, IGFBP-2, are associated with declining bone and muscle mass(11, 13, 15, 16). A potential source of the circulating IGF-1 may be muscle, as IGF-1 has been shown to be secreted by muscle (17). Finally, animal and correlative human data are consistent with Frost’s notion that during growth and aging, estrogen regulates the sensitivity of “mechanostat”(18).

## Conclusions and Remaining Questions

Questions to be addressed included how muscle and bone interact to obtain peak performance and what goes wrong in one tissue to cause or exacerbate disease in the other tissue. How do mechanical forces and paracrine signals between muscle and bone mediate coordinated growth, differentiation, and morphogenesis in development? Are there common signaling pathways coordinating muscle-bone interactions under different physiological situations? Will conditions under which muscle and bone do not co-vary be important for understanding abnormal or disease states? How can we translate results from developmental studies in animal models to human development, growth, and disease?

## Aging: Changes in Muscle and Bone, Linkages, and Shared Etiologies

Robust skeletal muscle mass is essential for maintaining homeostasis and whole body health(19). Aging is associated with the loss of skeletal muscle, and can lead to declines in physical functioning in older adults(20, 21). The underlying causes of sarcopenia are multifactorial and include decreased physical activity, increased cytokine activity, increased

irregularity of muscle unit firing, and a decrease in anabolic hormones(6, 22). With the loss of muscle mass and strength, and the concurrent increase in joint dysfunction and arthritis that occurs with aging, a decrease in physical function and disability becomes manifest.

The bone field has been successful in developing therapeutics for prevention and treatment of osteoporosis but the lack of a clear definition of sarcopenia, which literally means “poverty of flesh”, may have hindered the development of diagnostics and treatments(19) for this condition. In clinical terms the bone field is far more advanced than the muscle field because osteoporosis has been well defined on the basis of very clear parameters, while the definition of sarcopenia remains unsettled(23, 24). Depending on the definition used for sarcopenia, prevalence in 60 year-olds is reported to be over 20% while prevalence reaches over 50% in those 75 or older. With the aging of the population, these numbers are only going to increase(5, 23).

Despite the high prevalence and major health implications, sarcopenia still has no broadly accepted clinical definition or diagnostic criteria. Several recent consensus panels have proposed definitions of sarcopenia which all include some measure of muscle mass, muscle weakness and poor physical performance(6, 22, 25). Lessons can be learned from osteoporosis trials that could be applied to for the study of sarcopenia. It’s imperative that consensus be reached on the specific measures that should be used to assess and define sarcopenia. Muscle mass is poorly correlated with strength and mobility, while there is a stronger association of strength (for instance grip strength) with mobility. Strength declines more rapidly than mass with aging. Thus, measures of strength appear to be more important than mass in assessing physical performance. In addition, attention needs to be paid to the distinction between biomarkers that can be used for diagnosis of established sarcopenia so that corrective treatment/therapy can be initiated as compared to biomarkers that might prove to be “early warning signs” that are predictive of evolving sarcopenia. For diagnosis of existing sarcopenia, another approach would be to consider measures of mobility disability or functional performance tests to assign risk. Novel markers of evolving sarcopenia, such as measures of mitochondrial activity, and neuro-muscular activation may play a key role and need to be validated. New technologies will also be required to study this area.

The character and etiology of concomitant bone and muscle loss with aging is not clear. Muscle decline with age appears to occur before bone decline with age. With age, greater adiposity is observed in both bone marrow and muscle and fat infiltrates are also observed in nerves and capillaries. In the AGES cohort(26) high bone mass, irrespective of muscle mass, resulted in the lowest mortality, whereas low muscle, low bone, and low fat results in 2.1 greater risk of mortality. Gaps exist in knowledge regarding the relationship of the nervous system to balance and falls(27). The concept was offered that falling and increased fall-risk represent the final common pathway in the intersection between bone and muscle loss with advancing age. Common deficits in physical performance attributed to sarcopenia and bone loss may be due to neurologic mechanisms. Additionally, the effect of exercise on neural biology is not well known(28, 29).

## Conclusions and Remaining Questions

One major question was whether or not lessons can be learned from the bone field to study sarcopenia. Can rational approaches be designed to study and treat both debilitating conditions of aging? Key clinical measures of sarcopenia need to be identified that will drive routine clinical evaluations and drug/device development efforts for both effective treatment and ultimately prevention of sarcopenia. Biochemical markers of sarcopenia need to be identified that are useful in characterizing the disorder and to guide drug development and clinical therapy. The nature of the interaction between fat and muscle needs to be resolved.

Is sarcopenic obesity a valid concept? The biological pathways that link age-related changes in muscle and bone need to be identified in order to identify means to prevent and treat both osteoporosis and sarcopenia.

### Common Mechanisms Influencing Bone and Muscle Mass-‘Pleiotropy’

Peak bone and muscle mass are significantly influenced by genetic background and it is likely that loss of bone and muscle tissue is at least in part determined by genetic factors. There is growing evidence that there are pleiotropic genes that play important roles in both tissues, suggesting the possibility that the discovery of such genes might open up therapeutic options for treatment of osteoporosis and sarcopenia together(30).

Clearly products made by muscle can affect bone mass. Some progress has been made towards identifying circulating and local mediators that functionally couple muscle and bone, and may play a role in the age-related decline in muscle and bone mass, such as the growth hormone/insulin-like growth factor-1(IGF-1) axis and paracrine production of IGF-1 and fibroblast growth factor-23(31). Recent research has shown that inhibitors of the muscle growth inhibitor, myostatin, have beneficial effects on bone(32-34). However, a barrier to progress in the field has been the lack of interdisciplinary studies that combine expertise from the mineralized tissue and muscle fields to unravel the mechanisms underlying muscle-bone interaction.

The study of potentially pleiotropic genes for bone and muscle traits can be approached in several ways: 1) consider genes already known to have biologic functions on muscle and bone such as *GDF8 (myostatin)* or *PPARGC1A*; 2) agnostic approaches using genome wide linkage studies or genome wide association studies (GWAS) of skeletal and muscle phenotypes. Genome wide linkage has suggested the presence of pleiotropy; however this approach has not been successful in localizing signals to a specific gene. A second agnostic approach makes use of multivariate GWAS statistical techniques that identify genetic loci associated with multiple traits simultaneously. While this may be a useful approach, in general, the failure of common variants to explain a significant proportion of the variance in complex traits has led to the use of next generation sequencing to identify rarer variants contributing to complex traits. The analysis of rare variants for possible pleiotropy poses real challenges, since there may be multiple rare variants influencing muscle and bone phenotypes. The ultimate confirmation of pleiotropy will require that the suspected pleiotropic genes are tested in animal models.

Secreted factors such as myostatin, activins and pro-inflammatory cytokines represent potential underlying common mechanisms linking bone and muscle, yet little is known regarding how these factors work and effect muscle and bone mass, in particular during aging, and how their signaling pathways are related and interact(35, 36). Findings from in vitro and in vivo models can be used to compare and contrast mechanisms and pathway modulations of the age-related declines in muscle and bone mass. Various treatment approaches such as myostatin and pro-inflammatory cytokine inhibition have the potential to counteract both muscle and bone mass decline (37) or even a broader range of age-related diseases.

One of the most obvious potential mechanisms that might be shared between bone and muscle is the effect of growth factor signals. Specifically, growth hormone (GH) and insulin-like growth factor 1 (IGF-1) are proven anabolic factors in both bone and muscle but exactly how each factor works has been difficult to determine due to their interconnectedness. Recent studies using genetic mouse models targeting receptors for GH or IGF-1 receptor in bone (osteoblasts) or muscle have started to shed some light on the specificity of hormone action. GH’s effects in bone appear to be exerted indirectly via

IGF-1(38). These studies found that GH can function in the absence of the IGF-1 receptor in skeletal muscle to modulate the sensitivity of myoblasts to metabolic actions of insulin. These approaches are powerful as a means to delineate anabolic hormone action and are yielding new discoveries in function.

### Conclusions and Remaining Questions

The focus of this research should be on the process of moving from the animal data to humans and the interface between human and animal genetic approaches. How can human genome-wide association studies be translated into the transgenic animal model? Should we be thinking about muscle and bone together rather than studying them separately in parallel?

### Defective Mechanotransduction and Tissue Repair

Lack of gravity and immobilization has dramatic effects on both muscle and bone. Astronauts have been shown to lose bone mass 10 times faster than women in early menopause(39). Astronauts also experience muscle loss, but muscle loss can be recovered about six times faster than bone loss in astronauts. It has been assumed that the major effect of a lack of gravity is a lack of muscle loading on the bone. However, muscle disuse may have effects on bone beyond the lack of loading. In fact, muscle has been shown to produce cytokines in response to contraction and exercise(40) and may produce a different set of cytokines in response to unloading. Each tissue may contribute to the restoration or the repair of the other.

Investigations are being performed to determine the effects of reloading after disuse on both muscle and bone. Muscle injury actually occurs with reloading after a period of unloading along with a further decline in bone mineral density. Gains in muscle strength can be observed without an increase in muscle mass; the same phenomenon can be observed in bone, with measures of bone mass under-predicting gains in mechanical properties(41). This reinforces the need to measure functional properties in both tissues to appreciate the true impact of altered loading. If resistance training is performed in between two periods of hindlimb unloading, there is no loss of bone mass and an absolute gain in bone strength during the second period of unloading, suggesting that the bone 'remembers' the preceding anabolic stimulus. In this rodent model, eccentric plus isometric muscle contraction protocols yield the best effect on muscle strength and bone mass.

There is existing preclinical and clinical evidence to show that low magnitude mechanical signals are anabolic to both bone and muscle(42, 43). The frequency spectrum of muscle contraction decreases with aging, therefore these signals may be important components of the mechanical regulation of bone structure. Clinical studies have shown that introducing these mechanical signals using low intensity vibration (LIV) will stimulate bone and muscle formation, increase muscle force activity, and enhance healing. LIV stimulates mesenchymal stem cell proliferation and biases their differentiation towards osteoblastogenesis and away from adipogenesis(44). In the mouse, these signals were shown to build the musculoskeletal system, while suppressing the adipose burden, and helped to rescue an immune system compromised by obesity, suggesting that fate selection in hematopoietic progenitors can be determined by mechanical signals.

Significant gaps exist in our knowledge regarding the role of muscle in bone repair. Various sources of stem cells are involved in bone healing, including bone marrow cells, periosteum-derived cells, muscle-derived cells, and vascular and circulating-derived cells. Most research supports periosteum as a primary source of cells that undergoes expansion and differentiation to initiate the reparative process(45, 46). Periosteum is regulated by a number of signals that occur in bone injury, including increased expression of Cox-2. More severe

soft tissue and muscle injury coincident with fractures is highly associated with impaired healing in humans and in animal models. Recent work has demonstrated that muscle-derived stem cells take on a primary role in the reparative response in the setting of severe injury to the periosteum(47).

A special relationship exists between the immune system and muscle. A specialized phenotype of macrophages can have positive effects on muscle growth, in contrast to the consistently negative effects of osteoclasts on bone mass(48, 49). The M2 macrophage phenotype that predominates in injured muscle promotes muscle regeneration and supports satellite cell function, unlike M1 proinflammatory macrophages. Recent findings show that interleukin 10 is instrumental in inducing M1 macrophages to shift to the M2 phenotype following muscle injury. Genetic ablation of interleukin 10 signaling diminishes M2 macrophage populations in injured muscle and produces defects in muscle regeneration.

### Conclusions and Remaining Questions

What are the mechanosensitive intracellular signaling pathways that are stimulated in bone and muscle by exercise? How do these signals influence tissue healing? Are these pathways similar or different between the tissues? What are the signals generated by bone and muscle following injury? How do these signals interact to influence repair and regeneration of each tissue? How do the various sources of stem cells (bone marrow, periosteum, muscle, vascular and systemic circulation) contribute to the repair of bone and muscle tissues? How does this change with aging, various diseases, environmental influences, and the site and nature of the injury? How does different types of muscle injury impact recruitment of myeloid cells and what is the relationship between invasion of these cells and activation of myogenic stem cells? Answering these questions should lead to means to heal injury and restore loss of function and mass of both tissues.

### Preventing and Treating Muscle and Bone Loss

Obviously new therapeutics are needed not only for bone but also for muscle. A single therapeutic that could maintain both muscle and bone mass would be ideal. Clearly exercise has beneficial effects on both muscle and bone, but the ideal means to deliver these benefits for both tissues, especially with aging, need to be identified.

With aging, the skin produces less Vitamin D and sun exposure is reduced causing a decline vitamin D status. The roles vitamin D plays in calcium homeostasis and bone mineralization are well established but the effects of vitamin D on skeletal muscle function and fall risk remain obscure. In animals that are raised with a mutation in VDR a well described myopathy has been reported that is consistent with a role for Vitamin D on skeletal muscle differentiation and growth(50). In addition, observational studies in humans suggests that there is an association between vitamin D status (25\_OH D serum concentrations) and measures of physical functioning(51, 52). In trials where vitamin D has been supplemented, the effects on muscle strength and performance have been mixed. A recent meta-analysis revealed significant effects of vitamin D on muscle strength and performance when the baseline vitamin D levels were in the “insufficient” range (25 nmol/L). Future studies need to work on examining the potential effects of vitamin D therapy on skeletal muscle function and the relationship to the prevention of mobility limitations in older adults.

Myostatin, a known inhibitor of skeletal muscle growth has also been suggested to have target effects on bone and tendon(33, 53, 54). Several biologics have been in development targeting myostatin and myostatin signaling. An anti-ACVR2B-Fc has been shown to increase lean body mass, fat metabolism, and bone formation markers in postmenopausal women. However, a recent trial using this same agent in boys with muscular dystrophy was

suspended due to the development of unexpected gum and nose bleeds. Therefore more specific inhibitors for myostatin are needed and are presently in clinical trial development.

A relationship exists between obesity and metabolic syndrome in the elderly. It is also known that energy restriction and exercise induces changes in muscle and bone. A recently published trial examined the combined effects of an energy restricted diet and a regular exercise program on changes in muscle and bone in overweight older adults with mobility limitations(55, 56). In this 12 months study, individuals were subjected to either diet alone, exercise alone or the combination. Results showed that combining exercise with energy restriction can better target fat loss while better preserving muscle and bone mass. Based on these studies exercise plus energy restriction are significant mediators of weight loss in older adults that also result in favorable changes in muscle mass and BMD. Caloric restriction can extend longevity and even though individuals have low BMD, there are no fractures(57).

Fat and the nervous system clearly interact to affect both muscle and bone mass and function. There is potential for white fat to become the more desirable brown fat with exercise. The sympathetic nervous system plays an important role in the browning of white adipocytes but has a negative effect on skeletal remodeling. Recent work suggests that circulating myokines, such as irisin, which is induced by exercise, may enhance the generation of “beige” or brown-like adipocytes. Systemic administration of this protein has been shown to enhance lean mass but its effects on the skeleton have not been reported(58).

### Conclusions and Remaining Questions

Are there new opportunities in prevention and treatment of muscle and bone and what is the possibility of developing single agents to simultaneously treat both tissues as an alternative to treatments that are tissue specific? Is Vitamin D important for skeletal muscle and if so, what is the mechanism? What ActR2A/B ligands are important for both bone and muscle? What are the most promising therapeutic approaches to modulate their activity? Are there common mechanisms for loss of bone and muscle during energy restriction?

### Endocrine Functions of Muscle and Bone

Emerging data supports the concept that muscle secretes factors that target other tissues and are involved in glucose metabolism while simultaneously similar data has been emerging for bone(59). Therefore an integrated physiology must exist between muscle and bone. Muscle functions as an endocrine tissue. Interleukin-6 is secreted by muscle with exercise and has been shown to be responsible for glucose secretion by the liver, thereby acting as a ‘glucose sensitizer’. IL-6 acts as an insulin mimetic, not through typical insulin signaling but through AMPK. IL-6 can also act through the gut and pancreas to increase active GLP1 to increase lipolysis. Other factors such as CNTF (a gp130 receptor cytokine from the same family as IL-6) can act through AMPK to increase fat oxidation. Unfortunately, patients given human recombinant CNTF developed autoantibodies. Focus is now on the therapeutic utility of novel gp130Receptor cytokines(60, 61).

The Wnt/ $\beta$ -catenin signaling pathway is a major regulator of bone mass in the skeleton and of muscle development and growth. It is becoming clear that regulation of this pathway by osteocytes may play a centralized role in regulating bone mass(62). In particular sclerostin (encoded by the *Sost* gene), is highly expressed in osteocytes and inhibits Wnt signaling(63). Manipulation of sclerostin has therefore become a major target for development of novel bone anabolic agents. Therefore the Wnt/ $\beta$ -catenin pathway may play a role in the endocrine functions of muscle and bone. Data was presented showing crosstalk between muscle and the osteocyte. Osteocytes produce factors such as Wnt3a and PGE<sub>2</sub> that support myogenesis and intact muscle function(64). Alternatively, muscle produces unknown factors that protect



and preserve osteocyte viability in response to glucocorticoids(65). Muscle factors will synergize with fluid flow shear stress to activate the Wnt/ $\beta$ -catenin pathway in osteocytes. Therefore Wnt soluble factors play a role in muscle and bone crosstalk.

### Conclusions and Remaining Questions

Several questions were raised by these presentations. What are the secreted factors from each tissue and do they affect development, repair, regeneration, or function of the opposite tissue? What features are shared and what features are different between muscle and bone? Can therapeutics be developed that are beneficial for both tissues?

### Where Do We Go From Here?

The goal of the final session of the meeting was to identify key questions and identify means to answer them. First, the session chairs provided a brief summary of key highlights from each of their sessions and this was followed by a panel composed of NIH program officers and staff to provide information regarding sources of support and mechanisms to obtain funding. Areas were identified for collaborative investigation between muscle and bone investigators. The chairs and panelists attempted to draw together seemingly disparate observations in the two tissues to identify research opportunities. The goal was to identify a framework for future research that will consolidate present knowledge and drive basic findings into patient applications.

The session chairs provided a number of key questions which require answers. These include: 1). What components of muscle bone interactions are similar/different during growth and development as compared to maturity and as compared to aging? 2). How do muscle and bone communicate and regulate the other? Are these signals dependent on mechanical loading/disuse or do these signals synergize, enhance, or reduce the effects of loading/unloading? 3). What is the role of fat, neural regulation, tendons/ligaments on muscle-bone interactions? 4). What are the clinical measures of sarcopenia and how to use these to determine and develop treatments and how can we use them to determine and develop treatments? 5). What parameters (genetic control, function, signaling, factors, etc.) do muscle and bone share and how/when/where are they different? 6). “Should a greater focus be placed on studying muscle and bone together instead of separately? Should we be thinking about treating muscle and bone disease simultaneously? If so, what are the parameters?”

In order to answer these questions, opportunities are available to support collaborations between muscle and bone basic, translational and clinical investigators. Like other institutions, there have been ‘silos’ at NIH, but these walls between institutes are being remodeled into bridges. Examples of these new bridges are the Common Fund, the CTSA, and initiatives to support collaborative investigations such as the multi-PI RO1s. Another bridge is the Federal Working Group on Bone Diseases at NIH, an interagency committee that offers a forum for sharing information and facilitating the development of collaborative bone research activities based on each agency’s mission. Several other NIH components participate in working group activities including the National Institute on Aging, the National Institute of Diabetes, Digestive, and Kidney Disorders, the National Institute of Dental and Craniofacial Research, the National Center for Complementary and Alternative Medicine, and the National Cancer Institute. Other Federal agencies such as the Agency on Healthcare Research and Quality, Centers for Disease Control and Prevention, Food and Drug Administration, Department of Veterans Affairs, and the Department of Education are also active participants along with Voluntary Health, Scientific and Medical Organizations. Through this group and many other venues the NIH institutes coordinate and collaborate

with ASBMR, as well as groups such as the National Osteoporosis Foundation and US Bone and Joint Decade Institute.

It is necessary to share resources. There is a need to share tools, for example, rare and expensive animal models. Investigators were reminded that NIA supports an aging rodent colony of C57bl6 mice and aged Norway rats for both the internal and external scientific community. Tissue samples are also available from aged animals. <http://www.nia.nih.gov/research/dab/aged-rodent-colonies-handbook>. NIA also supports program projects that bridge animal to human research, the Pepper Center, clinical geriatrics and the means to translate discoveries into application through SBIRs. The NIA Infrastructure grant is intended to set up and support a collaborative group of scientists. NICHD supports the incorporation of pediatrics with a focus on muscle-bone interactions during growth and development. Attendees were reminded that growth during infancy is different from growth during puberty which is quite distinct from what happens with aging. Another entity that supports collaborations includes the Friends of NIH, fNIH, that supports collaborations between academia and pharmaceutical companies. Investigators are encouraged to visit the websites of each of these entities for more information.

As NIH has had a constrained budget, and more budget stringency may be on the horizon, the NIH must be creative and innovative to keep the most significant and important science going forward. Communication is important and it is hoped that this meeting will lead to better understanding between investigators. Collaborations must be nurtured and supported. There are training programs in muscle and bone including T32s and others. One example is NIAMS support through P30s for muscle-bone teams that provide novel technologies to analyze both bone and muscle from the same specimens.

In summary, the need for collaborations between muscle and bone investigators to answer important questions regarding bone and muscle interactions is imperative if future therapeutics for muscle and bone disease are to be developed. The NIH and other federal and non-federal agencies are working towards providing the support required for these initiatives. Working together new discoveries can be accelerated.

## Acknowledgments

Research reported in this publication was supported by the National Institute Of Arthritis And Musculoskeletal And Skin Diseases of the National Institutes of Health under Award Number R13AR063602. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This grant was funded by the following Institutes: the National Institute Of Dental & Craniofacial Research (NIDCR), the National Center for Complementary & Alternative Medicine (NCCAM), the Office Of the Director, National Institutes Of Health (OD), the National Institute On Aging (NIA), the National Instituted Of Arthritis And Musculoskeletal And Skin Diseases (NIAMS) and the Eunice Kennedy Shriver National Institute Of Child Health & Human Development (NICHD)

The meeting was also supported by Amgen, Inc., Lilly USA, LLC, Merck & Co, Inc., Warner Chilcott Company, LLC and locally by the University of Missouri-Kansas City, University of Missouri-Columbia, University of Missouri Science & Technology, University of Kansas Medical Center, and the Kansas City Area Life Sciences Institute.

The authors would like to thank the staff of ASBMR including Ann Elderkin, Stacey Barnes, Deb Kroll, Kirsten Mills, Melissa Huston, Erica Weiss, Lindsay Pullen and Holly Gumble for their support in planning for and overseeing the organization of the meeting.

The authors participated in the conception, design and planning of the meeting (Lynda Bonewald, Roger Fielding, Thomas Clemens, Karyn Esser, Douglas Kiel, Eric Orwoll, Regis O'Keefe), participated in the meeting itself in various roles (Lynda Bonewald, organizer; Roger Fielding, co-organizer; Thomas Clemens, Karyn Esser, Douglas Kiel, Eric Orwoll, Regis O'Keefe, organizing committee), and in the drafting and final content of this manuscript (Lynda Bonewald, Roger Fielding, Thomas Clemens, Karyn Esser, Douglas Kiel, Eric Orwoll, Regis O'Keefe).

Dr. Fielding is supported in part by U.S. Department of Agriculture under grant # 58-1950-0-014. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author and do not necessarily reflect the view of the U.S. Department of Agriculture.

## Appendix

### Participants in the Workshop

*Bone and Muscle Interactions during Development:* Thomas L. Clemens, Ph.D., Johns Hopkins University, Baltimore, Maryland, USA; Dawn DW Cornelison, Ph.D., University of Missouri, Columbia, Missouri, USA; Elazar Zelzer, Ph.D., Weizmann Institute of Science, Rehovot, Israel; Bradley B. Olwin, Ph.D., University of Colorado, Boulder, Colorado, USA; Mary B. Leonard, M.D., M.S.C.E., The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; Sundeep Khosla, M.D., Mayo Clinic, Rochester, Minnesota, USA; *Aging: Changes in Muscle and Bone, Linkages and Shared Etiologies:* Eric S. Orwoll, M.D., Oregon Health and Science University, Portland, Oregon, USA; Roger A. Fielding, Ph.D., Tufts University, Boston, Massachusetts, USA; Steven R. Cummings, M.D., San Francisco Coordinating Center, University of California, San Francisco, California, USA; Stephanie A. Studenski, M.D., M.P.H., University of Pittsburgh, Pittsburgh, Pennsylvania, USA; Tamara B. Harris, M.D., M.S., National Institute on Aging, NIH, Bethesda, Maryland, USA; Clifford J. Rosen, M.D., Maine Medical Center Research Institute, Scarborough, Maine, USA; *Common Mechanisms Influencing Bone and Muscle Mass- 'Pleiotropy':* Karyn Esser, Ph.D., University of Kentucky, Lexington, Kentucky, USA; Douglas P. Kiel, M.D., M.P.H., Institute for Aging Research, Hebrew SeniorLife and Harvard Medical School, Boston, Massachusetts, USA; Anne-Ulrike Trendelenburg, P.D., Ph.D., Novartis Institutes for BioMedical Research, Inc., Cambridge, Massachusetts, USA; Thomas L. Clemens, Ph.D., Johns Hopkins University, Baltimore, Maryland, USA; *Defective Mechanotransduction and Repair:* Regis J. O' Keefe, M.D., University of Rochester Medical Center, Rochester, New York, USA; Joseph A. Houmard, Ph.D., East Carolina University, Greenville, North Carolina, USA; Susan A. Bloomfield, Ph.D., Texas A&M University, College Station, Texas, USA; Clinton T. Rubin, Ph.D., Stony Brook University, Stony Brook, New York, USA; *Preventing and Treating Muscle and Bone Loss:* Roger A. Fielding, Ph.D., Tufts University, Boston, Massachusetts, USA; Nathan K. LeBrasseur, Ph.D., Mayo Clinic, Rochester, Minnesota, USA; Bess Dawson-Hughes, M.D., Tufts University, Boston, Massachusetts, USA; Teresa A. Zimmers, Ph.D., Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; Dennis T. Villareal, M.D., University of New Mexico School of Medicine, New Mexico VA Health Care System, Albuquerque, New Mexico, USA; *Emerging Areas:* Robert Marcus, M.D. Stanford University, Stanford, California, USA; Vincent J. Caiozzo, Ph.D., University of California, Irvine, California, USA; Gerard Karsenty, M.D., Ph.D., Columbia University Medical Center, New York, New York, USA; Mark A. Febbraio, Ph.D., Cellular & Molecular Metabolism Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, Australia; Mark L. Johnson, Ph.D., University of Missouri, Kansas City, Missouri, USA; James G. Tidball, Ph.D., University of California, Los Angeles, California, USA; *Panel Discussion - Where Do We Go From Here?* Lynda F. Bonewald, Ph.D., University of Missouri, Kansas City, Missouri, USA; Lyndon Joseph, Ph.D., National Institute on Aging, NIH, Bethesda, Maryland, USA; Joan A. McGowan, Ph.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, Maryland, USA; Glen Nuckols, Ph.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, Maryland, USA; John Williams, Ph.D., National Institute on Aging, NIH, Bethesda, Maryland, USA; Karen Winer, M.D., National Institute of Child Health and Human Development, NIH, Bethesda, Maryland, USA

Name	Affiliation	Conflicts	Commercial entity/no. of relationships
Susan A. Bloomfield	Texas A&M University - College Station	No	
Lynda F. Bonewald	University of Missouri - Kansas City	No	
Vincent J. Caiozzo	University of California - Irvine	No	
Thomas L. Clemens	Johns Hopkins University	No	
Dawn DW Cornelison	University of Missouri, Columbia	No	
Steven R. Cummings	San Francisco Coordinating Center, University of California San Francisco	No	
Bess Dawson-Hughes	Tufts University	No	
Karyn Esser	University of Kentucky	No	
Mark A. Febbraio	Cellular & Molecular Metabolism Laboratory, Baker IDI Heart and Diabetes Institute	No	
Roger A. Fielding	Tufts University	Yes	Essentient/Pronutria <sup>2,5</sup> , Regeneron <sup>2</sup> , Eli Lilly <sup>2</sup> , Cytokinetics <sup>2</sup> , Nestec, Ltd <sup>1,2</sup> .
Tamara B. Harris	National Institute on Aging, NIH	No	
Joseph A. Houmard	East Carolina University	No	
Mark L. Johnson	University of Missouri - Kansas City	No	
Lyndon Joseph	National Institute on Aging, NIH	No	
Gerard Karsenty	Columbia University Medical Center	No	
Sundeep Khosla	Mayo Clinic	No	
Douglas P. Kiel	Institute for Aging Research, Hebrew SeniorLife and Harvard Medical School	Yes	Eli Lilly <sup>2, 6</sup> , Merck <sup>2, 6</sup> , Amgen <sup>2, 6</sup> , Novartis <sup>6</sup> ,
Nathan K. LeBrasseur	Mayo Clinic	No	
Mary B. Leonard	The Children's Hospital of Philadelphia	No	
Joan A. McGowan	National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH	No	
Glen Nuckols	National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH	No	
Regis J. O' Keefe	University of Rochester Medical Center	No	
Robert Marcus	Stanford University	No	
Bradley B. Olwin	University of Colorado	No	
Eric S. Orwoll	Oregon Health and Science University	Yes	Eli Lilly <sup>1, 2</sup> , Amgen <sup>1, 2</sup> , Merck <sup>1, 2</sup> , Wright Medical Technology <sup>2</sup>
Clifford J. Rosen	Maine Medical Center Research Institute	No	
Clinton T. Rubin	Stony Brook University	Yes	Marodyne Medical <sup>6</sup> .
Stephanie A. Studenski	University of Pittsburgh	No	
James G. Tidball	University of California - Los Angeles	No	
Anne-Ulrike Trendelenburg	Novartis Institutes for BioMedical Research, Inc.	Yes	Novartis <sup>4</sup>

Name	Affiliation	Conflicts	Commercial entity/no. of relationships
Dennis T. Villareal	University of New Mexico School of Medicine, New Mexico VA Health Care System	No	
John Williams	National Institute on Aging, NIH	No	
Karen Winer	National Institute of Child Health and Human Development, NIH	No	
Elazar Zelzer	Weizmann Institute of Science	No	
Teresa A. Zimmers	Kimmel Cancer Center, Thomas Jefferson University	No	

Relationship key:

<sup>1</sup> =Research grant or financial support from commercial entities.

<sup>2</sup> =Consultant or member of advisory board to a commercial entity.

<sup>3</sup> =Participant in a speaker's bureau.

<sup>4</sup> =Employment or executive positions in pharmaceutical, medical device, or diagnostic companies.

<sup>5</sup> =Stock holdings in pharmaceutical, medical device, or diagnostic companies.

<sup>6</sup> =Any other situation or transaction in which you have a formal role or interest (eg, you serve on a bone-related organization's board, committee, or journal; a family member contracts with ASBMR, etc.).

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