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MEETING REPORT

Muscle and Bone

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Meeting Report from the 33rd Annual Meeting of the American Society for Bone and Mineral Research, San Diego, CA, USA, 16–20 September 2011

The field of musculoskeletal research was front and center at the 33rd annual ASBMR meeting, as the event opened with 'Plenary Symposium I—Muscle and Bone Interactions.' Dr Stephen Katz, director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), provided the introductory remarks. One of his notable messages to the ASBMR attendees was that NIAMS would be giving funding priority to those projects with collaborative efforts and scientific expertise across biological systems. Dr Katz emphasized that collaborations lead to greater interdisciplinary communication and knowledge, thus creating an unparalleled environment to enhance discoveries. Below are summaries of the four presentations delivered at the 'Muscle and Bone Interactions' symposium along with other highlighted talks and abstracts relevant to the field of musculoskeletal research.

Dr Thomas Clemens delivered the opening 'Muscle and Bone Interactions' presentation, which was titled 'The Growth Hormone/IGF-1 Axis in Skeletal Muscle.' He presented his recent genetic mouse model work describing direct and indirect mechanisms of growth hormone (GH) action in skeletal muscle. Skeletal muscle development is well known to be coordinated by GH and its downstream effector, insulin-like growth factor-1 (IGF-1); however, it is not clear which effects of GH on skeletal muscle development are direct and which are secondary via IGF-1. It is important to distinguish between direct and indirect GH actions in skeletal muscle because it will lead to more effective therapies in musculoskeletal diseases. Indirectly, GH was found to promote the normal processes associated with a fully functioning skeletal muscle via regulation of IGF-1. Directly, GH was found to facilitate insulin action in skeletal muscle, ultimately affecting the overall nutrient metabolism. The latter finding was somewhat surprising, but revealed a new mechanism of exploration, which may help explain the link between insulin resistance and poor muscle development and/or muscle atrophy. Given that muscle and bone activity are so intimately connected, the GH action on insulin sensitivity in skeletal muscle may also explain, in part, the increasingly recognized inverse relationship between insulin resistance and bone.[1–6]

In the second talk, Dr Gerald Shulman added an intriguing piece of the puzzle to the muscle–bone–insulin relationship in his presentation titled, 'Mitochondrial Biogenesis and Function in Aging, Obesity and Muscle Cell Physiology.' Shulman and his team have identified four key aspects of excessive intracellular lipid accumulation, which include excess caloric intake, defects in adipocyte metabolism, defects in mitochondrial fatty acid oxidation and gene variation in apolipoprotein C-III. As a result, Shulman provided a unifying hypothesis for insulin resistance, suggesting that any perturbation resulting in excessive intramyocellular lipid accumulation leads to skeletal muscle insulin resistance. This hypothesis represents a target of investigation in skeletal muscle that may reverse insulin resistance. Though Shulman did not discuss direct implications of excessive intramyocellular lipid content on bone, two abstracts were presented linking skeletal muscle fat to bone health. In one report of 444 young girls aged 9–12 years, investigators found that skeletal muscle fat content of the calf and thigh, as measured by peripheral quantitative computed tomography (pQCT), was inversely associated with pQCT-derived bone strength indices at trabecular and cortical sites of the tibia and femur.[7] In an oral presentation by McMaster University doctoral student Andy Wong,[8] a higher level of pQCT-derived skeletal muscle fat content of the calf was associated with greater risk of fragility fractures in female participants aged 50 years and older from the Canadian Multicentre Osteoporosis Study. The findings from these two abstracts add to our knowledge of the role of fat on bone health, suggesting that the deposition of fat within muscle may be associated with suboptimal bone health.

The skeletal muscle is capable of producing and secreting several hundred hormone-like factors, commonly referred to as myokines. To date, only a handful of myokines and their functions on bone have been investigated. In the third lecture, 'Myokines: Key Regulators of the Muscle–Bone Unit,' Dr Mark Hamrick[9] presented evidence for IGF-1, fibroblast growth factor-2 (FGF-2) and myostatin as important myokines for bone. Using animal and co-culture models, Hamrick *et al.* found that skeletal muscle is a local source for IGF-1 and FGF-2, two well-known osteogenic-related factors. In addition to being present in great supply in homogenized muscle tissue, IGF-1 and FGF-2 were localized to the muscle–bone interface *in vivo* and secreted from cultured myotubes *in vitro*. In addition, IGF-1 and FGF-2 receptors were localized to periosteum at the muscle–bone interface. Collectively, these data suggest that musculoskeletal growth may be regulated in part by paracrine mechanisms at the muscle–bone interface involving IGF-1

and FGF-2. Going further, Hamrick claimed that if bone can receive anabolic stimuli from muscle in the form of paracrine signals, then it is also possible that catabolic changes in muscle can produce anti-osteogenic changes in bone. Such a relationship has been revealed between bone and the muscle-derived factor myostatin (growth and differentiation factor-8), as myostatin deficiency or loss of myostatin function increases osteogenic differentiation of bone marrow-derived stem cells, bone mass and bone repair.[10–13] Given that muscle is the primary source of myostatin in the body, Hamrick suggested that conditions favoring muscle atrophy and increased myostatin secretion would in turn suppress bone formation and bone mass through myostatin's anti-osteogenic effects. This notion linking myostatin to muscle atrophy and bone loss has generated interest in myostatin antagonists. In an oral presentation, Dr Douglas Digirolamo presented muscle and bone data in three groups of mice given either one of two types of myostatin antogonist proteins (soluble activin type II receptor (ACVR2) or IIB receptor (ACVR2B)) or placebo.[14] Collectively, the study findings suggest that both ACVR2 and ACVR2B produce anabolic effects on muscle and bone; however, ACVR2's effect was greater on bone than muscle, whereas ACVR2B's effect was greater on muscle than bone. Currently, no human data exist on the effect of myostatin antagonists; however, cross-sectional data suggest that higher myostatin levels are associated with older age, smoking, physical inactivity, lower vitamin D levels, higher systemic inflammation, cancer, diabetes, obesity, chronic obstructive pulmonary disease and the human immunodeficiency virus.[15–20]

In the final 'Muscle and Bone Interactions' talk, Dr Shalender Bhasin presented 'Androgen Biology in Musculoskeletal Health and Frailty.' Bhasin delivered an insightful, historical overview of androgens, ranging from their harmful misuse by athletes to their therapeutic potential against frailty syndrome. Although testosterone supplementation has been shown to increase skeletal muscle size and strength in conditions of androgen deficiency, Bhasin noted that it is just as important to demonstrate androgen efficacy on other muscle-related outcomes such as physical function, a clinically relevant marker of an individual's overall health. In a recent investigation of testosterone treatment in frail elderly men with low testosterone levels,[21] investigators found that 6 months of testosterone therapy not only increased skeletal muscle mass and lower limb muscle strength (that is, isometric knee extension peak torque) but also improved measures of physical function (that is, The Physical Performance Test) and quality of life (that is, Aging Males' Symptom scale). However, the beneficial effects of 6-month testosterone treatment on muscle mass, muscle strength, physical function and quality of life were not maintained 6 months post treatment,[22] suggesting that short-term testosterone treatment may not be sufficient to interrupt the progression of frailty. Whether longer duration of testosterone treatment can produce sustained benefits on measures of musculoskeletal size, strength and function without increasing health risks remains to be determined. In further discussion, Bhasin noted that because of the long-term risks associated with testosterone use, the pharmaceutical industry has shifted efforts to develop selective androgen receptor modulators (SARMs). Although SARMS are currently in early stages of development, the available data suggest that they hold much promise to achieve anabolic effects without the adverse effects associated with testosterone.[23,24]

The Muscle-Bone Theme was continued in the Louis V Avioli Memorial Lecture, given by Dr Lynda Bonewald 'Osteocytes—The Great Communicators'. With significant advancement in research tools and techniques over the last decade, Bonewald noted that we have gained valuable insights into osteocyte biology, leading to validation of old theories and the generation of new ones. Osteocytes, which are known as essential regulators of osteoclast and osteoblast activity, were revealed by Bonewald and colleagues to be a source of soluble factors having key endocrine function on other organs, particularly the skeletal muscle.[25–27] Even more remarkable were the data presented by Bonewald's research team indicating that skeletal muscles secrete factors affecting osteocyte function and viability.[27–29] Incorporating this novel concept of an osteocyte-muscle crosstalk opens new avenues of research in the realm of musculoskeletal diseases.

Another notable highlight at the meeting included the Gerald D Aurbach Memorial Lecture by Dr Eric Olson titled, 'MicroRNA Control of Muscle Development and Disease.' Since their discovery less than two decades ago, hundreds of microRNAs have been identified as critical regulators of numerous biological processes by modulating gene expression at the post-transcriptional level. Ultimately, the revelation of microRNA downstream targets is key to understanding its specific function. However, because of the imprecise computational tools that are currently available, the identification of these microRNA targets has been a major challenge. Olson noted that much progress has been made in recent years developing and refining experimental approaches to identifying microRNA targets. As a result, many biological targets for muscle-specific microRNAs have been revealed, representing a wide range of genes in the myogenic program, from transcription regulators, signaling molecules, to structural proteins.

A feature of musculoskeletal research today is the great effort being devoted to understanding musculoskeletal interactions with other biological systems at the molecular, cellular and tissue levels. As a result, a wealth of novel information and ideas are being generated that will ultimately lead to translation of exciting new discoveries in the clinical realm. Collectively, a key theme of the muscle and bone research presented this year is that identification of molecules involved in musculoskeletal interactions hold the potential for the development of novel biomarkers and therapeutic strategies for musculoskeletal diseases.

Conflict of interest

The author declares no conflict of interest.

References

1. Ishii S, Cauley J, Srikanthan P, Crandall C, Huang MH, Danielson M *et al.* Insulin resistance, diabetes, and composite indices of femoral neck strength: findings from The Hip Strength Across the Menopausal Transition Study. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11006197-127&terms=).
2. Sayers A, Lawlor D, Sattar N, Tobias JH. Insulin inhibits cortical bone development independently of body composition: findings from a cross sectional analysis of pQCT parameters in adolescents. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11006633-127&terms=).
3. Pollock NK, Bernard PJ, Gower BA, Wenger K, Misra S, Allison J *et al.* Dose-response effect of vigorous aerobic exercise on bone turnover, insulin sensitivity, and adiposity in obese children: a randomized controlled trial. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11007345-122&terms=).

4. Wei J, Ferron M, Ducy P, Karsenty G. Insulin resistance takes place in bone of type 2 diabetic mice. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11006734-127&terms=).
5. Oei J, Castano-Betancourt M, Pols H, Dehghan A, Uitterlinden A, Rivadeneira F. Women with inadequately controlled type 2 diabetes are at increased risk of osteoporotic fractures despite higher bone mineral density: The Rotterdam Study. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11006073-29&terms=).
6. Ferron M, McKee M, Ducy P, Karsenty G. Intermittent injections of osteocalcin improve glucose metabolism and prevent type 2 diabetes in mice. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11006757-22&terms=).
7. Farr JN, Funk JL, Chen Z, Lisse JR, Blew RM, Lee VR *et al.* Skeletal muscle fat content is inversely associated with bone strength in young girls. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11006739-127&terms=).
8. Wong AK, Bhargava A, Beattie K, Gordon CL, Pickard L, Webber CE *et al.* Muscle density, a surrogate of intermuscular adiposity derived from pQCT, is an independent correlate of fractures in women. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11006306-25&terms=).
9. Hamrick MW, McNeil PL, Patterson SL. Role of muscle-derived growth factors in bone formation. *J Musculoskeletal Neuronal Interact* 2010;**10**:64–70.
10. Hamrick MW, Samaddar T, Pennington C, McCormick J. Increased muscle mass with myostatin deficiency improves gains in bone strength with exercise. *J Bone Miner Res* 2006;**21**:477–483.
11. Hamrick MW, Shi X, Zhang W, Pennington C, Thakore H, Haque M *et al.* Loss of myostatin (GDF8) function increases osteogenic differentiation of bone marrow-derived mesenchymal stem cells but the osteogenic effect is ablated with unloading. *Bone* 2007;**40**:1544–1553.
12. Kellum E, Starr H, Arounleut P, Immel D, Fulzele S, Wenger K *et al.* Myostatin (GDF-8) deficiency increases fracture callus size, Sox-5 expression, and callus bone volume. *Bone* 2009;**44**:17–23.
13. Elkasrawy MN, Hamrick MW. Myostatin (GDF-8) as a key factor linking muscle mass and bone structure. *J Musculoskelet Neuronal Interact* 2010;**10**:56–63.
14. Digirolamo D, Singhal V, Clemens TL, Lee SJ. Systemic administration of soluble activin receptors produces differential anabolic effects in muscle and bone in mice. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11007186-125&terms=).
15. Lee SJ. Regulation of muscle mass by myostatin. *Annu Rev Cell Dev Biol* 2004;**20**:61–86.
16. Allen DL, Hittel DS, McPherron AC. Expression and function of myostatin in obesity, diabetes, and exercise adaptation. *Med Sci Sports Exe* 2011;**43**:1828–1835.
17. Ju CR, Chen RC. Serum myostatin levels and skeletal muscle wasting in chronic obstructive pulmonary disease. *Respir Med* 2012;**106**:102–108.
18. Gonzalez-Cadavid NF, Taylor WE, Yarasheski K, Sinha-Hikim I, Ma K, Ezzat S *et al.* Organization of the human myostatin gene and expression in healthy men and HIV-infected men with muscle wasting. *Proc Natl Acad Sci USA* 1998;**95**:14938–14943.
19. Szulc P, Goetsch C, Schoppet M, Chapurlat R, Hofbauer LC. Myostatin serum concentrations in men – age-related changes and correlates – the STRAMBO study. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11006466-127&terms=).
20. Bowser M, Chutkan N, Martell J, Corpe R, Isales CM, Park MA *et al.* Age-related changes in the activin A-myostatin-follistatin system within the bone marrow microenvironment. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11007485-52&terms=).
21. Srinivas-Shankar U, Roberts SA, Connolly MJ, O'Connell MD, Adams JE, Oldham JA *et al.* Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2010;**95**:639–650.
22. O'Connell MD, Roberts SA, Srinivas-Shankar U, Tajar A, Connolly MJ, Adams JE *et al.* Do the effects of testosterone on muscle strength, physical function, body composition, and quality of life persist six months after treatment in intermediate-frail and frail elderly men? *J Clin Endocrinol Metab* 2011;**96**:454–458.
23. Bhasin S, Calof OM, Storer TW, Lee ML, Mazer NA, Jasuja R *et al.* Drug insight: testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. *Nat Clin Pract Endocrinol Metab* 2006;**2**:146–159.
24. Dalton JT, Barnette KG, Bohl CE, Hancock ML, Rodriguez D, Dodson ST *et al.* The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. *J Cachexia Sarcopenia Muscle* 2011;**2**:153–161.
25. Zhou X, Lau KW, Lara N, Bonewald LF, Baylink D, Sheng M *et al.* Evidence that osteocytes elaborate endocrine regulation of internal organs size: Data from the osteocytes IGF-1 conditional knockout mice. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11007721-22&terms=).
26. Wacker M, Tchikrizov V, Mannix J, Touchberry C, Stubbs J, Bonewald LF. Fibrolast growth factor 23 (FGF-23) alters gene expression of isolated cardiac ventricular muscle. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11007574-127&terms=).
27. Romero-Suarez S, Mo CL, Lara N, Jaehn K, Johnson M, Bonewald LF *et al.* The β-catenin activating factor, Wnt3a, stimulates skeletal muscle myogenesis. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11007458-29&terms=).
28. Lara N, Jaehn K, Romero-Suarez S, Mo CL, Lara N, Bonewald LF *et al.* A muscle derived soluble factor activates PI3K/β-catenin signaling in osteocytes. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11007510-89&terms=).
29. Jaehn K, Brotto L, Lara N, Mo CL, Johnson M, Brotto M *et al.* Skeletal muscle cells secrete factor(s) protecting bone cells from glucocorticoid induced cell death. *J Bone Miner Res* 2011;**26** (Suppl 1) (Available at http://www.abstracts2view.com/asbmr/view.php?nu=ASBMR11L_A11007363-127&terms=).