

# Summary - The role of vitamin D in musculoskeletal health

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Classically, vitamin D is viewed as a hormone essential for calcium homeostasis in that deficiency leads to impaired bone mineralization (rickets/osteomalacia). In this paradigm, vitamin D is ingested or cutaneously produced upon exposure to ultraviolet B radiation, transported bound to vitamin D binding protein to the liver and kidney, where subsequent 25 hydroxylation then 1 alpha hydroxylation is carried out, yielding the active or "hormonal" form, 1,25 dihydroxyvitamin D. It is widely accepted that vitamin D insufficiency/deficiency is epidemic worldwide and reflects inadequate sun exposure and/or sun avoidance.

This inadequacy is accepted to impair gastrointestinal calcium absorption leading to secondary hyperparathyroidism and accelerated bone turnover leading to bone loss and osteoporosis. Additionally, vitamin D deficiency is associated with proximal muscle weakness, thereby increasing the risk for falls and osteoporotic fracture.

As a result of the recognition that vitamin D inadequacy is extremely common, healthcare providers are more frequently measuring serum 25-hydroxyvitamin D [25(OH)D] and prescribing supplementation. Moreover, it is becoming increasingly recognized that vitamin D has paracrine/autocrine effects on multiple systems, not limited to calcium homeostasis, bone and muscle. This session reviewed current vitamin D knowledge in classical (musculoskeletal) diseases and non-classical diseases, clinical approaches to vitamin D inadequacy and explored potential future roles of vitamin D.

**Dr. Robert P. Heaney** presented an overview of vitamin D insufficiency calling this the "Iceberg nutrient" reflecting the observation that past focus on the role of vitamin D in musculoskeletal health is only the tip of the iceberg in regards to vitamin D's physiologic effects. He reviewed data documenting that elevations of circulating 25(OH)D concentration within the previously accepted "normal" range is associated

with substantial increases in calcium absorption; thus the "normal" range is not reflective of ideal vitamin D status. His presentation subsequently focused on the potential autocrine effects of vitamin D, touching on evidence that inadequacy impairs immune response to infectious agents and is associated epidemiologically with increased risk for a number of malignancies. In this regard, he shared preliminary results of observations of his group from a prospective trial in which vitamin D supplementation reduced overall cancer incidence in postmenopausal women.

**Dr. James C. Fleet** described the role of the vitamin D receptor in calcium regulation. The vitamin D receptor plays a complex role in control of bone health and recruits co-regulators, which may have activating, or repressing effects. In growing animals the primary defect of calcium metabolism in VDR knockout mice is at the intestine; loss of VDR causes calcium malabsorption and rickets that can be prevented by a high calcium diet. Additionally, VDR knockout mice reveal that VDR plays a role in suppression of bone formation.

**Dr. Neil Binkley** reviewed a clinical approach to the diagnosis and treatment of vitamin D inadequacy. Data presented suggests that the variability in 25(OH)D measurement has been reduced by widespread clinical availability of HPLC and LC/MS technologies, however, modest between laboratory variability remains. It is probable that availability of standard calibrators, currently being developed by the National Institute of Standards and Technology, will further reduce existing between laboratory variability thereby enhancing clinical identification of vitamin D inadequacy and facilitating monitoring of treatment. Available data regarding vitamin D supplementation approaches were reviewed. In the United States, pharmacologic options to replete vitamin D are limited in that only oral D<sub>2</sub> is available. Over-the-counter nutritional vitamin D supplements are not standardized. Clinicians need additional high-quality cholecalciferol options to remedy the epidemic of vitamin D inadequacy.

**Dr. Thomas A. Brown's** presentation focused on vitamin D analogs as potential anabolic agents. As proof of concept, data for one vitamin D analog, 2-Methylene-19-nor-(20S)-1,25-dihydroxyvitamin D<sub>3</sub> (2MD), was reviewed documenting that this compound dramatically increases bone mass, increases bone size and increases bone strength in rodents.

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Additionally, potential sites of D analog action, including at the level of D binding protein, VDR and transcription were reviewed. Numerous groups are advancing D analogs with novel pharmacologic properties and exploring additional potential therapeutic uses for these agents.

**Dr. John Adams** reviewed landmark work that his group is conducting which investigates the roles of 25-hydroxylated vitamin D metabolites as mediators of the human innate immune response. Bacterial products are recognized by plasma membrane toll-like receptors of macrophages. 1,25 dihydroxyvitamin D stimulates the innate immune response in anti-

gen presenting cells such as macrophages, increases phagocytosis, promotes antigen processing and increases superoxide synthesis. Importantly, the 1,25 dihydroxyvitamin D in this system does not originate from the circulation, but is generated locally in macrophages where it acts on macrophages and lymphocytes. Toll-like receptor ligand induced cathelicidin gene expression is impaired in the presence of extracellular 25(OH)D insufficiency. The local immunoregulatory effects of 1,25 dihydroxyvitamin D do not have whole organism calcium regulating effects until substantial amounts escape the local inflammatory microenvironment.