It is concluded that SARS-CoV-2 has helped to clarify the complexity of biology and has exposed the limitations of modeling strategies that do not include the application of case-based practice that can be described as "model-dependent realism"[1] as a means to discover the principle components of nature. The models are the valued product of the research that is mandated by the Helsinki accords when outcomes do not meet expectations. These models can facilitate the organization of all data in the appropriate translation to clinical care.

1 Hawking S., Mlodinow L. The Grand Design p 39–59, Bantom Books NY, 2010

Bone and Mineral Metabolism

BONE AND MINERAL METABOLISM MISCELLANEOUS

Oleanolic Acid Modulates 25-Hydroxyvitamin D_3 1-alpha-hydroxylase in Osteoblasts and Human Mesenchymal Stem Cells

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Objectives: 25-Hydroxyvitamin D_3 1-alpha-hydroxylase (CYP27B1) catalyzes the hydroxylation of 25-hydroxyvitamin D_3 ($25(OH)D_3$) to 1alpha,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), the bioactive form of vitamin D_3. Our previous studies suggested that oleanolic acid (OA), a pentacyclic triterpenoid presents in many food and herbs, can improve circulating $1,25(OH)_2D_3$ in ovariectomized (OVX) mice and increase CYP27B1 expression in human renal proximal tubular cells (HKC-8). However, the role of OA in regulating CYP27B1 in bone is far from clear. The present study is designed to study the effects of OA on CYP27B1 expressions and $1,25(OH)_2D_3$ production in bone cells. **Methods:** The mRNA and protein expressions of CYP27B1, as well as bone metabolism markers were determined in osteoblast-like UMR-106 cells in response to treatments of parathyroid hormone (PTH) (10^{-7} M) or OA (10^{-9} - 10^{-5} M) for 24 hours. By using excessive $25(OH)D_3$ (10^{-6} M) as substrate, cellular production of $1,25(OH)_2D_3$ was measured to determine CYP27B1 activity. To mimic the physiological condition, human mesenchymal stem cells (hMSCs) were pre-treated with $25(OH)D_3$ (10^{-7} M) for 12 hours, followed by OA treatment (10^{-9} - 10^{-6} M) for another 24 hours, the osteogenic effects of OA on alkaline phosphatase (ALP) activity and CYP27B1 expression were evaluated. **Results:** PTH (10^{-7} M, $p<0.001$) and OA (10^{-9} M, $p<0.05$) significantly upregulated mRNA and protein expressions of CYP27B1 in UMR-106 cells. 4-hour treatments of PTH (10^{-7} M) and OA (10^{-9} M) also stimulated the $1,25(OH)_2D_3$ production by 46.02 % ($p<0.001$) and 17.60 % ($p<0.01$), respectively. Moreover, the mRNA expressions of ALP and osteocalcin (OCN) involved in osteoblast differentiation, were upregulated in response to PTH and OA in UMR-106 cells ($p<0.05$). The protein expression of CYP27B1 was upregulated by treatment with OA in hMSCs supplemented with $25(OH)D_3$ (10^{-8} M, $p<0.05$ *vs.* supplement alone). Furthermore, OA (10^{-8} M) potentiated the effects of $25(OH)D_3$ on osteogenesis in hMSCs by enhancing ALP activity by 47.77 % ($p<0.01$). **Conclusions:** Our results indicated that the bone anabolic effects of OA are associated with its actions to improve local bioactivation of vitamin D_3 in osteoblasts and hMSCs, suggesting the involvement of paracrine or autocrine activities of $1,25(OH)_2D_3$ in mediating the actions of OA in bone.

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Bone and Mineral Metabolism

BONE AND MINERAL METABOLISM MISCELLANEOUS

The Effect of Dietary Vitamin D3 Level on Bone Osteometry and Mechanical Properties in Young Rats

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Recent knowledge indicates that vitamin D3 not only regulates the calcium-phosphate metabolism, but also as a hormone with steroidal features, has significant remedial-homeostatic ability and has a pleiotropic function in the body. Medical observations confirm the beneficial effect of elevated levels of vitamin D3 in the prevention or alleviation of the course of many diseases of the cancer and autoimmune basis, diabetes and coronary diseases. The deficiencies of this vitamin in children, adolescents and young women are observed, causing the rickets or bone fragility. As the increasingly limited role of obtaining vitamin D3 from the sun exposure, supplementation of food sources becomes particularly important. The aim of the study was to evaluate the effect of the increased dietary vitamin D3 level on health status using rats as the model animals. The experiment was carried out on 36 weaned rat Wistar, half female and male, 5–6 weeks old. Animals were divided into 3 groups. All rats obtained ad libitum the same feed mixture but differed in the vitamin D3 level (0, 1000 or 5000 IU/kg). Bone length and weight, cross-section area and wall thickness were measured, cortical index was calculated. The mechanical properties were determined using the 3-point bending test performed on a universal testing machine (Zwick Z010). The supports were placed at 40% of the total bone length and the measuring head loaded bone samples with a constant speed of 10 mm/min until fracture. The bone mineral density was determined using the dual-energy X-ray absorptiometry (DEXA) method on a DiscoveryWHologic X-ray densitometer. We observed that, the vitamin D3 presence in feed did not significantly affect the bone geometrical traits in young rats. The vitamin D3 supplementation, regardless its level, increased the bone mineral density by 8–12% ($P<0.05$) and some mechanical properties were improved ($P<0.05$) in comparison to group without vitamin D3 supplementation. Also, the femur bone of rats supplemented with vitamin D3 characterised by the higher share force (11–14%), work needed for destruction