Highlights from the 6th International Conference on Vitamin D Deficiency, “Nutrition and Human Health”, Abu Dhabi, United Arab Emirates, March 9-10, 2017

The 6th International Vitamin D Conference was held in Abu Dhabi on March 9-10, 2017 and was organized by Dr. Afrozul Haq. Drs. Sunil J. Wimalawansa and Carsten Carlberg joint Dr. Haq as co-editors of this special issue, in which 17 papers were accepted for publication.

The issue starts with a review by Wimalawansa et al. [1] about calcium and vitamin D in human health. In agreement with many scientists in the vitamin D field, they suggest that the vitamin D status, i.e. the serum 25-hydroxyvitamin D3 (25(OH)D3) level, should be above 75 nM, in order to sufficiently enhance gastrointestinal calcium absorption and mineralization of the osteoid tissue and for other system benefits. Based on the Institute of Medicine (IoM) report [2], a daily supplementation with 600 IU (15 µg) vitamin D3 suggested to be adequate for persons below the age of 71, not exposed to sunshine. However, Wimalawansa et al. argue that under these conditions only a very few individuals would reach serum 25(OH)D3 levels above 75 nM. In addition to safe sun exposure they suggest a daily intake of 1,000 IU (25 µg) vitamin D3 for persons with lighter skin and even 2,000 IU (50 µg) for dark-skinned individuals and older adults. They recommended, that for disabled, institutionalized or obese individuals, persons with gastrointestinal abnormalities and/or mal-absorption syndromes, and mothers during pregnancy and lactation, approximately 4,000 IU (100 µg) vitamin D3 per day for optimal physiological functions. The latter includes, muscle strength and neuromuscular coordination, release of hormones, subduing autoimmunity and curtailing the development of certain cancers. Together with the total daily calcium intake not exceeding 1,500 mg, the safe upper limit of oral daily supplementation is considered as 5,000 IU (125 µg) vitamin D3.

The glycoprotein sclerostin is produced by osteocytes and has anti-anabolic effects on bone formation. Yadav et al. [3] analyzed sclerostin serum levels in subjects with a baseline vitamin D status below 50 nM in a randomized, double blind, placebo-controlled trial investigating the effect of a single bolus vitamin D3 supplementation (300,000 IU, i.e. 7500 µg) or placebo on vascular function in non-diabetic chronic kidney disease stage 3 and 4. At baseline, serum sclerostin levels were similar in both the vitamin D3 group and the placebo group. However, 16 weeks after bolus supplementation the vitamin D3 group showed no change in sclerostin levels, while a significant decrease was noted in the placebo group. The change in sclerostin level after 16 weeks correlated negatively with changes in estimated glomerular filtration rate and positively with changes in uric acid concentrations. In conclusion, bolus vitamin D3 supplementation did not change sclerostin levels in non-diabetic stage 3 and 4 chronic kidney disease subjects. Kumar et al. [4] reported on a follow-up of this trial, in which subjects in the placebo group were given twice the 300,000 IU (7500 µg) vitamin D3 bolus at 8-weeks intervals followed by measurements of flow-mediated dilatation pulse wave velocity and circulating endothelial and inflammatory markers. Serum 25(OH)D3 and 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) levels significantly (p < 0.001) increased and flow-mediated dilatation improved. An endothelium-independent nitroglycerine-mediated vasodilatation may explain these changes.

Vitamin D deficiency is rampant in the Middle East, even in children and adolescents. Al-Daghri et al. [5] reported on different strategies as effective ways to combat the deficiency. They performed a 6-month multi-center, controlled clinical study with 884 school children from the region of Riyadh, Saudi Arabia, and compared daily application of four different brands of vitamin D3 fortified milk (200 ml) with vitamin D3 pills (1,000 IU, i.e. 25 µg). Analysis of covariance showed that after adjusting for baseline 25(OH)D3, age, gender and body mass index, the mean vitamin D status of children who were taking vitamin D3 pills (9.1 ± 0.8 nM) and milk brand 4 were significantly higher (7.3 ± 1.1 nM) than children taking milk brand 2 (6.1 ± 1.0 nM). However, children supplied with milk brands 1 and 2 exhibited a significant increase in total cholesterol level, while it dropped significantly in subjects taking milk brand 3. Taken together, different strategies in vitamin D supplementation elicited varying degrees of improvement in serum 25(OH)D3 levels. In another study, Al-Daghri et al. [6] investigated Saudi school children and school teachers (total 989 subjects) over a 6-month period. At baseline, the mean serum 25(OH)D3 concentration was approximately 30 nM in both adults and children, highlighting a significant hypovitaminosis D in this community and the lack of sun exposure in both groups. The mean serum 25(OH)D3 levels were raised in the group received oral vitamin D supplementation, w1,000 IU (25 µg)/day (increase of ~11 nM), followed by consumption of vitamin D3-fortified milk products (raised by ~7.5 nM) and the exposure to sunlight (increase of only ~4.5 nM). The latter suggest poor compliance to sun exposure among other factors.

Mandlik et al. [7] also investigated for 6 months the effects of daily vitamin D3 (1000 IU) and calcium (500 mg) supplementation in school children, in a semi-rural setting in India. Data were collected from 106 subjects (aged 6-12 years) and included anthropometric measures like height and weight, body composition analysis, three one-day dietary recalls and sunlight exposure, using a questionnaire. The mean...
baseline serum 25(OH)D$_3$ levels was 59.7 ± 11.2 nM, which rose to 79.8 ± 23.3 nM with no significant differences between genders. Children with a basal vitamin D status of below 45 nM showed the greatest benefit by supplementation. 44% of the children improved their serum 25(OH)D$_2$ levels to more than 75 nM. Interestingly, significantly higher percentage of children who were deficient at baseline (64%) was able to attain serum concentrations of higher than 75 nM as compared to children who had been vitamin D insufficient (43%) (p < 0.001). Vitamin D$_3$ supplementation, 1000 IU (25 µg)/day, significantly improved serum 25(OH)D$_3$ concentrations, above 75 nM, particularly in vitamin D deficient children.

Vitamin D and other micronutrient deficiencies are common during pregnancy, which is in part due to high demands for calcium during this period. Heyden and Wimalawansa [8] highlighted the importance of having vitamin D adequacy during pregnancy and demonstrated that hypovitaminosis D is associated with a higher incidence of fetal miscarriage, pre-eclampsia, gestational diabetes and bacterial vaginosis as well as with impaired fetal and childhood growth and development. They emphasized that clinicians need to be acutely aware of the risks associated with not identifying and correcting vitamin D deficiency, especially during pregnancy. Thus, prompt identification and correcting vitamin D deficiency by means of safe sun exposure and vitamin D supplements is essential for women who seek assistance with fertility or prenatal counseling, and those in their early pregnancy. Protective effects of vitamin D during pregnancy occur when the 25(OH)D$_3$ serum levels exceed 75 nM; in most mothers, this necessitates a daily intake of 4000 IU (100 µg) vitamin D$_3$.

Supporting the above concepts, von Websky et al. [9] demonstrated a high incidence of vitamin D deficiency in pregnant women. A sufficient supply of mother and child with vitamin D$_3$ and calcium during pregnancy ensures a healthy bone development of the fetus, whereas, lack of either of these nutrients can lead to the development of rickets in the child. A prevention of vitamin D deficiency in pregnant women and their children is an important goal. Taken together, it is strongly advised that clinicians taking steps to prevent the epidemic of vitamin D deficiency during pregnancy.

Prematurity and immaturity are the leading causes of perinatal and infant mortality and are a major public health problem around the world. Uwitonza et al. [10] demonstrated that maternal perinatal diseases (PDs) associated with preterm-birth with low birth weight newborns. Inflamed perinatal diseases generate high levels of pro-inflammatory cytokines that may have systemic effects on both the mother and the fetus. In addition, the bacteria that cause PDs produce endotoxins, potentially may have adverse effects in the fetus. An inadequate vitamin D status of the mother is associated with the genesis of PDs. Administration of vitamin D supplementation during pregnancy therefore may reduce the risk of maternal oral infections and adverse pregnancy outcomes. Thus, nutritional education should be emphasized during pregnancy so that the pregnant woman would ensure optimal nutritional status, including maintaining vitamin D levels through safe sunlight exposure and/or dietary supplements.

Gestational infection increased incidence of autism. The placenta is a major source of production of 25(OH)D$_2$ during pregnancy and this local production is an essential regulator of immune regulation during pregnancy. Ali et al. [11] investigated in rat animal models the effects of maternal vitamin D deficiency, on the baseline placental immune status and in response to established viral and bacterial immune activating agents. Vitamin D deficiency does not affect baseline inflammatory cytokines in the placenta, but immune-challenged placentas from male fetuses showed higher production of interleukins 6 and 1β. A dysregulated placental immune response could also have adverse implications for the developing brain and may increase the risks of developing autism.

The review article of Razzaque [12] discussed that serum 25(OH)D levels are not always the true reflection of vitamin D supplementation by diet and supplements. In contrast to a safe sunlight exposure, prolonged and disproportionate consumption of vitamin D supplements could lead to vitamin D intoxication, albeit incidences are very rare. Initial signs of vitamin D overdose are hypercalcemia, hypercalcuria and hyperphosphatemia. Calcium and phosphorus dys-regulation, induced by exogenous vitamin D supplementation if persisted, may lead to tissue and organ damage, even without developing hypervitaminosis D. A greater awareness of such clinical scenario would serve better to the affected individuals, as when hypercalcemia and/or hyperphosphatemia are already apparent.

The major circulating form of vitamin D is 25(OH)D$_3$. Tsuprykov et al. investigated, whether measurement of 25(OH)D$_2$ helps to assess the vitamin D status [13]. Majority of 25(OH)D in circulation is tightly bound to carriers, especially to vitamin D binding protein (DBP); smaller amounts are bound to albumin and lipoproteins, while small amounts are circulating in the free form—the biologically active form. Routine vitamin D assays do not distinguish between 25(OH)D, DBP-bound 25(OH)D, albumin-bound 25(OH)D and free 25(OH)D. Thus, diseases that changing the levels of DBP or albumin would have a significant impact on measured total 25(OH)D levels. In addition, the sex-steroid estrogen stimulates the synthesis of DBP explaining why total 25(OH)D levels are higher during pregnancy as compared to non-pregnant women while the concentrations of free 25(OH)D may remain similar. In the kidney, 25(OH)D-DBP as well as 25(OH)D-albumin complexes are filtered through the glomeruli and taken up by low density lipoprotein-related protein 2 (megalin) in the proximal tubule. Consequently, all types of kidney diseases that are characterized by tubular damage are associated with a loss of 25(OH)D-DBP complexes in the urine. Tsuprykov et al. [13] suggest that the measurement of free 25(OH)D levels could be more appropriate under certain conditions.

Shah et al. [14] pointed out three common analytical techniques for qualitative and quantitative analysis of 25(OH)D: i) immunoassays measure approximately 240 samples per hour with reasonable sensitivity (a range of 8.5-990 nM 25(OH)D$_3$), ii) high-performance liquid chromatography (HPLC), a low-cost method that provides a high throughput but less sensitive, and iii) liquid chromatography-mass spectrometry (LC-MS) with the highest sensitivity. LC-MS offers a high level of separation and permits identification of vitamin D-related metabolites. There is a need for developing an analytical method that combines the high detection capabilities of liquid chromatography-tandem mass spectrometry (LC-MS/MS) with the rapid, automated format of immunoassays. In contrast to immunoassays, LC-MS/MS can differentiate between 25(OH)D$_2$ and 25(OH)D$_3$ as well as epimers. The latter may not have clinical relevance or use, but can be important in research studies. In this study, Shah et al. [15] used an Emirati population to validate the assay for different vitamin D metabolites, epimers and isobars. They demonstrated the method is reliable, reproducible, and robust for the detection of 25(OH)D.

Al-Daghri et al. [16] performed an intervention study evaluating the levels of apolipoproteins among 120 Saudi adults with vitamin D deficiency at baseline and 6 months later when they achieved full vitamin D status through vitamin D$_3$ supplementation. Serum 25(OH)D levels increased significantly (p < 0.0001) from 32.5 ± 10.8 nM to 63.3 ± 16.5 nM. Moreover, serum levels of apolipoproteins C1, C2, C3 and E significantly (p < 0.01) increased, while apolipoprotein B decreased. However, after stratification for gender, apolipoproteins C2 and C3 increased significantly (p < 0.01) only in males and apolipoprotein C1 only in females. Moreover, apolipoprotein B decreased significantly (p = 0.002) only in females. This dimorphism may explain gender disparity in cardiometabolic health.

Individuals with the autoimmune disease multiple sclerosis (MS) are known to have lower serum 25(OH)D levels compared to healthy controls. Bettencourt et al. [17] investigated 244 unrelated Portuguese MS patients and 198 ethnically matched healthy controls. The mean serum 25(OH)D level of MS patients was with 39.9 ± 22.0 nM; significantly (p < 0.0001) lower than in healthy controls, the 55.4 ± 23.4 nM of healthy controls. A negative correlation was
observed between 25(OH)D levels and scores for Expanded Disability Status Scale as well as Multiple Sclerosis Severity Scale. Lower serum 25(OH)D levels were also found in patients with a recent disease onset, supporting the role of vitamin D deficiency as a risk factor for MS.

In the last article of the special issue Carlberg et al. [18] report about phase II of the VitDbol vitamin D intervention trial (NCT02063334) representing a new type of safe human in vivo experiments, in which an oral vitamin D₃ bolus (2000 µg) is used to induce within 1-2 days changes in the epigenome of peripheral blood mononuclear cells (PBMCs). One individual was exposed three times directly before each supplementation as well as one and two days after. Chromatin was isolated from PBMCs without any further in vitro culture and at all 9 time-point chromatin accessibility was measured at 5205 genomic loci. The 853 most prominent of these were classified into 70 significantly (p < 0.0001) changing early, 361 delayed and 422 non-responding genomic regions. The most prominent region of the vitamin D responsive chromatin sites within the human genome is the human leukocyte antigen cluster in chromosome 6. This study demonstrates that under in vivo conditions a vitamin D bolus causes significant changes at hundreds of loci within the epigenome of human leukocytes.

References


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