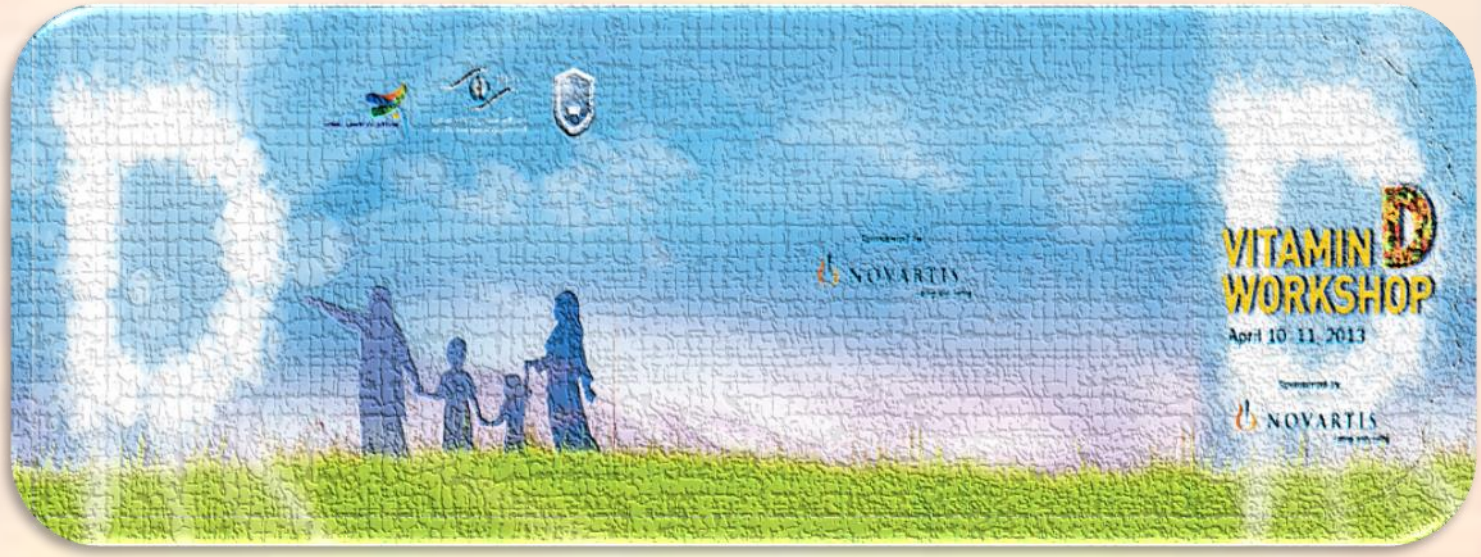

Proceedings of the 2013 Vitamin D Workshop
April 10-11, 2013

Holiday Inn Al-Qasr, Riyadh, Saudi Arabia

16 CME Credit Hours

Message from the Chairman

At this point in time, majority of us in the medical and scientific community are aware of the importance of vitamin D in health and disease. Majority of us agree that some of the basic questions about the physiology and pathology of vitamin D have been answered in terms of prevention, diagnosis, treatment and toxicity. Furthermore we concur that this fat soluble vitamin is something that we cannot ignore, especially in this region of the world.

Having mentioned such, it is but apparent that we all meet and discuss to start off from where we left, and share our work within the last 2 years. More importantly, I, on behalf of all the vitamin D enthusiasts would like to hear from our experts on what's latest and where we are headed in this field. Our exchange of knowledge will definitely be vital to all the medical practitioners and researchers, who in their daily lives will translate this newly found increased awareness to the benefit of the entire community.

As the director of the Prince Mutaib Chair for Biomarkers of Osteoporosis (PMCO), I would like to express my sincerest thanks to our beloved rector, his excellence, Professor Badran Al Omar for his overwhelming support in the realization of our noble goals. This gratitude is extended to the Biochemistry department and the College of Science in King Saud University. Special thanks to the PMCO scientific committee and researchers for realizing this concept of organizing a vitamin D workshop that we are about to experience. Of course we are grateful to the generosity of Novartis for sponsoring this event and believing in our cause. Lastly and most important of all, we thank you, the participants, who are undoubtedly the main benefactors of this event. We hope you enjoy and appreciate what we have meticulously prepared for you, and we hope you will share the knowledge that you will gain in this event.

Professor Nasser M. Al-Daghri, PhD
Prince Mutaib Chair for Biomarkers of Osteoporosis, KSU
Director
Biomarkers Research Program, KSU
Deputy Director

VITAMIN D WORKSHOP 2013

FINAL SCIENTIFIC PROGRAM

DAY 1			**DAY 2**		
Session 1 – Vitamin D Basics: Biochemistry and Epidemiology Chairman: Prof. Nasser Al-Daghri			Session 3 – Clinical Relevance of Vitamin D Chairman: Dr. Omar Al-Bagha		
8:00-9:00	Registration		9:00-9:30	Vitamin D and Cardiovascular Diseases	Prof. Sunil Wimalawansa
9:00-9:30	Opening Remarks	Prof. Nasser Al-Daghri	9:30-10:15	Guidelines for Vitamin D Treatment	Dr. Fahad Al-Shahrani
9:30-10:00	Vitamin D Basics: History, Functions and Bioavailability	Prof. Sunil Wimalawansa	10:15-10:30	Coffee Break/Posters	
10:00-10:30	Vitamin D Deficiency Epidemiology	Dr. Yousef Al-Saleh	10:30-11:00	Sunshine in a Bottle	Dr. Yousef Al-Saleh
10:30-11:00	Genetics of Osteoporosis/Vitamin D – State of the Art	Dr. Omar Al-Bagha	11:00-11:30	Case Discussions	Dr. Fahad/Dr. Naji
11:00-11:15	Coffee Break/Posters		11;30-1:00		
11:15-12:00	Vitamin D and Biomarkers	Prof. Riad Sulimani	Session 4 – Treatments for Vitamin D (Chairman: Prof. Sunil Wimalawansa)		
12:00-12:45	Vitamin D Sufficiency: Definitions and consequences	Prof. Sunil Wimalawansa	1:00-1:30	PMCO Studies: Overview	Prof. Nasser Al-Daghri
12:45-2:00	Prayer/Lunch		1:30-1:45	Diabetes Therapy and Vitamin D	Dr. Shaun Sabico
Session 2—Vitamin D Sufficiency and Deficiency: Chairman: Prof. Riad Sulimani			1:45-2:00	Vitamin D Receptor Polymorphisms	Alia Al-Iqniebi
2:00-2:30	Vitamin D and Children	Dr. Mohsen Alattawi	2:00-2:15	Break	
2:30-3:00	Vitamin D and Cancer	Dr. Soundar Krishnaswamy	2:15-2:30	Vitamin D Quantification	Dr. Sobhy Yakout
3:00-3:15	Break		2:30-3:15	Vitamin D and Associated Disorders	Dr. Naji Aljohani
3:15-3:45	Vitamin D and Pregnancy	Dr. Mona Founda	3:15-3:30	Open Discussion/ Closing Remarks	Session Chair
3:45-4:15	Vitamin D and Diabetes Mellitus	Eman El-Shehri			

may need an extra 2,000 IU/day to maintain normal serum 25(OH)D levels; over 30 ng/nL (75 nmol/L).

Wimalawansa SJ. "Vitamin D: All you need to know." Text Book, 2012

Vitamin D Basics: History, Functions and Bioavailability

Professor Sunil J. Wimalawansa, MD, PhD, MBA, DSc
University of Medicine & Dentistry of New Jersey

Vitamin D is a fat-soluble secosteroid. In 1916, sunlight was recognized as a treatment for rickets. The chemical structure of vitamin D was identified in 1926. In 1975, the protein receptor that binds the active vitamin D metabolite in the nucleus of cells—the vitamin D receptor was identified. Among the several forms of metabolites, the two physiologically relevant forms are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Pre-vitamin D_3 is formed in the skin following photolyzed by ultraviolet light (UV), and spontaneously isomerizes to vitamin D_3. Small quantities of vitamin D also present in foods. Vitamin D is transported to the liver, hydroxylated into prohormone 25-hydroxycholecalciferol ([25(OH)D], calcidiol. In the proximal renal tubules it hydroxylated, (A) via PTH-driven, C1 hydroxylation to active vitamin D [1,25$(OH)_2$D)], calcitriol, and (B) via 24-hydroxylase—inactive vitamin D [24,25$(OH)_2$D]. In addition to enhancing calcium absorption and mineralization, vitamin D is essential for many physiological functions, including neuromodulation, muscle strength and coordination. Daily administration of oral formulations of vitamin D_2 and D_3 are considered equivalent. However, when administered intermittently, vitamin D_2 is less potent and has a shorter duration of action than does D_3. While vitamin D sufficiency prevents falls and fractures, WHI study suggested that every 10 ng/mL decrease in serum vitamin D levels doubles the risk of hip fractures, especially when the levels are less than 30 ng/mL. An additional 1,000 IU of vitamin D/day is generally sufficient for lighter-skinned individuals, older people and dark-skinned individuals

Vitamin D Deficiency Epidemiology

Dr. Yousef Al-Saleh, MD
King Saud University for Health Sciences

The recent discovery of the extra-skeletal effects of vitamin D deficiency has undoubtedly triggered enormous attention in the fields of endocrinology, immunology, and other major medical areas, secondary to the widespread deficiency documented on a global scale. The Kingdom of Saudi Arabia (KSA) has not been spared, and documents one of the highest rates of vitamin D deficiency world-wide. Despite increasing evidence, little efforts have been done to counter-act vitamin D deficiency in KSA, and the Gulf region in general in terms of public awareness and campaign to eradicate, if not minimize a highly preventable deficiency. In this review, the build-up of local studies on vitamin D deficiency are highlighted spanning 3 decades of scientific evidence, with emphasis on the prevalence observed in different regions and associated diseases that are specific to the kingdom with the hope of strengthening the need for intervention.

Vitamin D and Bone Turnover Biomarkers

Prof. Riad Sulimani, MD
King Saud University

Relationship between levels of 25 hydoxy vitamin D and different types of bone turnover markers (BTMs) have been extensively studied yet results have been inconsistent. BTMs appear to be elevated in vitamin D deficient individuals especially if such levels are truly deficient (and even in the insufficient range). Response of BTMs to treatment with vitamin D have been inconsistent. In some reports, BTMs tend to decline with vitamin D supplementation. However, other studies did not confirm this tendency .Indeed, some studies revealed rising levels of resorptive markers initially during treatment with vitamin D suggesting possible transient high turnover state. It has been argued whether vitamin D is truly necessary for bone remodeling or just for bone mineralization. It is to be stressed that one of the main factors for the inconsistent results is related to the biologic and laboratory variables mentioned above.

Follow up of patients treated with vitamin D should include the clinical assessment related to their clinical presentation and consequences of vitamin D deficiency and osteomalacia. Monitoring of vitamin D levels, coupled with bone profile and including serum alkaline phosphatase are necessary for monitoring patients being treated with vitamin D ± calcium supplements. It is unlikely that measurement of BTMs at baseline and after courses of vitamin D supplementation will add extra clinical benefit. Further studies and meta-analyses will be needed to define more precisely the relationship of vitamin D/BTMs in vitamin D deficient individuals and the effects of vitamin D supplementation on the bone remodeling/mineralization processes and the consequent possible changes on BTMs.

Genetic Determinants of Osteoporosis

Omar Albagha, PhD
Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK.

Osteoporosis is a common disease characterised by low bone mineral density (BMD), microarchitectural deterioration of bone tissue, and an increased risk of fracture. Genetic factors play a key role in regulating bone mineral density, ultrasound properties of bone, bone turnover and contribute to the pathogenesis of osteoporotic fracture. In most cases, osteoporosis is caused by the combined effects of several different genes and their interaction with environmental influences such as diet, lifestyle and exposure to the sun. Several genes have been implicated in the regulation of bone mass such as vitamin D receptor gene (VDR), oestrogen receptor alpha gene (ESR1) and lipoprotein receptor-related protein 5 gene. Recent genome wide association studies have identified more than 50 genes to be associated with bone mass and revealed 14 genes associated with fracture risk. Genetic studies in osteoporosis have advanced our knowledge of the pathogenesis of the disease and identified genes which highlight new molecular pathways for regulation of bone mass. These new genes could be used as target for the design of new drugs for the prevention and treatment of bone disease. This talk will give an overview of the genetics of osteoporosis focusing on the VDR gene.

Holick, M.F., et al., *Endocrine society clinical practice guideline.* J Clin Endocrinol Metab, 96: 1911-30, 2011.

Vitamin D Sufficiency: Definitions and Consequences

Professor Sunil J. Wimalawansa, MD, PhD, MBA, DSc
University of Medicine & Dentistry of New Jersey

More than half of the world's population lacks adequate exposure to sunshine and thus, cannot maintain serum vitamin D levels in the physiological range. Low vitamin D status is endemic and common among the vulnerable groups including elderly. Controversy of vitamin D continues, while its deficiency and the associated morbidities are increasing worldwide. Ultraviolet rays should provide >80% of vitamin D requirements in humans, while diet and supplements augment it. Measurement of serum 25-hydroxyvitamin D [25(OH)D] is the most reliable way to evaluate vitamin D status. Low vitamin D levels aggravate a variety of non-skeletal disorders including cancer, diabetes, metabolic syndrome, infectious diseases and autoimmune disorders. Hormone $1,25(OH)_2D$ regulates blood calcium and phosphate, promoting mineralization, and growth and remodeling of bone. Thus, vitamin D insufficiency leads to poorly calcified brittle bones, while sufficiency prevents these, including rickets and osteomalacia and increase falls. Vitamin D also modulates neuromuscular functions, decrease inflammation, and modulates actions of several key genes that regulate cell proliferation, differentiation and apoptosis. Whether widespread vitamin D deficiency is related to increasing incidences of cancer, obesity, insulin resistance, type 2 diabetes is uncertain. Thus, deficiency status leads to exacerbation of a variety of human disorders including cancer and cardiovascular diseases. Most scientists agree that the minimum desirable serum 25(OH)D level is 30 ng/mL (75 nmol/L). To achieve this, most adults need between 1,000 and 2,000 IU of extra vitamin D per day.

Vitamin D and Cancer

Soundararajan Krishnaswamy
Biomarkers Research Program, KSU

Vitamin D is involved in a variety of biological activities and the anticancer potential of vitamin D stems from its ability to affect – directly or indirectly (e.g., by transactivation) – the expression of genes involved in the regulation of cell growth, apoptosis, angiogenesis and inflammation, the four key mechanisms underlying the development and progression of cancer. The important oncogenes regulated by vitamin D, as revealed by in vitro studies, include MYC, P73, hypoxia-inducible factor 1 (HIF-1), IL-8, NFkB, cyclooxygenase 2 (COX2) and CDKN1A. As regards epidemiological studies, although the findings of single reports are sometimes conflicting, most pooled analyses do suggest deficient vitamin D to lead to cancer development. As for therapeutic effect, single agent vitamin D has not been consistently associated with positive tumor response in clinical trials and the therapeutic effect becomes significant on occasions when the histological subtypes of tumors are considered. Meta-analyses on the relationship between serum levels of vitamin D and cancer incidence reveal both tumor suppressing and tumor promoting effects suggesting that the potential for both harm and benefit may depend on dose, timing and duration of exposure, tissue specificity, lifestyle factors, and interaction with genetic background.

Vitamin D and Pregnancy

Dr. Mona Fouda
King Khalid University Hospital

Vitamin D, a fat-soluble molecule acquired through exposure to sunlight or diet, has been identified as a steroid hormone precursor that modulates long-term programming of human health. Low vitamin D intakes during perinatal development have traditionally been linked to poor bone health. However, scientists are beginning to realize that vitamin D deficiency during perinatal development is a risk-modifying factor for a range of diseases, including multiple sclerosis, schizophrenia, heart disease, type 1 diabetes and cancer. Inadequate vitamin D nutrition during perinatal development is a threat to human health. It has been proposed that metabolic imprinting may be responsible for the long term program effects of 25(OH)D. Metabolic imprinting is an adaptive process that fine tunes the expression of specific genes, without directly altering the DNA sequence, to produce a phenotype that is best suited to survive in its predicted environment. In this presentation we will try to highlight the evidence in the literature that supports the importance of normal maternal vitamin D for healthy outcomes in their offspring and the recommendations for optimal vitamin D therapy in pregnant women.

Vitamin D and Cardiovascular Diseases

Professor Sunil J. Wimalawansa, MD, PhD, MBA, DSc
University of Medicine & Dentistry of New Jersey

Vitamin D plays an important role in cardiovascular health by regulating blood pressure, heart, and healthful endothelial and smooth muscle cell functions. Observational studies have suggested links between vitamin D deficiency and a higher risk for hypertension. Several studies have suggested that the protective effect of vitamin D on the heart and the vascular system is exerted via the renin-angiotensin hormone system. Vitamin D attenuate the renin-angiotensin-aldosterone system, and indirectly suppressing the synthesis and secretion of rennin; thus suppressing angiotensin II secretion. $1,25(OH)_2D$ also suppresses cellular inflammation in cardiac cells and endothelial and smooth muscle cells, thus improve the endothelial functions. There is also evidence to suggest that optimizing serum 25(OH)D levels would attenuate the age-associated increase of systolic blood pressure. Although evidence indicates biological associations linking low vitamin D with endothelial dysfunction and cardiovascular disease, no RCT evidence is available yet that vitamin D supplementation prevents cardiovascular disease. Therefore, clinical trials should be design and carry out to test the hypotheses that vitamin D supplementation has cardiovascular protection and to assess the optimal serum 25(OH) levels D necessary to achieve such benefits. Observational studies have suggested protective effects of 25(OH)D on cardiovascular diseases, thus calling for national policies to recommend higher serum levels of vitamin D, safe sun-exposure, food fortification, and dietary and supplemental vitamin D.

Vitamin D Treatment

Dr. Fahad Alshahrani, MD, CCD
King Abdulaziz Medical City

Considering that vitamin D deficiency is very common in all age groups and that few foods contain vitamin D, adequate sunlight exposure is the most cost effective means of obtaining vitamin D. whole body exposure to enough UBV radiation or sunlight to provide a mild reddening of the skin has been calculated to provide the equivalent of 10000 IU vitamin D3. Duration of exposure depends on skin pigmentation and intensity of the sunlight. However, concerns regarding the association between sunlight and skin cancer have limited this approach, perhaps to the extreme, although it remains viable option for those unable or unwilling to benefit from oral supplementation.

Endocrine society suggests vitamin D2 or D3 for treatment of vitamin D deficiency:

- Initial dose 50,000 units weekly or 6000 daily for 8 weeks to achieve 25-hydroxyvitamin D level > 75 nmol/L.
- Maintenance therapy with 1500- 2000 IU daily.
- Increase dose 2-3 times if patient is obese, malabsorption, or taking medication affecting vitamin D metabolism.

Toxicity, has not been observed at doses less than 10000 IU daily, although such doses are seldom required except in malabsorption.

Diabetes Therapy and Vitamin D

Shaun Sabico, MD
Biomarkers Research Program, KSU

Little or no research has determined the effect of vitamin D3 supplementation in conjunction with non-pharmacological and pharmacological approaches in the type 2diabetes mellitus (DMT2) population. The purpose of this study was to determine the effect of vitamin D3 supplementation in a cohort of DMT2 patients on rosiglitazone, diet, insulin and/or different oral hypoglycemic agents (i.e., insulin + oral agents, metformin, and sulfonylureas) and compare them with a non-DMT2 control cohort. A total of 499 randomly selected subjects divided into 2 groups [non-DMT2 Controls=151; DMT2=348]. All DMT2 patients were given 2000 IU vitamin D3 daily, while the control group received none but were advised to increase sun exposure. Anthropometrics, glucose, lipid profile and 25-hydroxyvitamin D were measured at baseline, and at 6 and 12 months. Circulating 25-hydroxyvitamin D concentrations improved in all patient groups and the controls. The metformin group showed the highest change in circulating vitamin D levels both at 6 months (62.6%) and 12 months (50.6%) as compared to baseline ($p < 0.001$). Significant improvements were observed in systolic blood pressure, total- and HDL-cholesterol in male patients on insulin + oral agents after vitamin D supplementation (p-values<0.05). Significant decreases in triglycerides were also observed in the rosiglitazone and insulin + oral hypoglycemic agent groups both at 6 and 12 months of supplementation (p-values<0.001). Vitamin D therapy at a dose of 2000 IU appears to alter cardiovascular disease risk factors under particular anti-diabetes regimens. Effects on well-being and other parameters need further study.

Vitamin D Receptor Polymorphisms

Alia Iqniebi, MSc
King Saud University

Osteoporosis is characterized by reduced bone mass, alterations in the microarchitecture of bone tissue, reduced bone strength, and an increased risk of fracture. Prevalence of osteoporosis among Saudi populations is in the range of 35–48 %. PTH is a key regulator of calcium metabolism and high level of PTH is an independent risk factor for fracture. The study aims to explore the effects of genetic variation in the PTH gene in relation to osteoporosis incidence in elderly women, we have analyzed four PTH gene variants (rs6254, rs1459015, rs10500783 and rs10500784) and serum PTH levels. Two hundred postmenopausal Saudi females (100 osteoporosis patients and 100 age matched healthy controls) were genotyped for four SNPs of PTH gene using TaqMan assay. Serum PTH levels were measured using ELISA. The mean PTH levels of various genotypes were compared. TT genotype of rs6254 and CT genotype of rs10500783 were significantly associated with increased risk of osteoporosis [OR 2.9, 95% CI (1.4, 5.8); p=0.004], [OR 3.7 95%CI (1.8, 7.4); p<0.001] respectively. CC genotype of rs1459095 and AA genotype of rs10500784 were significantly associated with elevated PTH levels (p<0.03), while CC genotype of rs10500783 was associated with low PTH levels (p=0.03). PTH genetic variants are associated with increased risk of osteoporosis and elevated PTH levels.