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Highlights from the 20th Workshop on Vitamin D in Orlando, Mar. 28–31, 2017

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The 20th Workshop on Vitamin D was held at the Rosen Center Hotel in Orlando Florida from March 28–31, 2017. The Workshop was organized by John White (Chair, McGill University, Montreal, Canada) and Peter Ebeling (Co-Chair, Monash University, Melbourne, Australia), with the invaluable support of JoEllen Welsh (CFO, SUNY Albany, NY) and Roxanne Hall (Meetings Plus). Invited presentations and topical sessions were chosen by the Workshop Executive Committee, with input from the Program Advisory committee (http://www.vitamindworkshop.org). The Workshop, which attracted 219 attendees from 29 countries, began the evening of March 29 with an opening reception and 24 Plenary Poster presentations. The following three days were filled will exciting science, divided into 13 sessions of oral presentations covering topics in basic science, clinical research and

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epidemiology, a debate on the topic “RCT are the only appropriate way to demonstrate the role of vitamin D in human health”, as well as 174 poster presentations. Delegates who presented at the Workshop were invited to submit manuscripts for peer reviewed publication in this special edition of the Journal of Steroid Biochemistry and Molecular Biology. Each manuscript was peer reviewed according to Journal standards. Guest editors were Dr. White, along with Dr. Martin Hewison (University of Birmingham, UK) and Dr. James Fleet (Purdue University, IN). Topical summaries of all oral sessions and the debate are presented below.

The first day started with opening remarks by the Chair, Dr. John White, followed by **Session I** entitled the **Year in Vitamin D: Basic and Translational** presented by Dr. James Fleet (Purdue University, IN). Dr. Fleet provided an excellent overview of some of the key publications to come out the vitamin D field in 2016–2017, focusing primarily on basic science research. The presentation began with a reminder of the large number of vitamin D receptor (VDR)-binding sites throughout the genome, including both ligand-dependent and −independent sites, with recent work showing how many of these sites overlapped with binding sites for nuclear factor-kappa B (NF-κB) under inflammatory conditions. Dr. Fleet also highlighted the role of topologically associating domains (TADs) in facilitating gene transcription, with $1,25(OH)_2D$ promoting TADs via CCCTC-binding factor (CTFC) as part of its actions on the regulation of gene expression. In addition to this new facet of transcriptional regulation by $1,25(OH)_2D$-VDR, Dr. Fleet described a role for vitamin D as a regulator of microRNA (miRNA) expression, with the potential to impact both vitamin D metabolism (CYP27B1 and CYP24A1 expression) and responses (VDR expression), as well as a wide range of other signalling pathways. Another key development in the last year has been the appreciation of how genetic variants contribute to the circulating concentrations of vitamin D metabolites, notably 25(OH) D. To illustrate this, Dr. Fleet presented work by his own group that documented loci for varying serum levels of 25(OH) D in different strains of mice. Other highlights in this session included a description of the potential role of vitamin D in fetal programming, and how effects of vitamin D-deficiency on fetal development may be sex-specific. Several recent publications documenting expression of VDR in osteoclasts and muscle cells were also described. Turning to non-classical effects of vitamin D, Dr. Fleet described recent animal model studies that showed modest effects in suppressing tuberculosis (TB) infection, but with more striking effects in suppressing inflammation associated with TB. Other immunomodulatory effects described included vitamin D-mediated regulation of immunoglobulin production, and prevention of colitis in inflammatory bowel disease (IBD) models. Dr. Fleet ended his presentation by describing studies that explored disease associations with 25(OH)D through analysis of local versus systemic production of $1,25(OH)_2D$.

The subject of **Session II** was **Vitamin D, Immunity and the Microbiome**, which was opened by Dr. Corinne Maurice (McGill University, Montreal, QC) who provided an overview of our rapidly growing understanding of the relationship between humans and their resident microbial communities. Dr. Maurice highlighted the complexity of the interactions between the gut microbiota and its host, and the technologies that are currently being used to explore this relationship. Dr John Baines (Max Planck Institute, Plön, Germany) then

described work by multi-national collaborators documenting genome-wide association analysis (GWAS) of the gut microbiota, how this may be linked to the *VDR* gene locus, and potential relevance of this for diseases such as IBD. Moving away from the microbiota, Dr. Vassil Dimitrov (McGill University, Montreal, QC) demonstrated that $1,25(OH)_2D$ could suppress inflammatory T cell responses indirectly by inducing cell-surface expression of programmed death-ligand 1 (PD-L1) on co-cultured epithelial or myeloid cells, with anti-inflammatory effects of vitamin D being blocked by antibodies to PD-L1. In the final presentation in this session, Dr. Dean Larner (University of Birmingham, Birmingham, UK) described mouse studies showing that vitamin D-deficiency was associated dysregulated inflammatory responses in both pregnant mice and in placentas associated with their litters. These inflammatory responses influenced the survival of fetuses in a sex-specific manner, but may also have detrimental effects on surviving offspring.

Session III, Vitamin D and Suppression of Malignancy got underway with a talk by Dr. Jorge Muscat (Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA) on regulation by the VDR of hepatic stellate cell (HSC) fibrosis and hepatocellular carcinoma (HCC) via the signaling adapter protein p62. The levels of p62, which can interact with multiple signaling pathways implicated in promotion of cell survival and growth, rise in response to several oncogenic stimuli. Dr. Muscat's group found that HSCs can restrain HCC in a manner that requires p62 expression, and that p62 binds the VDR and RXR. This interaction appears to be critical for the reprogramming by the VDR of HSCs to inhibit HCC development. This was followed by two talks suggesting that $1,25(OH)_2D$ or its analogs may be efficacious in cancer therapies in combination with established chemotherapeutic agents. The first was by Dr. Pamela Hershberger (Roswell Park Cancer institute, Buffalo, NY), who provided evidence for efficacy of $1,25(OH)_2D$ against non-small cell lung carcinoma (NSCLC). As NSCLC progresses, it acquires resistance to therapies with tyrosine kinase inhibitors, and cells undergo epithelial to mesenchymal transition. Dr. Hershberger presented studies designed to evaluate the capacity of $1,25(OH)_2D$ to maintain an epithelial phenotype and overcome resistance to third generation tyrosine kinase inhibitor osimertinib in the H1975 model of NSCLC, which carries T790 M mutations in the epidermal growth factor receptor. Acquisition osimertinib resistance coincided with a loss of epithelial markers, an effect that was reversed by co-treatment with 1,25(OH)2D3. Moreover, the combination of $1,25(OH)_2D$ and osimertinib was more efficacious than monotherapies at arresting malignant cell proliferation, revealing a potential role for vitamin D analogs in therapies for osimertinib-resistant NSCLC. Dr. B.L. Bunch, also of the Roswell Park Cancer Institute then presented work showing that vitamin D can enhance and prolong the response of bladder cancer cells to cisplatin therapy. The group found that this effect required TAp73, which is a pro-apoptotic member of the p53 family induced after DNA damage. $1,25(OH)_2D$ and cisplatin combined to induce the expression of TAp73 and its cofactor BAX in two bladder cancer models. Further work showed that TAp73 also functioned as a cofactor of the VDR. The last talk in the session by Dr. Durazo-Arvizu presented the results of a multi-centre project to address the reverse J-shaped association seen in some epidemiological studies between circulating 25(OH)D levels and all-cause mortality. The study used data from NHANES III (1988–1994) and NHANES 2001–2010 (39,839 participants; 7110 deaths). Researchers evaluated the association between 25(OH)D values standardized using the

Vitamin D Standardization Program (VDSP) and all-cause mortality in Non-Hispanic Whites (NHW), Non-Hispanic Blacks (NHB) and Mexican Americans (MA). Notably, no J-shaped association was observed in any of the subgroups studied, although the study did reveal that the risk of death increased steadily as serum total 25(OH)D levels decreased for NHW and NHB, but not for MA.

Session IV, Structure/Function and Vitamin D Analogs was composed of a single talk by Dr. James Gleason (McGill University, Montreal, QC) on bifunctional vitamin D analogs. Dr. Gleason and colleagues took advantage of the fact that $1,25(OH)_2D$-resistant cancers generally retain VDR expression and vitamin D signaling to develop an extensive series of bifunctional vitamin D analogs, or hybrids, that incorporate inhibition of histone deacetylases (HDACs), another therapeutic target in cancer, into the backbone of a VDR agonist. Dr. Gleason presented data on bifunctionality of secosteroidal and second generation non-secosteroidal variants of these hybrids. Most recent experiments showed that non-secosteroidal hybrid compounds are bioavailable and efficacious against an aggressive mouse model of vitamin D-resistant triple-negative breast cancer under conditions in which a combination of $1,25(OH)_2D$ and a clinically used HDAC inhibitor was inactive.

This was followed by **Session V**, which presented a fascinating series of talks focused on **Vitamin D, UV Light and Skin Biology**. The session got underway with a presentation by anthropologist Dr. Peter Elias (VA Medical Centre, UCSF, San Francisco) entitled “Dilution of epidermal pigmentation during human evolution”. It is widely believed that dark human skin pigmentation evolved to protect against the damaging effects of UV-B, in particular its action as a mutagen of DNA. In addition, heavy melanisation of skin acidifies the outer epidermis and augments barrier function in hot, dry climates. However, as Dr Elias discussed, with human migration to cooler, wetter climates such adaptations were less desirable and pigmentation diminished. This reduced the metabolic demands of skin, freeing up energy for more urgent needs such as heat production, and facilitated cutaneous vitamin D synthesis. Dr. David Foster (Harvard Medical School, Boston, MA) studies the signaling pathways and downstream hormonal responses in skin that link UV radiation to cutaneous synthesis of melanin. Dr. Foster’s group found that UV exposure induces expression of melanocyte stimulating hormone (MSH), a product of the pro-opiomelanocortin gene (POMC). They also found that UV induced production of beta-endorphin and used mouse models to show that this production led to opiate-like alterations in pain/nociceptive thresholds. Dr. Rebecca Mason (University of Sydney, Australia) then presented a talk on the role of $1,25(OH)_2D$ in facilitating DNA repair in UV-irradiated skin keratinocytes. As UV irradiation depletes cells of energy and DNA repair is quite energy-intensive, the group analyzed the effects of $1,25(OH)_2D$ on the metabolic profile of irradiated cells. They found that $1,25(OH)_2D$ treatment substantially enhanced glycolysis in UV-irradiated cells, and induced autophagy and mitophagy, which would free-up carbon units necessary for biosynthesis of precursors of DNA repair. Dr. Y. Zhang from Dr. Fritz Gombart’s group (Oregon State University, Corvallis, OR) closed the session with a talk on $1,25(OH)_2D$ delivery in wound healing. Cathelicidin antimicrobial peptide (CAMP), expression of which is strongly induced by $1,25(OH)_2D$, is an important component of wound healing responses. Dr. Gombart’s group showed that delivery of $1,25(OH)_2D$ encapsulated in poly(e-

caprolactone) (PCL) nanofibers led to its sustained release and to induced CAMP production in *in vitro* models and in skin *in vivo* in a human *CAMP* transgenic mouse model.

Session VI focused on **Vitamin D Metabolism**, and got underway with a talk by Dr. Michael Levine (Children's Hospital of Philadelphia and University of Pennsylvania) on the numerous sequence variants in the human *CYP2R1* gene, which encodes a vitamin D 25-hydroxylase. Dr. Levine noted that ~1% of the African-American population carries a CYP2R1 null mutation, a figure that may rise to 8% in specific African subpopulations. He presented evidence that specific single nucleotide polymorphisms in the regulatory region of the gene appear to influence promoter activity, and provided an extensive characterization of numerous CYP2R1 coding variants in the human population, some of which substantially alter catalytic activity. This was followed by Dr. B.D. Chapron (University of Washington, Seattle), who presented a talk on the role of megalin in vitamin D homeostasis. While the role of megalin in endocytosis of DBP-bound vitamin metabolites has been well characterize animal models, less is known about its role in humans. Dr. Chapron presented the results of a series of studies using a recently developed 3-dimensional proximal tubule microphysiological system. Megalin-dependent endocytosis of DBP was demonstrated and the combined studies suggested that DBP may have a role in intracellular trafficking of $1,25(OH)_2D$ bound to DBP. Other findings using the system suggested that $1,25(OH)_2D$ may suppress megalin expression, which is contrary to previously published work. Dr. K.P. Schlingmann (Munster, Germany) then presented the results of a multi-centre study on mutations in genes affected vitamin D metabolism in idiopathic infantile hypercalcemia (IIH). IIH is a rare hereditary disorder that gives rise to severe hypersensitivity to vitamin D and hypercalcemia. Dr. Shlingmann presented the genetic characterization of a large pediatric cohort (406 patients) with IIH and/or nephrocalcinosis/nephrolithiasis (NC/NL). 36% of patients were found to carry mutations in *CYP24A1* or in genes encoding renal proximal-tubular sodium-phosphate co-transporters (CYP34A1, CYP34A3). Complete loss of CYP24A1 or CYP34A1 usually led to IIH, whereas bi-allelic or even heterozygous mutations in all genes was associated with NC/NL. The session terminated with Dr. René St-Arnaud (Shriner's Hospital, Montreal, QC), who presented the results of a collaboration with Dr. Glenville Jones (Queen's University, Kingston, ON). The group created three mouse lines with different knock-in mutations in the *Cyp24a1* gene, which were either inactivating (R396W), or gave raise to altered vitamin D metabolite catabolism (A326G and V391L). The R396W mutation was more lethal than a complete knockout, with all mice dying of hypercalcemia despite normal $1,25(OH)_2D$ levels. Mice carrying the A326G variant (found in the opossum) displayed elevated levels of 23-hydroxylation and lactone formation and suppressed 24-hydroxylation, whereas 24-hydroxylation was elevated in the V391L mutant and lactone formation was strongly suppressed.

The second day started with **Session VII, Transcriptional Regulation by VDR**. The first presentation was by Dr. Mark Meyer (University of Wisconsin, Madison, WI) on the mechanism and genomic enhancer location for the regulation of the mouse *Cyp27b1* gene by $1,25(OH)_2D$, PTH and FGF23. ChIP-seq directed observations followed by CRISPR/Cas-mediated genome editing resulted in the identification of genomic enhancers for control of $1,25(OH)_2D_3$ production by PTH, FGF23 and $1,25(OH)_2D$. The PTH enhancer deletion was

found to result in a biological phenotype similar to the *Cyp27b1* null mouse. The second presentation was by Dr. J. Wesley Pike, also of the University of Wisconsin, who presented findings related to the regulation of *Cyp24a1* in kidney and in non-renal target cells. A more extensive collection of regulatory regions relevant to *Cyp24a1* expression was identified. These regulatory regions were found to be dynamically modulated in kidney in response to PTH, FGF23 and $1,25(OH)_2D$ and in non-renal target cells in response to $1,25(OH)_2D_3$. Differential contributions of *Cyp24a1* promoter proximal and downstream regulatory regions to regulation in response to $1,25(OH)_2D_3$ were noted. The results provided new insight into the mechanism of regulation of the *Cyp24a1* gene. In the third presentation of this session, using a human monocyte cell line, Dr. Carsten Carlberg (University of Eastern Finland) noted that Ets family transcription factor PU.1 is an important genome-wide modulator of VDR signals. In the last talk of the session, Dr. Seong Min Lee (University of Wisconsin, Madison, WI) showed, using a humanized VDR mouse model (human VDR is expressed in VDR null mice), that 10-fold less than normal VDR expression rescued the VDR null phenotype, suggesting that wild type VDR levels are well above what is needed to maintain mineral homeostasis. In addition, hVDR-S208 mice were generated with loss of the VDR phosphorylation site. The hVDR 208A mutant rescued the VDR null phenotype, suggesting that the absence of phosphorylation of VDR at this site does not alter VDR mediated transcription.

The subject of **Session VIII** was **Vitamin D and Healthy Aging**. The first presentation was by Dr. Francois Feron of Université Aix-Marseille (France). He reported, using a mouse Alzheimer's Disease (AD) model, that supplementing those mice with vitamin D (7500 IU/kg compared to control, 1000 IU/kg) from 3 weeks of age for 8 months rescued memory defects in female but not male mice. The second presentation by Dr. Ray Kreienkamp (St. Louis University Medical School, St. Louis, MO) focused on Hutchinson Gilford Syndrome (HGPS), a premature aging syndrome caused by accumulation of progerin, a lamin A mutant protein. Using HGPS patient derived cells, Dr. Kreienkamp showed that $1,25(OH)_2D$ treatment counteracts VDR loss in these cells and improves the phenotype of the HGPS cells including unrepaired DNA damage. In addition, $1,25(OH)_2D$ treatment results in a decrease in progerin levels, suggesting the targeting vitamin D/VDR is a potential therapeutic strategy for improving HGPS patient health. This was followed by Dr. Stephanie Sisley (Baylor College of Medicine, Houston, TX), who showed that $1,25(OH)_2D$ given directly into the paraventricular nucleus (PVN) of the hypothalamus lowers plasma glucose. Loss of VDR in the PVN causes impaired glucose tolerance in males but not in females. Dr. Sisley noted that vitamin D metabolites have impaired transport across the blood brain barrier, which may be a possible explanation for conflicting clinical studies using dietary vitamin D supplementation. The last presentation in this session was by Dr. J. Brent Richards (McGill University, Montreal, QC). Single nucleotide polymorphisms (SNPs) associated with low 25(OH)D levels were used to assess the relationship between genetically lowered 25(OH)D levels and risk of disease. Using this Mendelian randomization approach, evidence was presented supporting a role for reduced 25(OH)D levels in the etiology of some diseases, such as multiple sclerosis, but a lack of association with other diseases previously associated with reduced circulating 25(OH)D in epidemiological studies.

Session IX was a **Joint Plenary** of the Vitamin D Workshop and the International Aldosterone Conference presented by Dr. Victor Corces of Emory University (Atlanta, GA), who is renowned for his innovative work on genome structure and regulation. Dr. Corces' talk provided a fascinating "high-altitude" overview of the 3D genome, and the role of higher order structures in chromatin in regulating gene transcription during development and differentiation. He provided insights into how different epigenetic modifications of chromatin control genome structure and presented some of the cutting-edge techniques used to analyse higher order genomic structures and their dynamics on a genome-wide scale.

Session X featured a **Debate** on the topic **"RCT are the only appropriate way to demonstrate the role of vitamin D in human health"**. For more than 30 years, vitamin D has been associated with an increasing number of possible extra-skeletal effects, and this has been amply discussed at all past Vitamin D Workshops, and published in thousands of papers. The preclinical data using gene expression, cellular effects and animal models have provided evidence for a wide variety of physiological effects of the vitamin D endocrine system. Many of these preclinical data have been supported by cross sectional or longitudinal observational data. However, the formal proof of causality is still missing in many cases. The strategy to convince scientists, clinicians, health authorities, and lay people of the (beneficial) effects of better vitamin D status is hotly debated. Therefore, a debate was organized to present arguments in favor of randomized controlled trials (RCTs), or alternatively in favor of long-term observational data, as the ultimate decision maker whether or not vitamin D supplementation has extra-skeletal health effects. Dr. Rolf Jorde (Tromso, Norway) clearly defended the position that observational data can only be "hypothesis generating" or help in designing the optimal studies but that ultimately, "*The only way to firmly prove positive vitamin D effects is by doing the properly designed randomized controlled trials (RCTs*)." Dr. Robert Scragg (Auckland, New Zealand), by contrast, defended the position that RCTs are not the only way to come to firm and practical conclusions regarding the link between vitamin D status and extra-skeletal health. Indeed, he summarized a *set of reasons why RCTs of vitamin D supplementation are prone to a range of limitations*. These include low response rates that affect their external validity; lack of recruitment of vitamin D deficient people, lack of appropriate duration of interventions (certainly if vitamin D status during several decades influences outcomes), lack of compliance and retention, easy access for participants to vitamin D supplements, blood testing which increases contamination, and unblinding. This problem of hierarchy of clinical evidence based on observational data, Mendelian randomization studies or RCTs is of course not unique to vitamin D. As expected, the lively debate and extensive discussions did not generate a real consensus. The chair of the debate, Roger Bouillon (Leuven, Belgium) concluded that maybe only a combination of data generated from RCTs, observational data and Mendelian randomization studies will allow us to generate sufficient data to guide clinicians and patients. In the meantime, the very large number of ongoing RCTs dealing with vitamin D (about 3000 in the NIH trial register in 2017) is convincing evidence that many clinical scientists still believe that RCTs may generate the best answers.

Session XI, **Vitamin D and Breast Cancer**, featured three talks. Dr. JoEllen Welsh (SUNY Albany, US) gave an overview of the field, presenting both epidemiologic data

demonstrating a high incidence of vitamin D deficiency in breast cancer patients, as well as reviewing genomic profiling, which revealed many $1,25(OH)_2D$-responsive targets in both normal mammary cells and in breast cancer. She described new studies which are focused on the effect of $1,25(OH)_2D$ on tumor cell metabolism, survival and outgrowth of stem cells as well as the impact of obesity. Many challenges in dissecting the exact role of $1,25(OH)_2D$ signaling in breast cancer relate to the heterogeneous nature of the disease and the differing effects of vitamin D on specific molecular subtypes of the disease. Dr. Brian Feldman (Stanford, Palo Alto, US) presented data demonstrating that ablation of the vitamin D receptor in breast cancer cells accelerates tumor growth and enhances metastatic potential. In murine models of breast cancer vitamin D signaling was shown to inhibit expression of Id1, which promotes tumor progression. Of note, a negative correlation between serum vitamin D levels and breast cancer Id1 expression is seen in humans. Dr. Luz Tavera-Mendoza (Boston, USA) presented data demonstrating that the vitamin D receptor induces autophagy and an autophagic transcriptional signature in breast cancer cells, in cell models with luminal-like characteristics. $1,25(OH)_2D$ induced an autophagy profile in normal mammary tissue as well, but this profile was progressively lost in patients with metastatic breast cancer. Studies in mice demonstrated that vitamin D dose-responsively modulates autophagy in the normal mammary gland. However, knockdown of the vitamin D receptor in luminal cell models enhances autophagy, suggesting that the vitamin D signaling pathway regulates this process by both activation of gene transcription and repression of autophagy genes.

Session XII featured two presentations on **Vitamin D Biology in Non-traditional Models**. Dr. Yves Nys (Nouzilly, France) discussed several novel features of eggshell formation in birds, notably, that the deposition of minerals on the eggshell membrane does not involve a cell-mediated process, but rather, is regulated by matrix proteins. Eggshell formation involves deposition of 10% of the hen's total body calcium per day in the form of calcium carbonate, thus many adaptive processes are induced in egg laying hens to maintain calcium homeostasis. Dr. Kathleen Dumas (Novato, US) discussed beneficial effects of Vitamin D on protein homeostasis and longevity in *C. elegans*. Since extracts of worms fed vitamin D can activate the human vitamin D receptor and contain an HPLC peak characteristic of $1,25(OH)_2D_3$, she concluded that *C. elegans* is capable of activating vitamin D. She discussed studies demonstrating that vitamin D3 induces expression of stress response pathway genes, including SKN-1/Nrf2 and prevents the age-dependent accumulation of insoluble proteins, preventing toxicity caused by human β-amyloid expression.

Session XIII focused on **Clinical trials** and covered several recent large clinical vitamin D intervention trials. Dr. Chris Gallagher started this session with an excellent summary of the major published clinical trials on vitamin D that had adequate sample sizes, a reasonable follow-up time, and were double blind placebo controlled. His review showed negative findings for vitamin D supplementation in the area diabetes and metabolic syndrome, upper respiratory infections, physical function and falls, and colon cancer. Dr. Kerry Sanders followed this by providing and overview of the epidemiology and clinical trials on falls and bone fractures. She noted that the adverse effects observed in several randomized clinical trials (RCT) and discussed the increased fracture rate with vitamin D supplementation in

these trials may be related to high dose, intermittent dosing regimens. Dr. Joan Lappe then gave us a preview of her now published 4-year RCT of 2000 IU/d vitamin D and 1.5 g/d calcium supplementation in 2303 healthy postmenopausal women. There was an inverse relationship between serum 25 hydroxyvitamin D levels and all cause cancer risk, and the intervention reduced new cancers (hazard ratio = 0.697, p = 0.064). Dr. Camilla Damsgaard finished the session by reporting a clinical trial that defined the dietary requirement for vitamin D in Danish children aged 4–8 years old. Their study showed that 19.5 μg/d of vitamin D3 (780 IU/d) would be necessary to keep wintertime serum 25-hydroxyvitamin D levels greater than 50 nmol/L. This is higher than the value recommended by the US Institute of Medicine for this age group (i.e. 600 IU/d)

Session XIV, Vitamin D, Inflammation, and Diabetes covered a number of topics related to the potential anti-inflammatory role of vitamin D in health. Dr. Amy Riek started the session by discussing how monocytes from vitamin D deficient patients have a phenotype of non-classical cells, and that this switched to a more classical phenotype when the subjects were supplemented with vitamin D (4000 IU/d for 4 mo). The vitamin D deficient monocytes had higher cholesterol ester levels and were better at taking up oxidized cholesterol while 25-hydroxyvitamin D treatment of cultured monocytes reduced cholesterol uptake. This suggests vitamin D may modulate cholesterol metabolism by monocytes and thereby influence cardiovascular disease. Dr. Carlos Bernal-Mizrachi then presented research that addressed a potential fetal programming role for vitamin D. By using a combination of fetal and post-natal treatments with vitamin D deficient or sufficient diets, he showed that fetal vitamin D deficiency as well as post-natal deficiency increased insulin resistance. Their *in vitro* data showed that macrophages exposed to in utero vitamin D deficiency make them secrete higher levels of proinflammatory cytokines that induce adipose insulin resistance. Dr. Martin Hewison discussed the regulation of T cells by vitamin D in the context of rheumatoid arthritis (RA). Their studies showed an intriguing difference in the response of blood or synovial fluid-CD4+ T cells to $1,25(OH)_2D$. In particular, $1,25(OH)_2$ D was immunosuppressive in blood T cells (reduced IL-17 and IFN gamma production) but this effect was significantly blunted in synovial fluid T cells. Synovial fluid CD4+ T cells are memory T cells so this suggests phenotype commitment limits the anti-inflammatory effects of $1,25(OH)_2$ D on T cells. Dr. Erica Mandell finished the session by talking about a novel role for vitamin D in the developing rat lung. She reported that pups from vitamin D-deficient mothers have abnormal airway, alveolar, and vascular growth that leads to compromised lung function. These pups were also more susceptible to hypoxia after birth. Collectively this suggests vitamin D deficiency could alter the risk for neonatal development of respiratory disease.

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