Vitamin D: Beyond Bone

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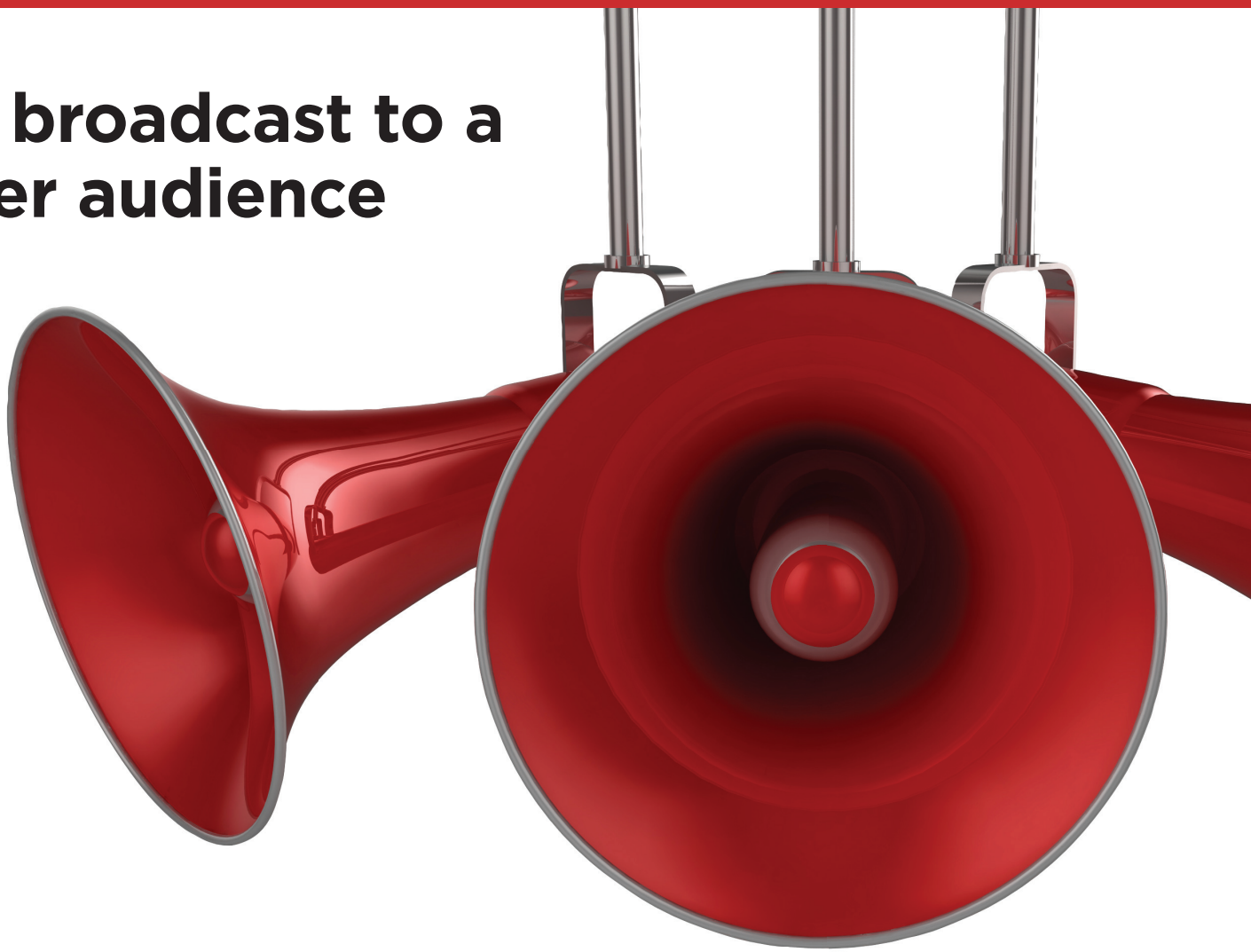

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1. SERUM IGF-I CONCENTRATION INCREASES FOLLOWING TREATMENT WITH VITAMIN D: A PROOF OF PRINCIPLE STUDY

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Insulin-like growth factor I (IGF-I) concentrations were reported to increase with 25-hydroxyvitamin D (25OHD) values in population studies, but it is unclear whether a cause-effect relation underlies this association. Mice genetically deficient of SRC-3, a transcriptional coactivator for the vitamin D receptor, have significantly lower circulating IGF-I than wild-types. To determine in principle whether vitamin D does affect IGF-I levels, we measured serum 25OHD and IGF-I, baseline and after 12 weeks, in 25 outpatients (referral diagnoses: osteoporosis and/or metabolic syndrome), of whom 12 were given 7,000 IU cholecalciferol/week and 13 were not treated (controls). Age was 61.5±8.7 years; 25OHD was below 30 ng/ml in all subjects, but one. The study was performed in Genova, Italy, at latitude 44° North. IGF-I and 25OHD concentrations were assessed after overnight fasting by radioimmunoassay and chemiluminescent immunoassay, respectively. Treatment with cholecalciferol significantly increased 25OHD levels from 12.2 ± 6.6 ng/ml to 25.2 ± 7.85 ng/ml (p <0.01), while no significant change was observed among controls (from 15.95 ± 8.8 ng/ml to 19.5 ± 9.95 ng/ml). At baseline, serum IGF-I was non-significantly lower in controls than in the treated group (157.5 ± 39.75 ng/ml vs. 188.8 ± 60.3 ng/ml). Cholecalciferol significantly raised IGF-I concentrations by 31.3 ng/ml (p =0.01). In contrast, there was no significant variation in IGF-I values without treatment.
Based on this evidence that 7,000 IU/week (1,000 IU/day) of cholecalciferol increase the amount of circulating IGF-I, we suggest that the relationship between 25OHD and IGF-I concentrations described in cross-sectional analyses may be causal.

2. VITAMIN D AND SEROLOGIC RESPONSE TO INFLUENZA VACCINE IN ADULTS OVER 50 YEARS OLD

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Marshfield Clinic Research Foundation, Marshfield, Wisconsin at the time study was conducted

Emerging evidence has linked vitamin D with immune response to vaccination and infection. We determined whether serum 25-hydroxyvitamin D (25(OH)D) predicts serologic response to influenza vaccination measured by hemagglutinin antibody inhibition (HAI) titer in adults. We conducted a prospective cohort study of 1103 community-dwelling adults ≥50 years old over two influenza seasons (fall 2008-spring 2009 and fall 2009-spring 2010) in Marshfield, WI and Nashville, TN. Pre- and 21–28 day post-vaccination HAI titers to 3 vaccine components, body mass index (BMI), and serum 25(OH)D were measured. Seroprotection was defined as HAI ≥40; seroconversion as ≥4-fold increase in HAI pre- to post-vaccination. Mean (SD) serum 25(OH)D was 31 ± 10 ng/mL; 28.5% participants were vitamin D deficient (<25 ng/mL). Vitamin D deficiency did not predict seroconversion for any vaccine components in 2008-2009 (odds ratio [OR]: 95% confidence interval [CI] 1.2: 0.7-2.2; 0.97: 0.6-1.6, and 0.98: 0.5-1.8) for A/H1N1, A/H3N2 and B subtypes, respectively, after controlling for age, gender, BMI, and pre-vaccination HAI. Vitamin D deficiency also did not predict seroconversion in 2009-2010 or pre-vaccination seroprotection in either season. Vitamin D deficiency was associated with odds of post-vaccination seroprotection for seasonal A/H1N1 in 2008-2009 (OR:CI 1.8: 1.0–3.2). No consistent association was

found between serum 25(OH)D levels or vitamin D deficiency and serologic response to influenza vaccination in adults over age 50. Funding Source: CDC 5 U18 IP000183-02, CDC 1 U18 IP000184-01, K23 A1074863-01A1 (Talbot)

3. GENETIC VARIANTS IN VITAMIN D RESPONSIVE GENES AND PULMONARY FUNCTION: ASSOCIATIONS WITH FEV_1 AND FEV_1/FVC

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Higher serum levels of 25-hydroxyvitamin D [25(OH)D] were associated with better pulmonary function in one of two cross-sectional studies. Using a targeted approach to study genes with prior *in vitro* evidence of regulation by vitamin D, we identified 13 genes differentially expressed by tertile of serum 25(OH)D in lung epithelial cells from individuals. Next, we investigated sequence variants in the 13 genes in relation to pulmonary function phenotypes in the Health ABC cohort study, using linear regression models stratified by race. A nominal $p<0.02$ was used as a significance threshold for main effect analyses, and further adjustment for multiple testing was applied. 5 SNPs in two genes (*DAPK1, SGPP2*) were associated with the measure of forced expiratory volume in 1 second (FEV_1) in European-Americans (p-values: $2.8x10^{-3}$ to $1.9x10^{-2}$). In African-Americans, 18 SNPs in 6 genes (*SGPP2, RSAD2, FSTL1, DAPK1, KCNS3,* and *KAL1*) were associated with FEV_1 (p-values: $1.11x10^{-4}$ to $1.65x10^{-2}$) and 2 SNPs in *SGPP2* were significant using Bonferroni correction. The largest effect observed in African-Americans was an increase of 244 mL associated with a genotype in *KCNS3,* and in European-Americans a 104 mL decrease in FEV_1 for a genotype in *DAPK1.* In European-Americans, 1 SNP in *KLF4* ($p=1.2x10^{-2}$) was associated with the ratio of FEV_1/FVC. In African-Americans, 14 SNPs in 3 genes (*KAL1, FSTL1, SGPP2*) were associated with the ratio (p-values: $1.3x10^{-3}$ to $1.9x10^{-2}$). There was consistency in the findings across both race and phenotype for *SGPP2,* a phosphatase that plays a role in pro-inflammatory pathways. Overall, these findings support a mechanism for the 25(OH)D—pulmonary function association.

4. CORRELATION BETWEEN VITAMIN D STATUS AND LIPID PROFILE AMONG ADOLESCENTS FROM THE HEALTH SURVEY

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INTRODUCTION: Adolescence is a period of important body and metabolic variations. Chronic diseases developed during adolescence leads to higher chances of becoming an affected adult. Vitamin D is related with other systems besides bone metabolism and it might be associated with the development of chronic diseases. The purpose of the study was to evaluate the vitamin D status and its correlation to lipid profile in a group of adolescents. **METHODS:** A total of 113 adolescents (56.6% male), mean age 16.2 years (SD=1.5) from the Health Survey-São Paulo (ISA-SP 2008), Brazil, were enrolled in the study. A single blood sample was collected after an overnight fasting and weight and height were measured. Student T, Pearson's Chi-Square and Pearson's Correlation tests were performed using PASW Software. Results were considered significant if $p<0.05$. **RESULTS:** Mean BMI was 21.5 kg/m² (SD=4.7), and mean

waist circumference was 77.7cm (SD=11.1). The prevalence of serum vitamin D insufficiency (<30ng/mL) was 60.2%, higher among boys (70.3% vs 46.9%; p=0.012). Mean vitamin D concentration was 28.8 ng/mL (SD=11.6 ng/mL). The prevalence of low HDL-c concentration (<35mg/dL) was 15.9%, also higher among boys (23.4% vs 6.1%; p=0.013). Total cholesterol (>170mg/dL) and LDL-c (>110mg/dL) concentrations were considered inadequate in 7.1% and 3.5% of the sample, respectively. Positive correlations were observed between serum total cholesterol and vitamin D (r=0.367; p=0.003) and between LDL-c and vitamin D (r=0.328; p=0.008). **CONCLUSIONS:** The high prevalence of vitamin D insufficiency and HDL-c inadequacy, especially among boys, indicates a need for supplementation and nutritional support.

5. SERUM VITAMIN D STATUS IN A SAMPLE OF OLDER MEN AND WOMEN WITH MALNUTRITION ASSOCIATED SARCOPENIA

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Studies suggest serum vitamin D values ≥24ng/ml are associated with reduced falls [1] and values ≥30ng/ml may be important for improving/maintaining muscle strength [2]. Optimal vitamin D is suggested to be 30 - 60 ng/ml [3]. Malnourished, sarcopenic men and women (n=328), >65 yrs of age from 8 countries across Europe and North America were sampled. Only 35% of participants were ≥30ng/ml, however, females were more likely than males to have serum vitamin D lower than 30ng/ml (p=0.03). Using ANOVA, there was a tendency (p=0.07) for gait speed ($m \cdot s^{-1}$) and lean leg mass (kg, p=0.09) to be better in those with serum vitamin D values ≥30ng/ml. Using the Wilcoxon rank sum test, those with serum vitamin D values < 30ng/ml exhibited slower gait speed scores (p=0.03), lower EQ5D questionnaire scores (p<0.01), lower arm lean masses (p=0.03), higher PTH values (p=0.03), and tendencies for hand grip strength to be lower (p=0.08). Bone mineral content was significantly higher in men (p<0.01) with serum vitamin D ≥30ng/ml, but not women. Serum vitamin D <30ng/ml is prevalent in sarcopenic, malnourished older men and women, which may contribute to the decline in strength and functionality. References: 1. Bischoff-Ferrari *et al*., British Medical Journal 2009;339:b3692, 2. Forrest & Stuhldreher, Nutrition Research 31;48–54, 3. Shinchuk & Holick, Nutrition in Clinical Practice 22;297–304.
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6. SOFT BONES, HARD ARTERIES: THE ROLES OF VITAMIN D, "THE OTHER K", AND ANTIBIOTICS

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Three "parallel" lines of research intersect: (1) cardiovascular research into arterial and aortic-valve calcification, (2) vitamin K research, (3) vitamin D research. An informal survey found that specialists whose patients took a vitamin K–blocking anticoagulant (warfarin) were all unaware there were two kinds of vitamin K (K1 = phylliquinone, K2 = menaquinones) and unaware of implications for arterial and aortic valve calcification; all knew "green leafy vegetables" lowered International Normalized Ratio (INR) but none knew of calcium-modulating K2 nor its bacterial origins. Vitamin K is recognized as a possible confound in vitamin D studies (Stojanovic et al. 2011), but rarely explored in research on Vitamin D's role in osteoporosis and cardiovascular calcification. Vitamin K researchers noticed the "calcification paradox" of soft bones and hard arteries early. Cardiovascular researchers tended to see this as due to "aging", but recently looked closely at the role of inflammatory signals in both (Hjortnaes et al. 2010). K2's blocking of inflammatory signals fits into that paradigm (Matsuda et al. 2010, Ohsaki et al. 2010, Yamaguchi & Weitzmann 2011) in ways congruent with D's complex immunological interactions (Hewison 2012). Kidd (2010) discusses synergy of D and K2 and possible mechanisms. Conversely, arterial calcification by high-dose vitamin D was accelerated when warfarin interfered with K2 (Price et al. 2000). Does the U-shaped function of D benefit/harm (Stojanovic et al. 2011) depend partly on vitamin K status of subjects?

Does antibiotic use with humans and food animals exacerbate widespread K2 deficiency? Adequate coagulation can mask deficient calcification control by K2.

7. IMPACT OF CHOLECALCIFEROL REPLETION ON ERYTHROPOIETIN REQUIREMENTS IN VITAMIN D–DEFICIENT HEMODIALYSIS PATIENTS: PILOT DATA FROM A RANDOMIZED CONTROLLED TRIAL

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Vitamin D deficiency is common in hemodialysis patients. Uncontrolled studies suggest correction of Vit D deficiency is associated with decreased erythropoietin (EPO) requirements. To characterize this relationship, we examined the impact of D3 repletion on EPO requirements in 79 Vit D–deficient (25OH-D level <25 ng/mL) hemodialysis patients randomized to receive D3 (n=51) or standard of care (no repletion, n=28) in a 2:1 ratio. Patients randomized to D3 received 50,000 IU/wk to a goal 25OH-D of >35ng/mL. Changes in Vit D level, hemoglobin (Hb), and EPO requirements were assessed at 3 months. EPO (Darbepoetin) doses were adjusted by nursing staff as per dialysis unit protocol (target Hb 10-12 g/dL). Baseline characteristics were similar between groups, as were baseline Vit D levels (median 13.5 vs 13.1, p=0.623), baseline Hb (mean Hb 11.8 g/dL vs 11.4 g/dL, p=0.155), and baseline EPO requirements (median Darbepoetin dose 40 units/wk vs 50 units/wk, p=0.262). Patients randomized to D3 had a rise in 25OH-D levels at 3 months (11.9 to 44.1 ng/mL, p<0.001, n=30), with a corresponding fall in EPO requirements (50.00 to 40.32 units/wk, p=0.029, n=30) despite no change in Hb (11.9 to 11.5 g/dL, p=0.180, n=30). No change in Vit D level, Hb, or EPO dose was observed in control patients at 3 months (n=15). Patients randomized to D3 did not experience hypercalcemia. Our preliminary data from this ongoing randomized controlled trial suggest that treatment of Vit D–deficient dialysis patients with D3 is safe, effective, and may result in lower EPO requirements.

8. VITAMIN D STATUS IN FEMALE HEALTHCARE EMPLOYEES OF CHILDBEARING AGE

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Vitamin D deficiency has been associated with increased obstetrical and perinatal risks including gestational diabetes mellitus, premature delivery and emergent c-section. To assess vitamin D sufficiency among medically literate, insured women of childbearing age, we measured 25-OH-vitamin D in 5,628 female healthcare employees health care aged 15-49. Of these, 1,710 (32.4%) did not meet 2010 IOM guidelines for vitamin D sufficiency (≥ 20 ng/ml), 3,684 (65.5%) did not meet 2010 international guidelines (≥30 ng/ml), and 4,874 (86.6%) did not meet 2011 Endocrine Society guidelines (40-60 ng/ml). Only 2,644 (46.97%) reported taking any vitamin D. Participants who reported vitamin D3 intake equal to that found in prenatal and multivitamins (200-400 IUs) (n=430), 17.7% had 25-OH-vitamin D levels <20 ng/ml, 59.5% had levels <30 ng/ml, and 85.3% had levels <40 ng/ml. Mean 25-OH-vitamin D serum levels and standard deviations for reported vitamin D3 daily intakes of 2001-3,000 IUs and 3,001-4,000 IUs and >4,000 IUs were 39.52 ng/ml (16.16), 38.57 ng/ml (17.06) and 37.98 ng/ml (16.40) respectively. For all of these reported intakes, women with a BMI ≥ 30 ng/ml exhibited significantly lower 25-OH-vitamin D status compared to those women with BMI <30 (p <.0001). Female healthcare workers of child bearing age demonstrate a high incidence of vitamin D deficiency. Daily prenatal or multivitamin supplementation does not ensure adequate 25-OH-vitamin D levels. A BMI ≥30 represents a substantially increased risk of suboptimal 25-OH-vitamin D. Reported vitamin D intake significantly above current recommendations does not result in elevated serum levels.

9. PLASMA VITAMIN D IS INDEPENDENTLY ASSOCIATED WITH LUNG FUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Patients with COPD primarily suffer from lung function impairment. Besides this, COPD is more and more believed to be a systemic disease and as such, high prevalence of vitamin D deficiency has been described. An association between lung function parameters and plasma vitamin D levels has been shown previously in the healthy (1), but never in a group of patients with COPD. The objective of the present study was to investigate whether there is an independent association between lung function parameters and plasma vitamin D levels in a group of 157 COPD patients admitted for pulmonary rehabilitation at Ciro+, the Netherlands. Plasma 25(OH)vitamin D levels, body mass index [BMI, weight in kg/(height in m)^2] and lung function parameters [forced expiratory volume in 1s (FEV_1), forced vital capacity (FVC) and diffusing capacity of the lung (D_LCO)] were measured. There were 57% males, mean age was 65±9y, mean FEV_1 was 47.2±17.9% predicted, mean FVC was 94.6±20.6% predicted and mean DLCO was 53.2±19.7% predicted. Pearson correlation coefficient showed significant correlations between plasma vitamin D concentration and FEV_1 ($r=0.29$, $p<0.01$), FVC ($r=0.29$, $p<0.01$) and DLCO ($r=0.22$, $p=0.01$). Multivariate regression analyses revealed that, after correction for age, gender and BMI, vitamin D concentration was independently associated with FEV_1 (beta=0.22, $p<0.01$), FVC (beta=0.24, $p<0.01$), DLCO (beta=0.25, $p<0.01$). In conclusion, there is evidence that vitamin D plays a role in the lung pathology of patients with COPD, which needs further investigation.

10. THE ROLE OF VITAMIN D IN REGULATION OF APOPTOTIC SIGNALING PATHWAYS IN OBESITY

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Modulation of apoptosis is emerging as a promising strategy for prevention and treatment of obesity because removal of adipocytes through this process will result in reducing body fat and long-lasting maintenance of weight loss. Effects of 1,25$(OH)_2$-vitamin D_3 (1,25D) on apoptotic cell death are mediated via multiple signaling pathways that involve common regulators and effectors converging on cellular Ca^{2+} (Sergeev, 2005, 2009, 2012); however, the 1,25D-regulated, Ca^{2+}-dependent apoptotic molecular targets have not been identified in adipose tissue. We investigated the mechanism by which 1,25D regulates apoptosis in adipocytes. The results obtained demonstrated that 1,25D induced, in a concentration- and time-dependent fashion, the apoptotic Ca^{2+} signal (a sustained, prolonged increase in concentration of intracellular Ca^{2+}) in mature mouse 3T3-L1 adipocytes. The 1,25D-induced increase in cellular Ca^{2+} was associated with activation of the Ca^{2+}-dependent μ-calpain and the Ca^{2+}/calpain-dependent caspase-12. The activation of these proteases was sufficient for effecting morphological and biochemical changes attributed to apoptosis. The 1,25D-induced increase in cellular Ca^{2+} was also associated with the reduced lipid accumulation in mature adipocytes. A murine diet–induced obesity (DIO) model was used to evaluate the role of vitamin D in adiposity. The DIO mice (C57BL/6J) fed the high–vitamin D and, especially, high-vitamin D plus high-Ca diet demonstrated the decreased body and fat weight gain and improved markers of adiposity and vitamin D status (plasma concentrations of glucose, insulin, adiponectin, 25(OH)D, 1,25$(OH)_2$D, and PTH). The findings obtained imply that the 1,25D-induced cellular Ca^{2+} signal can act as an apoptotic initiator that directly recruits Ca^{2+}-dependent apoptotic effectors capable of executing apoptosis in adipose tissue. Targeting of Ca^{2+} signaling and the vitamin D/Ca^{2+}-dependent calpains and caspases in adipocytes can represent an effective approach for chemoprevention and treatment of obesity. These findings also indicate the need to reevaluate the roles of vitamin D and calcium in obesity.

11. A ROLE FOR VITAMIN D IN REGULATING MESOLIMBIC CIRCUITS AND DIET-INDUCED OBESITY

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Obesity rates have increased over the past two decades. Vitamin D3 deficiency rates have increased within a similar timeframe and evidence suggests an inverse relationship between circulating vitamin D3 levels and body mass index. However, a causative role for this deficiency in the development of obesity has not been established. Using mice, we show that a high-fat (HF) diet with reduced vitamin D3 enhanced the development of diet-induced obesity, as both food intake and bodyweight were increased. Neural circuits that are involved with the overconsumption of palatable foods and intake of drugs of abuse include dopamine-signaling neurons. To evaluate a potential interaction between dopamine and D3 dietary deficiency, amphetamine experiments were conducted. Chronically deficient mice consumed more amphetamine orally, and displayed reduced locomotor activity after an acute amphetamine injection. Immunofluorescent evaluation of vitamin D receptor (VDR) revealed expression on dopamine-signaling neurons in both the ventral tegmental area and nucleus accumbens, suggesting a potential role for VDR activity in regulating genes involved in dopamine transmission. qPCR analysis of calcitriol-treated mice revealed upregulation of dopamine receptor 2, tyrosine hydroxylase, and dopamine transporter in these brain regions. Complimentary to the deficiency studies, calcitriol-treated mice displayed less HF food intake and bodyweight gain, as well as reduced consumption of amphetamine. Additionally, treated mice showed increased locomotor activity after acute amphetamine. Our data provide causative evidence for dietary levels of D3 in the development of obesity, psychostimulant intake, and promotes future studies examining the potential benefits of calcitriol treatments.

12. VITAMIN D, THE EVOLUTION OF HUMAN SKIN COLOR, AND HEALTH DISPARITIES

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Anthropologists argue that skin color is an evolutionary adaptation to ultraviolet light (UV). Dark skin is protective against UV and is found in populations that have lived near the equator for many generations. In population groups that migrate to lower UV areas away from the equator, skin tones gradually become lighter because individuals in the population with lighter skin have the evolutionary advantage of higher serum vitamin D and its associated health benefits. This theory suggests that health disparities will be found in all populations that include diverse skin colors. We tested this theory using National Health and Nutrition Examination Survey (NHANES) data from 12,505 individuals, which can be generalized to the non-institutionalized U.S. population age 13 and older. We used self-rated health as a measure of health status, race/ethnicity as a proxy for skin color, serum 25(OH)D measurements as an indicator of vitamin D nutriture, and statistical techniques appropriate for the complex survey design of NHANES. After controlling for the covariates gender, interview language, country of birth, tobacco use, age, body mass index, and leisure exercise as well as the socioeconomic variables education and family income, we found that remaining disparities in self-rated health are greatly reduced (medium skin color) or eliminated (dark skin color) by controlling for serum 25(OH)D levels. Although socioeconomic factors are the strongest determinant of skin-color based health disparities in the U.S. population, it may not be possible to eliminate health disparities in the U.S. without eliminating the skin-color related disparities in vitamin D nutriture.

13. AN EXPLORATORY STUDY TO IDENTIFY THE ROLE OF CALCIUM AND VITAMIN D IN FETAL BONE GROWTH COMPARED TO MATERNAL BONE LOSS AMONG PREGNANT ADOLESCENTS

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Vitamin D and calcium (Ca) are known to be important for bone health as identified by the Institute of Medicine. Pregnant adolescents may have increased demands for Ca and vitamin D but few studies have focused on this group. We recently completed a longitudinal study of 171 pregnant adolescents (ages 13-18 y) to assess the role of Ca and vitamin D on maternal and fetal bone health. Maternal bone (assessed by heel ultrasound) and fetal bone growth (assessed by fetal biometry) was monitored from 1-3 times over pregnancy. Fetal bone was found to be significantly influenced by maternal Ca intake and vitamin D status (25(OH)D). Adolescents had a net loss in heel bone across pregnancy but unlike the fetal data, maternal bone loss was not impacted by maternal Ca intake or vitamin D status. The strongest determinant of maternal bone loss over pregnancy was pre-pregnancy BMI with obese teens losing less bone than lean teens. The purpose of this study is to identify the determinants of maternal bone loss across pregnancy and to assess possible associations between maternal bone loss and fetal bone growth across gestation. The results of this study could provide important insights into the metabolic regulation of maternal bone turnover and fetal bone development and also help identify behaviors for optimal maternal and fetal bone health among pregnant adolescents.

14. VDR IS ESSENTIAL FOR PANCREATIC CANCER CELLS TO SURVIVE GEMCITABINE TREATMENT

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Gemcitabine is a nucleoside analog that is a major treatment modality for pancreatic cancer. Unfortunately, gemcitabine only extends survival by a few months. We performed a genome-wide siRNA screen to identify genes in pancreatic cancer cells (Panc1) that promoted their survival to gemcitabine. VDR was one of the survival genes that was further investigated. Stable knockdown of VDR increased sensitivity of cells to gemcitabine relative to parental cells. Re-expression of WT VDR, but not ligand or transactivation mutants, restored gemcitabine resistance. Sensitization was also achieved with TEI9467, a VDR antagonist. Sensitization was not observed with agonist. Tumor formation in mice after VDR depletion was significantly reduced compared to parental cells. Overriding the DNA damage checkpoint imposed by gemcitabine is known to sensitize cells to killing. However, checkpoint override was not the mechanism by which loss of VDR enhanced cell killing. Thus, VDR specifies an essential survival mechanism that is distinct from DNA damage checkpoint. Despite this difference, the degree of gemcitabine sensitization was similar between cells depleted of VDR compared to cells depleted of Chk1. 6 of 27 validated survival genes from our screen possess VDRE's within their promoters. We also found RUNX2 to be essential for cells to survive gemcitabine treatment. We conclude that VDR and RUNX2 specify a transcription program that is essential for survival of pancreatic cancer cells to gemcitabine. Inhibition of VDR may be used to improve gemcitabine outcomes of pancreatic cancer patients.