VITAMINA D - VITAMIN D

- Salehpour A, Shidfar F, Hedayati M, Farshad AA, Tehrani AN, Mohammadi S.
Molecular mechanisms of vitamin D plus Bisphenol A effects on adipogenesis in human adipose-derived mesenchymal stem cells. *Diabetol Metab Syndr*. 2021 13(1):41. doi: 10.1186/s13098-021-00661-4.P

Background: Obesity is considered a major health concern and mounting evidence suggests that the exposure to environmental endocrine disruptors, including Bisphenol-A (BPA), may enhance the risk to develop the disease. Moreover, growing documents propose that the vitamin D may contribute to adipogenic signaling and lipid accumulation during adipocyte differentiation. We focused on the molecular mechanism of vitamin D and BPA in human adipose-derived mesenchymal stem cells (hADMSCs) which vitamin D and BPA may influence adipose tissue development and function.
Methods: Human adipose-derived mesenchymal stem cells were cultured for 14 days in lipogenic differentiation media containing continuous concentrations of vitamin D plus BPA (0.1 nM or 10 nM). The expression of adipogenic markers including the peroxisome proliferator-activated receptor γ (PPARγ), CCAAT-enhancer-binding protein α (C/EBP α) CCAAT-enhancer-binding protein β (C/EBP β), fatty acid synthase (FASN), lipoprotein lipase (LPL), sterol regulatory element-binding protein-1c (SREBP1c), insulin-induced gene-2 (INSIG2), vitamin D receptor (VDR), estrogen receptor-beta (ER-β), fatty acid-binding protein-4 (FABP4), and glucose transporter-4 (GLUT4) was measured using Quantitative polymerase chain reaction (qPCR) and enzyme-linked immunosorbent assay (ELISA). Lipid accumulation was visualized with staining with Oil Red O.
Results: In the morphological assessment of mesenchymal stem cells treated with a concentration of 10 nM vitamin D plus BPA, more lipid accumulations were observed in comparison with the group with 0.1 nM concentration. Treatment of hADMSCs with vitamin D plus BPA (0.1 nM) significantly inhibited the induction of PPARγ, C/EBP β, C/EBP α, and FASN related to adipocyte differentiation and development. However, the exposure of cells to the concentration of 10 nM vitamin D plus BPA induced the expression of these genes associated to the adipogenesis. The remarkable increase in the level of SREBP1c was associated to the suppression of INSIG2 in treated preadipocytes with 10 nM vitamin D plus BPA. Our findings showed that the expression of VDR, ERβ, GLUT4, and FABP4 were upregulated through differentiation with the highest concentrations in 0.1 nM vitamin D plus BPA group for VDR, ERβ, and GLUT4.
Conclusions: Vitamin D plus BPA at concentration of 10 nM boosted the adipogenesis during the critical stages of adipocytes development, whereas it seems to inhibit this process at concentration of 0.1 nM.

- Di Nisio A, Rocca MS, De Toni L, Sabovic I, Guidolin D, Dall'Acqua S, Acquasaliente L, De Filippis V, Plebani M, Foresta C.
Endocrine disruption of vitamin D activity by perfluoro-octanoic acid (PFOA). *Sci Rep.* 2020; 10(1):16789. doi: 10.1038/s41598-020-74026-8.

Perfluoroalkyl substances (PFAS) are a class of compounds used in industry and consumer products. Perfluorooctanoic acid (PFOA) is the predominant form in human samples and has been shown to induce severe health consequences, such as neonatal mortality, neurotoxicity, and immunotoxicity. Toxicological studies indicate that PFAS accumulate in bone tissues and cause altered bone development. Epidemiological studies have reported an inverse relationship between PFAS and bone health, however the associated mechanisms are still unexplored. Here, we present

computational, in silico and in vitro evidence supporting the interference of PFOA on vitamin D (VD). First, PFOA competes with calcitriol on the same binding site of the VD receptor, leading to an alteration of the structural flexibility and a 10% reduction by surface plasmon resonance analysis. Second, this interference leads to an altered response of VD-responsive genes in two cellular targets of this hormone, osteoblasts and epithelial cells of the colorectal tract. Third, mineralization in human osteoblasts is reduced upon coincubation of PFOA with VD. Finally, in a small cohort of young healthy men, PTH levels were higher in the exposed group, but VD levels were comparable. Altogether these results provide the first evidence of endocrine disruption by PFOA on VD pathway by competition on its receptor and subsequent inhibition of VD-responsive genes in target cells.

- Elkafas H, Ali M, Elmorsy E, Kamel R, Thompson WE, Badary O, Al-Hendy A, Yang Q. **Vitamin D3 Ameliorates DNA Damage Caused by Developmental Exposure to Endocrine Disruptors in the Uterine Myometrial Stem Cells of Eker Rats.** *Cells*. 2020;9(6):1459. doi: 10.3390/cells9061459.PMID: 32545544

Early-life exposure of the myometrium to **endocrine**-disrupting chemicals (EDCs) has been shown to increase the risk of uterine fibroid (UF) prevalence in adulthood. **Vitamin** D3 (VitD3) is a unique, natural compound that may reduce the risk of developing UFs. ...Early-life exposure of the myometrium to endocrine-disrupting chemicals (EDCs) has been shown to increase the risk of uterine fibroid (UF) prevalence in adulthood. Vitamin D3 (VitD3) is a unique, natural compound that may reduce the risk of developing UFs. However, little is known about the role and molecular mechanism of VitD3 on exposed myometrial stem cells (MMSCs). We investigated the role of, and molecular mechanism behind, VitD3 action on DNA damage response (DDR) defects in rat MMSCs due to developmental exposure to diethylstilbestrol (DES), with the additional goal of understanding how VitD3 decreases the incidence of UFs later in life. Female newborn Eker rats were exposed to DES or a vehicle early in life; they were then sacrificed at 5 months of age (pro-fibroid stage) and subjected to myometrial Stro1+/CD44+ stem cell isolation. Several techniques were performed to determine the effect of VitD3 treatment on the DNA repair pathway in DES-exposed MMSCs (DES-MMSCs). Results showed that there was a significantly reduced expression of RAD50 and MRE11, key DNA repair proteins in DES-exposed myometrial tissues, compared to vehicle (VEH)-exposed tissues ($p < 0.01$). VitD3 treatment significantly decreased the DNA damage levels in DES-MMSCs. Concomitantly, the levels of key DNA damage repair members, including the MRN complex, increased in DES-MMSCs following treatment with VitD3 ($p < 0.01$). VitD3 acts on DNA repair via the MRN complex/ATM axis, restores the DNA repair signaling network, and enhances DDR. This study demonstrates, for the first time, that VitD3 treatment attenuated the DNA damage load in MMSCs exposed to DES and classic DNA damage inducers. Moreover, VitD3 targets primed MMSCs, suggesting a novel therapeutic approach for the prevention of UF development.

Montes-Grajales D, Olivero-Verbel J.
Structure-based Identification of Endocrine Disrupting Pesticides Targeting Breast Cancer Proteins. *Toxicology*. 2020 J439:152459. doi: 10.1016/j.tox.2020.152459.

Endocrine disrupting pesticides (EDPs) are exogenous compounds that disrupt endocrine activity. Human exposure to EDPs can occur through occupational contact, and through the consumption of food, milk and water with trace amounts of these pollutants. Several EDPs are epidemiologically linked to breast cancer or are considered as possible carcinogens. However, current evidence is not fully conclusive and their mechanisms of action remain unknown. Thus, the potential interactions

between 262 EDPs and 189 proteins associated with breast cancer were evaluated by using a virtual high-throughput screening approach, with AutoDock Vina 1.1.1. The molecular coordinates were previously downloaded from Protein Data Bank and EDCs DataBank, and used for preparation and optimization in Sybyl X-2.0. The best affinity score (-11.0 kcal/mol) was obtained for flucythrinate with the nuclear receptor for vitamin D (VDR). This synthetic pyrethroid, along with other EDPs, such as fluvalinate, bifenthrin, cyhalothrin and cypermethrin, are proposed as multi-target ligands of several proteins related to breast cancer. In addition, the validation of our protocol showed a good accuracy in terms of binding pose prediction and affinity estimation. This study provides a guide to prioritize EDPs for which further in vitro and in vivo analysis could be done to evaluate the risk and possible mechanisms of action of these contaminants and their potential association with breast cancer.

- Etzel TM, Braun JM, Buckley JP

Associations of serum perfluoroalkyl substance and vitamin D biomarker concentrations in NHANES, 2003-2010. *Int J Hyg Environ Health*. 2019 ;222(2):262-269. doi: 10.1016/j.ijheh.2018.11.003.

Perfluoroalkyl substances (PFAS) are persistent endocrine disrupting chemicals found in industrial and commercial products. Previous research has shown that other endocrine disrupting chemicals such as phthalates and bisphenol A may alter circulating levels of vitamin D; however, no research has examined associations between PFAS and vitamin D biomarkers. We conducted a cross-sectional analysis of 7040 individuals aged 12 years and older participating in the 2003-2010 cycles of the United States National Health and Nutrition Examination Survey (NHANES). Concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and total 25-hydroxyvitamin D [25(OH)D] were measured in serum samples. We used multivariable linear regression to estimate covariate-adjusted differences in total 25(OH)D or prevalence odds of vitamin D deficiency per log2 change in PFAS concentrations. We also assessed potential effect measure modification by gender, age, and race/ethnicity. PFAS were detected in over 98% of the samples. In adjusted models, each 2-fold increase in PFOS was associated with 0.9 nmol/L (95% CI: 0.2, 1.5) lower total 25(OH)D concentrations, with associations significantly stronger among whites (β: -1.7; 95% CI: -2.6, -0.7) and individuals older than 60 years of age (β: -1.7; 95% CI: -2.9, -0.5). Each 2-fold increase in PFHxS was associated with 0.8 nmol/L (95% CI: 0.3, 1.3) higher total 25(OH)D, and this association was not modified by age, gender, and race/ethnicity. PFOA and PFNA were not associated with total 25(OH)D. When assessing prevalence odds of vitamin D deficiency, we observed similar patterns of association with PFAS concentrations. Our results suggest that some PFAS may be associated with altered vitamin D levels in the United States population, and associations may vary by chemical, age, and race/ethnicity. Prospective epidemiological studies are needed to confirm our findings and determine their implications for vitamin D-associated health outcomes in children and adults.

- Kim JK, Khan A, Cho S, Na J, Lee Y, Bang G, Yu WJ, Jeong JS, Jee SH, Park YH.

Effect of developmental exposure to bisphenol A on steroid hormone and vitamin D3 metabolism. *Chemosphere*. 2019 237:124469. doi: 10.1016/j.chemosphere.2019.124469.

High exposure to bisphenol A (BPA) in children has been associated with the outcomes of several diseases, including those related to developmental problems. To elucidate the mechanism of BPA mediated developmental toxicity, plasma and urine from rats exposed to BPA was analyzed with high resolution metabolomics, beginning from post-natal day 9, for 91 days. Female and male rats were orally administered 5 different BPA doses to elucidate dose- and sex-specific BPA effects.

Regarding dose-specific effects, multivariate statistical analysis showed that metabolic shifts were considerably altered between 5, 50 and 250 mg BPA/kg bw/day in treated rats. A nonmonotonicity and monotonicity between BPA dose and metabolic response were major trajectories, showing overall metabolic changes in plasma and urine, respectively. Metabolic perturbation in the steroid hormone biosynthesis pathway was significantly associated with dose- and sex-specific BPA effects. Intermediate metabolites in the rate-limiting step of steroid hormone biosynthesis down-regulated steroid hormones in the 250 mg treatment. Further, our study identified that BPA increased urinary excretion of vitamin D3 and decreased its concentration in blood, suggesting that perturbation of vitamin D3 metabolism may be mechanistically associated with neurodevelopmental disorders caused by BPA. Three metabolites showed a decrease in sex difference with high BPA dose because female rats were more affected than males, which can be related with early puberty onset in female. In brief, the results demonstrated that BPA induces dose- and sex-specific metabolic shifts and that perturbation of metabolism can explain developmental problems.

- Lee CT, Wang JY, Chou KY, Hsu MI

1,25-Dihydroxyvitamin D(3) modulates the effects of sublethal BPA on mitochondrial function via activating PI3K-Akt pathway and 17beta-estradiol secretion in rat granulosa cells.
J Steroid Biochem Mol Biol. 2019 185:200-211.

Bisphenol A (BPA), an endocrine-disrupting chemical, is capable of producing reproductive toxicity. BPA results in mitochondrial DNA (mtDNA) deletion and mitochondrial dysfunction; however, the effect of BPA on the mitochondria of ovarian granulosa cells is not clear. Further, 1,25-dihydroxyvitamin D3 (1,25D3) may play a role in reproduction, because its receptor, VDR, contributes to the inhibition of oxidative stress and predominantly exists in the nuclei of granulosa cells. Hence, the role of 1,25D3 in BPA-mediated effects on mitochondrial function was examined in this study. Primary rat granulosa cells treated with BPA, 1,25D3, or both were subjected to molecular/biochemical assays to measure cell survival, mtDNA content, mtDNA deletion, superoxide dismutase activity, levels of proteins related to mitochondrial biogenesis, and mitochondrial function. We found that cell viability was dose-dependently reduced and reactive oxygen species (ROS) levels were increased by BPA treatment. BPA administration elevated Mn-superoxide dismutase (MnSOD) expression but negatively regulated total SOD activity. 1,25D3 treatment alone increased 17β-estradiol secretion, ATP production, and cellular oxygen consumption. In cells treated with both agents, 1,25D3 enhanced BPA-induced MnSOD protein upregulation and blocked the BPA-mediated decline in total SOD activity. Furthermore, 1,25D3 attenuated BPA-mediated mtDNA deletion but showed no effect on BPA-induced increases in mtDNA content. Although BPA had no influence on the levels of peroxisome proliferator-activated receptor-γ coactivator-1 α, nuclear respiratory factor-1, mitochondrial transcription factor A, or cytochrome c oxidase subunit IV, 1,25D3 plus BPA markedly increased mitochondrial biogenesis-related protein expression via the PI3K-Akt pathway. Moreover, BPA-mediated negative regulation of cytochrome c oxidase subunit I levels and 17β-estradiol secretion was attenuated by 1,25D3 pre-treatment. Our results suggest that 1,25D3 attenuates BPA-induced decreases in 17β-estradiol and that treatment with 1,25D3 plus BPA regulates granulosa cell mitochondria by elevating mitochondrial biogenesis-related protein levels.

- Bartoňková I , Dvořák Z .

Assessment of endocrine disruption potential of essential oils of culinary herbs and spices involving glucocorticoid, androgen and vitamin D receptors. *Food Funct*. 2018 9: 2136-2144.

Essential oils (EOs) of culinary herbs and spices are consumed on a daily basis. They are multicomponent mixtures of compounds with already demonstrated biological activities. Taking into account regular dietary intake and the chemical composition of EOs, they may be considered as candidates for endocrine-disrupting entities. Therefore, we examined the effects of 31 EOs of culinary herbs and spices on transcriptional activities of glucocorticoid receptor (GR), androgen receptor (AR) and vitamin D receptor (VDR). Using reporter gene assays in stably transfected cell lines, weak anti-androgen and anti-glucocorticoid activity was observed for EO of vanilla and nutmeg, respectively. Moderate augmentation of calcitriol-dependent VDR activity was caused by EOs of ginger, thyme, coriander and lemongrass. Mixed anti-glucocorticoid and VDR-stimulatory activities were displayed by EOs of turmeric, oregano, dill, caraway, verveine and spearmint. The remaining 19 EOs were inactive against all receptors under investigation. Analyses of GR, AR and VDR target genes by means of RT-PCR confirmed the VDR-stimulatory effects, but could not confirm the anti-glucocorticoid and anti-androgen effects of EOs. In conclusion, although we observed minor effects of several EOs on transcriptional activities of GR, AR and VDR, the toxicological significance of these effects is very low. Hence, 31 EOs of culinary herbs and spices may be considered safe, in terms of endocrine disruption involving receptors GR, AR and VDR.

- Khalil N, Ebert JR, Honda M, Lee M, Nahhas RW, Koskela A, Hangartner T, Kannan K.
Perfluoroalkyl substances, bone density, and cardio-metabolic risk factors in obese 8-12 year old children: A pilot study. *Environ Res.* 2018 160:314-321.

Background and objective: Perfluoroalkyl substances (PFASs), including perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA), have been associated with adverse bone, and metabolic changes in adults. However association of PFASs with bone health in children is understudied. Considering their role as endocrine disruptors, we examined relationships of four PFASs with bone health in children.
Methods: In a cross sectional pilot study, 48 obese children aged 8-12 years were enrolled from Dayton's Children Hospital, Ohio. Anthropometric, clinical and biochemical assessments of serum were completed. Serum PFASs were measured by UPLC-ESI-MS/MS. In a subset of 23 children, bone health parameters were measured using calcaneal quantitative ultrasound (QUS).
Results: While PFASs exposure was associated with a consistent negative relationship with bone health parameters, among four PFASs tested, only PFNA showed a significant negative relationship with bone parameter (β [95% CI], = - 72.7 [- 126.0, - 19.6], p = .010). PFNA was also associated with raised systolic blood pressure (p = .008), low density lipoprotein cholesterol (LDL-C; p < .001), and total cholesterol (TC; p = .014). In addition, both PFOA and PFOS predicted elevation in LDL-C, and PFOA predicted increased TC, as well. In this analysis, PFASs were not strongly related to thyroid hormones, 25-hydroxy vitamin D, liver enzymes, or glucose homeostasis.
Conclusion: PFASs exposure in obese children may play a role in adverse skeletal and cardiovascular risk profiles.

- Pěnčíková K, Svržková L, Strapáčová S, Neča J, Bartoňková I, Dvořák Z, Hýžďalová M, Pivnička J, Pálková L, Lehmler HJ, Li X, Vondráček J, Machala M.
In vitro profiling of toxic effects of prominent environmental lower-chlorinated PCB congeners linked with endocrine disruption and tumor promotion. *Environ Pollut.* 2018 237:473-486.
We evaluated in vitro toxicities of environmental LC-PCBs found in both indoor and outdoor air (PCB 4, 8, 11, 18, 28 and 31), and selected hydroxylated metabolites of PCB 8, 11 and 18, using reporter gene assays, as well as other functional cellular bioassays. We focused on proce …

19The mechanisms contributing to toxic effects of airborne lower-chlorinated PCB congeners (LC-PCBs) remain poorly characterized. We evaluated in vitro toxicities of environmental LC-PCBs found in both indoor and outdoor air (PCB 4, 8, 11, 18, 28 and 31), and selected hydroxylated metabolites of PCB 8, 11 and 18, using reporter gene assays, as well as other functional cellular bioassays. We focused on processes linked with endocrine disruption, tumor promotion and/or regulation of transcription factors controlling metabolism of both endogenous compounds and xenobiotics. The tested LC-PCBs were found to be mostly efficient anti-androgenic (within nanomolar - micromolar range) and estrogenic (at micromolar concentrations) compounds, as well as inhibitors of gap junctional intercellular communication (GJIC) at micromolar concentrations. PCB 8, 28 and 31 were found to partially inhibit the aryl hydrocarbon receptor (AhR)-mediated activity. The tested LC-PCBs were also partial constitutive androstane receptor (CAR) and pregnane X receptor (PXR) agonists, with PCB 4, 8 and 18 being the most active compounds. They were inactive towards other nuclear receptors, such as vitamin D receptor, thyroid receptor α, glucocorticoid receptor or peroxisome proliferator-activated receptor γ. We found that only PCB 8 contributed to generation of oxidative stress, while all tested LC-PCBs induced arachidonic acid release (albeit without further modulations of arachidonic acid metabolism) in human lung epithelial cells. Importantly, estrogenic effects of hydroxylated (OH-PCB) metabolites of LC-PCBs (4-OH-PCB 8, 4-OH-PCB 11 and 4'-OH-PCB 18) were higher than those of the parent PCBs, while their other toxic effects were only slightly altered or suppressed. This suggested that metabolism may alter toxicity profiles of LC-PCBs in a receptor-specific manner. In summary, anti-androgenic and estrogenic activities, acute inhibition of GJIC and suppression of the AhR-mediated activity were found to be the most relevant modes of action of airborne LC-PCBs, although they partially affected also additional cellular targets.

- **J**ohns LE, Ferguson KK, Cantonwine DE, McElrath TF, Mukherjee B, Meeker JD.
Urinary BPA and Phthalate Metabolite Concentrations and Plasma Vitamin D Levels in Pregnant Women: A Repeated Measures Analysis. *Environ Health Perspect.* 2017 125(8):087026. doi: 10.1289/EHP1178.

Background: In addition to its well-established role in maintaining skeletal health, vitamin D has essential regulatory functions in female reproductive and pregnancy outcomes. Phthalates and bisphenol A (BPA) are endocrine disruptors, and previous research has suggested that these chemical agents may disrupt circulating levels of total 25(OH)D in adults.
Objectives: We investigated the relationships between repeated measures of urinary phthalate metabolites and BPA and circulating total 25(OH)D in a prospective cohort of pregnant women.
Methods: The present study population includes participants (n=477) in a nested case-control study of preterm birth drawn from a prospective birth cohort of pregnant women at Brigham and Women's Hospital in Boston, Massachusetts. Urine and blood samples were collected for biomarker measurements at median 10 wk and 26 wk of gestation.
Results: In repeated measures analysis, we observed that an interquartile range (IQR) increase in urinary mono-3-carboxypropyl phthalate (MCPP) was associated with a 4.48% decrease [95% confidence interval (CI): -7.37, -1.58] in total 25(OH)D. We also detected inverse associations for metabolites of di(2-ethylhexyl) phthalate (DEHP) [percent difference (%Δ)=-2.83 to -2.16]. For BPA, we observed a nonsignificant inverse association with total 25(OH)D in the overall population. Our sensitivity analysis revealed that the associations for some metabolites (e.g., MEHP) varied by race/ethnicity, which may reflect potential differences in susceptibility. In agreement with findings from repeated measures analysis, we reported that DEHP metabolites and BPA were significantly associated with an approximate 20% increase in the odds of vitamin D deficiency (≤20 ng/mL) [odds ratio (95% CI): 1.19 (1.06, 1.35) for molar sum of DEHP metabolites and 1.22 (1.01, 1.47) for BPA] at median 10 wk and 26 wk, respectively.

Conclusions: Our results provide suggestive evidence of the potential for environmental exposure to phthalates and/or BPA to disrupt circulating vitamin D levels in pregnancy.

Erratum in *Environ Health Perspect* 2019 127(1):19002. doi: 10.1289/EHP4855.

- Bartonkova I, Grycova A, Dvorak Z.

Profiling of Vitamin D Metabolic Intermediates toward VDR Using Novel Stable Gene Reporter Cell Lines IZ-VDRE and IZ-CYP24. *Chem Res Toxicol.* 2016 29:1211-22.

Variety of xenobiotics, including therapeutically used vitamin D analogues or environmental and alimentary endocrine disruptors, may interfere with vitamin D receptor (VDR) signaling, with serious physiological or pathophysiological consequences. Therefore, it is of topical interest to have reliable and efficient in vitro screening tools for the identification of agonists and activators of human VDR. We present here two novel stably transfected human reporter cell lines allowing rapid, high-throughput, and selective identification of VDR agonists and activators. Human colon adenocarcinoma cells LS180 were stably transfected with reporter plasmids CYP24_minP-pNL2.1[Nluc/Hygro] (IZ-CYP24 cells contain the -326/-46 sequence from the human CYP24A1 promoter) or VDREI3_SV40-pNL2.1[Nluc/Hygro] (IZ-VDRE cells contain three copies of vitamin D response elements VDRE-I from the human CYP24A1 promoter). Both cell lines remained fully functional for over two months in the culture and also after cryopreservation. Luciferase inductions ranged from 10-fold to 25-fold (RLU 10(6)-10(7)) and from 30-fold to 80-fold (RLU 10(3)-10(4)) in IZ-VDRE and IZ-CYP24 cells, respectively. Time-course analyses revealed that detection of VDR activators is possible as soon as after 8 h of incubation. Cell lines were highly selective toward VDR agonists, displaying no cross-activation by retinoids, thyroids, and steroids. As a proof of concept, we used IZ-VDRE and IZ-CYP24 cells for profiling analogues of vitamin D, and intermediates in vitamin D2 and vitamin D3 metabolic pathways against VDR transcriptional activity. The data obtained revealed significant activation of VDR not only by obligatory ligands calcitriol and ergocalcitriol but also by their precursors and degradation products.

- Erden ES, Genc S, Motor S, Ustun I, Ulutas KT, Bilgic HK, Oktar S, Sungur S, Erem C, Gokce C.I

Investigation of serum bisphenol A, vitamin D, and parathyroid hormone levels in patients with obstructive sleep apnea syndrome. *Endocrine*. 2014 45:311-8.

Obstructive sleep apnea syndrome (OSAS) is a common health problem, and associated with obesity, metabolic syndrome (MetS), and diabetes. Growing evidence shows that 25-hydroxyvitamin-D3 (25-OH-D) insufficiency and high parathyroid hormone (PTH) levels may be correlated to glucose intolerance, MetS, obesity, and cardiovascular abnormalities similar to OSAS. Bisphenol A (BPA) is an endocrine disruptor agent which exerts a wide variety of metabolic effects. It has estrogenic activity and its exposure may contribute to weight gain, obesity, impaired glucose metabolism, and the development of diabetes, also similar to OSAS. The aim of this study is to investigate the relationships between OSAS and serum BPA, 25-OH-D, and PTH levels. This study enrolled 128 subjects, with all of the OSAS patients having been diagnosed by polysomnography. The 128 subjects were divided into three groups: a control (n = 43), a moderate OSAS (n = 23) (AHI = 15-30), and a severe OSAS groups (n = 62) (AHI > 30). The serum BPA, 25-OH-D, and PTH levels for each subject were analyzed. 25-OH-D was lower in both OSAS groups, and PTH was higher in the OSAS groups than in the control subjects. The BPA levels were higher in the severe OSAS group than the moderate OSAS and control. There was a positive correlation between the BPA and body mass index, and a negative correlation between the 25-OH-D and BPA levels in all of the individuals. OSAS is related to high BPA and PTH levels, and low vitamin D levels.

There is a positive association between BPA levels and OSAS, and the severity of OSAS. These results suggest that the BPA levels may have a role in the pathogenesis of OSAS.