Effects of endocrine disrupting compounds on Vitamin D circulating levels

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Summary

Vitamin D3 (cholecalciferol) is an inactive prohormone, which is derived either from 7- dehydrochlesterol conversion in the skin by solar ultraviolet B radiation, or from food. Vitamin D is a hormone produced by the kidneys that helps control the concentration of calcium in the blood, and is a key point for bone metabolism.
Studies on endocrine disruptors started a long time ago. In 1996, Kavlock et al. introduced the definition of endocrine disrupting compound (EDC) to describe agents/molecules that interfere with the synthesis, secretion, transport, binding, or elimination of natural hormones in the body. The EDCs are highly heterogeneous, and can be classified in two categories: naturally occurring and synthesized (i.e. bisphenol A BPA and phthalates). Synthetic EDCs can be classified as persistent organic pollutants and short-lived pollutants, categories that include phthalates and bisphenol A, found ubiquitously in plastic.
Several studies have evaluated the effect of EDCs on health, showing that the exposure of BPA and phthalates results in adverse health outcomes, including bone loss. BPA can affect bone health by decreasing the plasma calcium level and inhibiting calcitonin secretion, and by interfering via the RANKL pathway, apoptosis pathway and Wnt/β-catenin signaling pathway. Urinary phthalate metabolites have been associated with low BMD and high osteoporosis risk in postmenopausal women.
Epidemiological studies suggest that both phthalates and BPA may alter sex and thyroid hormones in pregnant women. Since active vitamin D metabolite is similar in structure to that of classic sex steroid hormones, and its nuclear receptors belong to the same superfamily of sex steroids and thyroid hormone receptors, it might be hypothesized that BPA and phthalates could alter the vitamin D axis.
Vitamin D insufficiency is very common worldwide, especially in elderly and osteoporotic subjects, in whom it worsens bone fragility. Epidemiological studies show that the prevalence of hypovitaminosis D is very high and is possibly re-emerging as a global health problem.
Recent studies underline an inverse association between urinary metabolites of BPA and phthalates and total plasma 25 (OH) D, suggesting the hypothesis that these compounds may alter the circulating levels of vitamin D both in pregnant women and in the adult population.

KEY WORDS: Vitamin D; phthalates; endocrine disruptors; bisphenol A.

Introduction

Vitamin D

Vitamin D3 (cholecalciferol) is an inactive prohormone derived from the steroid group, which is derived from 7-dehydrocholesterol (provitamin D3), which is converted to 7-dihydrocholecalciferol (vitamin D3) in the skin by the action of ultraviolet radiation (1).
A second source of vitamin D is derived from the diet and may be of animal (D3cholecalciferol) or plant origin (D2 ergocalciferol).
Vitamin D from the skin and food is then metabolized in the liver by 25-hydroxylase (microsomal CYP2R1, mitochondrial CYP27R1) to 25-hydroxycholecalciferol [25(OH)D3] (2), the major circulating form of vitamin D, used as a biomarker to determine the vitamin D status in patients' serum, due to its prolonged half-life of 2-3 weeks.
Calcidiol, or 25-hydroxycholecalciferol [25(OH)D3], binds to a transporting protein (DBP) and is transported to the kidney where it is metabolized to its active form, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] *via* the action of α1-hydroxylase (CYP27B1), or to 24,25 dihydroxycholecalciferol *via* 24-hydroxylase (CYP24A1) (3). The active metabolite of vitamin D is 1,25 dihydroxycholecalciferol or calcitriol.
This activation step is regulated by circulating parathyroid hormone (PTH), calcium and phosphorus serum levels, whereas it is inhibited by FGF23 (fibroblast growth factor 23). PTH inhibits its production, whereas FGF23 increases it (4).
In turn, 1,25(OH)2D3 controls PTH secretion *via* a negative feedback mechanism: vitamin D insufficiency or inadequacy causes an increased secretion of PTH and a consequent increased bone reabsorption. In the meantime, the deficiency in vitamin D levels impairs bone mineralization.

Vitamin D carries out its effects by binding to a nuclear receptor (VDR); the vitamin D receptor (VDR) is activated on binding to the agonist (1,25 dihydroxycholecalciferol), forming a heterodimer with the retinoid X receptor (RXR). This complex translocates to the nucleus to bind to vitamin D response elements. It forms a complex [1,25-(OH)2D-VDR-RXR] bound to DNA that downregulates the transcription of various genes related to bone metabolism (PTH and PTHrp), inflammatory response (IL2, IL12, TNFα, IFNα, GM-CSF) and cellular proliferation (EFG-R, c-myc, K16) (5).

The main actions carried out by binding of vitamin D to VDR are the following:

- regulation of calcium and phosphorus levels in the blood by increasing intestinal absorption, reducing tubular reabsorption and inhibiting PTH secretion
- involvement in cell proliferation and differentiation
- regulation of cell proliferation and oncogenesis
- modulation of the inflammatory and immune responses
- involvement in peptide hormone secretion.

The vitamin D receptor is not only located in the classic organs regulating calcium and phosphorus metabolism, but also in many other cells, such as keratinocytes, bone marrow cells, α-pancreatic cells, cardiomyocytes, macrophages, lymphocytes and others.

Vitamin D, in addition to its integral role in bone metabolism and calcium homeostasis, has also been correlated to increased muscle strength in older people (6), and to decreased tendency to fall. There is also consistent evidence of a beneficial effect of vitamin D in relation to bone mineral density (7, 8), lower extremity function, dental health, fractures, and colorectal cancer (9). Of great interest is the role vitamin D can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, cardiovascular diseases, fibromyalgia, and chronic fatigue syndrome (10). Moreover, low vitamin D serum levels have been found in several mental disorders (11).

It has been demonstrated that vitamin D insufficiency is a very common disease worldwide, especially in elderly and osteoporotic subjects, in whom it worsens bone fragility. Vitamin D insufficiency is increased by lack of sunlight exposure, altered intestinal absorption of calcium and vitamin D, decreased dietary calcium intake, decreasing ability of the skin to synthesize vitamin D and many other causes (Figure 1) (12-14).

Hypovitaminosis D

According to the Endocrine Society Guidelines, the normal level of 25(OH)D to ensure adequate bone health is > 30 ng/mL, however the following situations could occur:

- insufficiency: 25-hydroxycholecalciferol 20-30 ng/ml
- deficiency: 25-hydroxycholecalciferol 10-19 ng/ml
- severe deficiency: 25-hydroxycholecalciferol ≤ 10 ng/mL.

The goal is to achieve a 25(OH) D level of about 20 ng/mL and, if possible, above 30 ng/mL.

However, the latter value is difficult to achieve.

Vitamin D deficiency occurs all over the world. Many epidemiological studies have been conducted showing that hypovitaminosis D is a global health problem, mainly in the Middle East, China, Mongolia and India (15).

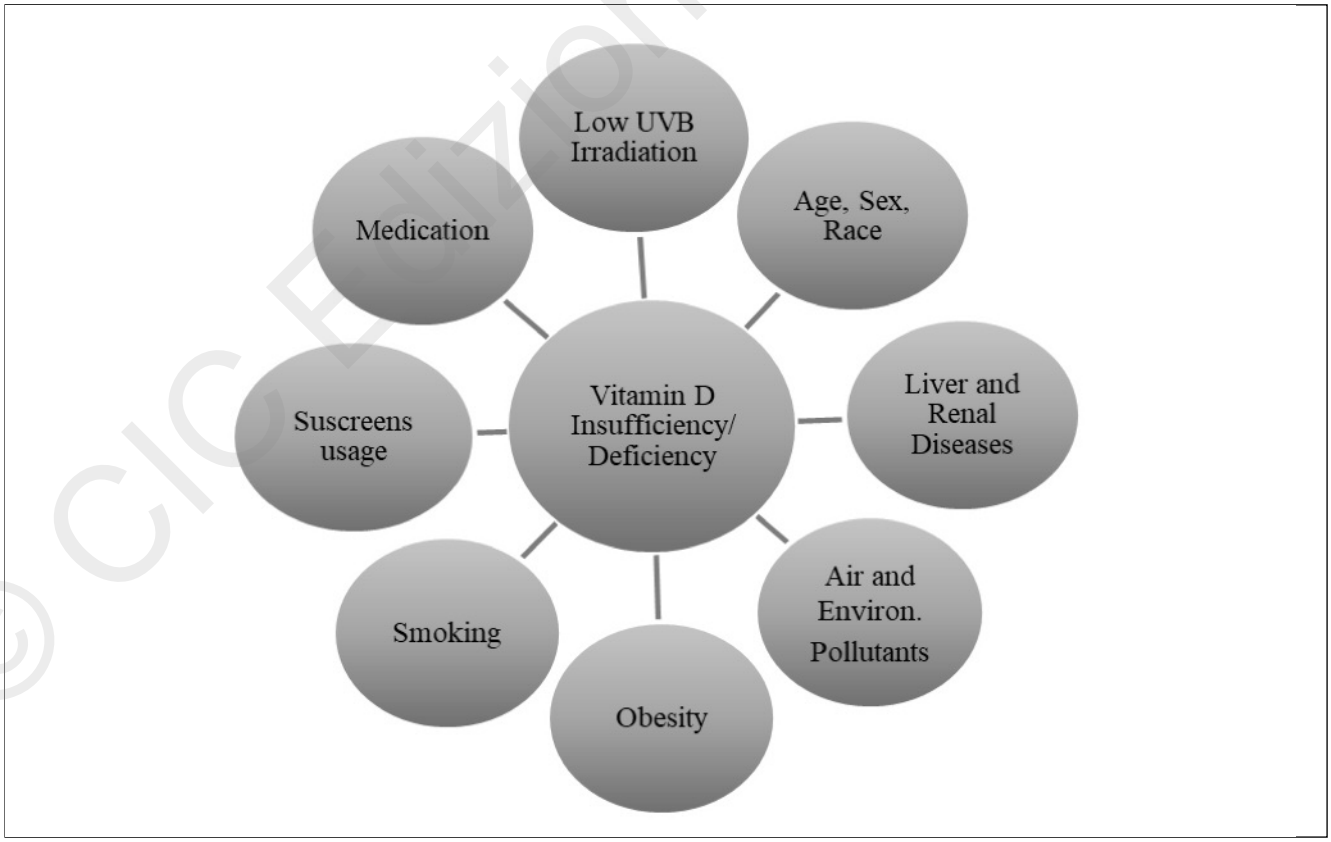

Figure 1 - Vitamin D insufficiency/deficiency.

Hypovitaminosis D in epidemiologic studies is also associated with muscular weakness, decreased physical performance, falls, and vertebral fractures. Related to this, in recent years many studies on vitamin D have been published, and many associations with different diseases, not related to mineral homeostasis, have been seen, such as cardiovascular disease, autoimmune disease (including type 1 diabetes and multiple sclerosis), type 2 diabetes, several types of cancer, depression, and infectious pathologies including tuberculosis and respiratory infections (16).
The model of vitamin D receptor (VDR) knockout mouse developed hyperparathyroidism and rickets, as well as diseases not related to mineral homeostasis, such as: hypertension, impaired insulin secretion, skeletal muscle deficits, left ventricular hypertrophy and failure, and cardiac fibrosis. Moreover, skin cancer occurred in VDR knockout mice (17-23).
In several large cohort studies in humans, a predictive correlation has been demonstrated between low serum 25 (OH)D levels and increased risk of incident hypertension, myocardial infarction and sudden cardiovascular death (24-28).
Furthermore, an association of type II diabetes (T2D), metabolic syndrome and obesity has been evaluated in patients with poor vitamin D status (29). In addition, the hypothesis that vitamin D could have a role in the pathogenesis of autoimmune diseases, such as multiple sclerosis (MS), type 1 diabetes mellitus (T1D), and rheumatoid arthritis (RA), has been proposed for patients who live far from the equator. A worsening of the diseases occurred in conditions of low ultraviolet radiation exposure (30-32).
In another study that included 2546 postmenopausal women, six risk factors related to the risk of nonvertebral fracture were identified, one of which was serum level of 25-hydroxyvitamin D ($p< 0.001$) (33).
Bonnen et al. performed a meta-analysis assessing only the effect on hip fractures of calcium and vitamin D supplements. A total of 45.509 individuals were analyzed, with a reduction in hip fracture of 18%. Most of the studies show a beneficial effect of vitamin D supplements on fracture reduction, primarily hip fracture (34).

Endocrine disrupting compounds

Endocrine disrupting compounds (EDCs) are chemicals that have been defined as "any agents or molecules able to interfere with the synthesis, secretion, transport, binding, or elimination of natural hormones in the body that are responsible for development, behavior, fertility, and maintenance of homeostasis (normal cell metabolism)" (35).
In recent years, many scientific studies have been conducted to understand the health impacts of EDCs, increasing knowledge on the subject and progressively raising awareness of ED-related concerns (36).
The European Commission has stated specific provisions to regulate EDCs included in the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals, n. 1907/2006) regulation that "aims to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances".
The class of EDCs is highly heterogeneous, including EDCs that occur naturally, and those that are synthesized: drugs, pesticides, compounds used in the plastics industry, industrial by-products and pollutants, body care products, and naturally produced botanical chemicals.
Some EDCs are persistent organic pollutants or are pervasive in the environment, and may be bio accumulate; others are short-lived pollutants, and rapidly degrade in the environment or in the human body.
Health effects attributed to endocrine disrupting compounds include a wide range of reproductive problems: changes in hormone levels, early puberty, brain and behavior problems, impaired immune functions, and the onset of various types of cancers.

Bisphenol A (BPA) is a fundamental molecule in the synthesis of some plastics and additives. It is used in synthesis of polyester, polysulphonates, polyketal ketones, as an antioxidant in some plasticizers, and as an inhibitor of PVC polymerization.
BPA is a key monomer in the production of epoxy resins and in the most common forms of polycarbonate, which is almost unbreakable, and is used for a large number of products (37).
Products using bisphenol A-based plastics have been in commercial use since 1957. Until a few years ago, the European Food Safety Authority considered that "BPA poses no health risk to consumers of any age group (including unborn children, infants and adolescents) at current exposure levels" [EFSA - No consumer health risk from bisphenol A exposure 21 January 2015], but the European Chemicals Agency recently concluded that BPA should be listed as a substance of very high concern, due to its properties as an endocrine disruptor.
A paper published by the ANSES's Working Group shows how BPA fulfills the definition of an EDC by having effects on several important physiological functions and how disruption of estrogenic pathways is considered central in the mediation of these effects (36).

Phthalates are esters of phthalic acid, used as plasticizers added to plastics to increase their flexibility, transparency, durability, and longevity. They are used primarily to soften polyvinyl chloride (PVC), but also in a large variety of products, such as: adhesives and glues, agricultural adjuvants, building materials, personal-care products, medical devices, detergents and surfactants, packaging (included food packaging), children's toys, pharmaceuticals, food products, and many others.
In general, phthalates are considered "not persistent" organic compounds due to their rapid capability to biodegradation. The class of phthalates includes many different molecules. One of the most common among those is DEHP. DEHP is commonly used in medical devices, but also in food and food packaging (38). Therefore, hospital patients probably have the highest degree of exposure to this compound. In the general population, diet is considered one of the main sources of DEHP and other phthalates, and in particular fatty foods, such as milk, butter, and meats.
DEHP is used in the plastic for bottled water, but this does not seem to be major source of threat of exposure to this phthalate. In a paper by Hanno et al., the Authors describe that several studies show that the ingestion of DEHP from food is far greater than from any other source and can be as much as 1000 times higher than from tap and bottle water (39).
Up to now, phthalates and bisphenol A have been recognized to have endocrine disrupting effects and to act as toxi-

cological agents, having a wide range of toxic effects demonstrated on human health. Due to their chemical characteristics and their weak bond with the polymeric structure, because of their physical and chemical factors such as heat and acidity, those compounds are gradually released into the external environment, contaminating water, soil and sediments, and later the rest of the agro-food chain (40).
Several studies have evaluated the effect of EDCs on health, showing that the exposure of BPA and phthalates results in several adverse health outcomes, including bone loss.

EDCs and vitamin D interaction

BPA can affect bone health by decreasing the plasma calcium level and inhibiting calcitonin secretion, and by interfering *via* the RANKL pathway, apoptosis pathway and Wnt/β-catenin signaling pathway (41).
The effect of exposure to ECDs was studied by Min in a sample of 398 postmenopausal women, aged >50 y. They evaluated whether, and how, eleven urinary phthalates were associated with total hip and femur neck bone mineral density (BMD) and osteoporosis. Results of the study showed that an increase of urinary phthalate metabolites was associated with reduced BMD and high osteoporosis risk. The Authors concluded that exposure to phthalates, even at low levels, may impair bone metabolism and BMD in postmenopausal women (42).
Epidemiological studies suggest that both phthalates and BPA may alter sex and thyroid hormones in pregnant women (43, 44).
Since active vitamin D metabolite is similar in structure to that of classic sex steroid hormones (Figure 2), and its nuclear receptor belongs to the same superfamily of sex steroids and thyroid hormone receptors, it might be hypothesized that BPA and phthalates alter the vitamin D axis.
While some studies have shown the relationships between BPA and phthalates and bone health, less is known about the effects that these compounds may have on circulating levels of vitamin D.
To date, knowledge is mainly concentrated on the impact of endocrine disrupting chemicals, such as air pollutants or organic persistent pollutants, on vitamin D deficiency.
Cadmium is a common environmental pollutant, widely distributed in the environment and with a long biological half-life in organs. It has carcinogenic effects when inhaled in tobacco smoke, and has been shown to exert significant effects on the reproduction system (ovarian and reproductive tract morphology). Cadmium exposure during pregnancy has been linked to decreased birth weights and premature birth.
Moreover, cadmium has shown toxicity on bone. Although the mechanisms underlying this effect are not yet clear, several models have been suggested. A study by Youness et al. (45) provided evidence that "chronic exposure to cadmium chloride induced hypercalcemia due to negative calcium balance, alteration in phosphate homeostasis, with the presence of secondary hyperparathyroidism in addition to inhibition of renal 1-α-hydroxylase activity that led to the reduction of serum level of 1,25 (OH)2D3 activity". These data suggest a possible association between cadmium, as an endocrine disruptor, and low levels of vitamin D.
A major scientific review recently published by Hoseinzadeh showed that some common atmospheric pollutants could be responsible for the decreased levels of vitamin D. Ozone,

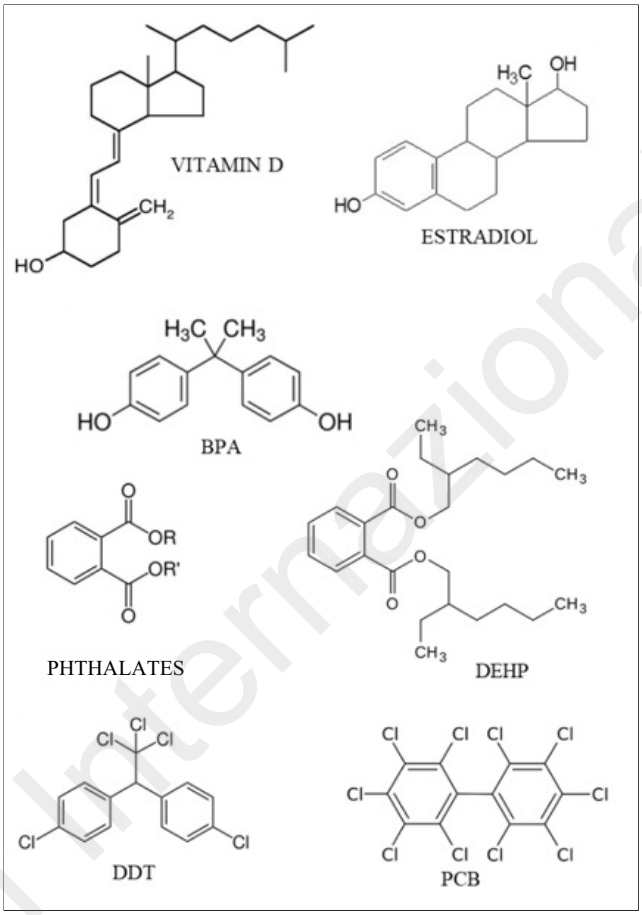

Figure 2 - Structural formula of vitamin D and pollutants.

carbon monoxide, particulate matter, nitrogendioxide, and sulfur dioxide are the five most common air pollutants that have generally been used to evaluate air quality. In the urban areas affected by air pollution, the reduction of UV irradiance is high, and as UVB is necessary for vitamin D formation, the effect of air pollutants on UVB irradiance should be a health concern. In effect, mainly in the areas where the particulate matter is highly concentrated, the reduction of UV irradiation is remarkable, decreasing by 2-20% (46).
A similar observation was done by Kelishadi et al. (47). In this study, the association between air pollutants and vitamin D deficiency was observed in children aged 4-10 years, living for at least 1 year in Iran, in a highly polluted area.
Moreover, an independent inverse association of the quality of the air with the levels of vitamin D emerged and explained the high prevalence of hypovitaminosis D in children living in sunny regions.
Considering these previous studies, a strong correlation between air pollution and low levels of vitamin D can be shown. At the same time, a close association between low vitamin D levels and obesity is well documented.
A review published by Barrea et al. (48) provides a general overview of the possible associations among vitamin D levels, air pollution and obesity. The Authors propose an intriguing hypothesis suggesting that the misuse of some sunscreens, combined with unhealthy diet and lifestyle, may cause vitamin D deficiency, not only through a reduction of UVB absorption, but also because they could act as endocrine disruptors. These factors can lead to obesity, which

in turn helps segregate significant amounts of vitamin D in the adipose tissue, thus further lowering vitamin D levels.
Results of several studies show that persistent organic pollutants are associated with low vitamin D levels in animal models, and exposure to PCBs was correlated with possible changes in the expression of the vitamin D receptor in the zebrafish (49).
The hypothesis that exposure to persistent organic pollutants (POPs) could impair metabolism of vitamin D is confirmed by some studies on human beings.
A cross sectional study performed in the U.S. general population, 1.275 subjects aged 20 years or more, suggested significant inverse associations between serum concentrations of several Organochlorine (OC) pesticides: dichlorodiphenyltrichloroethane (p,p′-DDT), dichlorodiphenyldichloroethene (p,p′-DDE), β-hexachlorocyclohexane (β-HCH) and serum25(OH)D levels, suggesting that exposure to some OC pesticides leads to vitamin D deficiency in humans (50).
Another study conducted by Morales et al. (49) reported data about the relationship between vitamin D levels and the concentration of some OC pesticides: p,p′-DDT, p,p′-DDE, HCB (hexachlorobenzene), β-HCH and polychlorinated biphenyls (PCBs) in 2031 pregnant women. Results explain the inverse association between blood concentrations of PCBs and 25(OH)D and the absence of a relationship between POPs and 25(OH)D.
In 2014, Erden et al. showed both the negative correlation between the serum vitamin D and BPA urinary levels in a sample of 128 subjects (85 affected by obstructive sleep apnea syndrome and 43 healthy volunteers) and the positive correlation between BPA urinary levels and body mass index (BMI). The Authors concluded that “obstructive sleep apnea syndrome is related to high BPA, PTH, and low vitamin D levels when compared with healthy controls” (51).
A study by Johns et al. (52) also showed an inverse association between BPA urinary levels and total 25(OH)D. This study first investigated the potential associations between environmental exposure to phthalates and total vitamin D. The NHANES study (2005-2010), was a cross-sectional study designed to collect health and nutritional data from a nationally representative sample of the resident civilian non-institutionalized U.S. general population. A sub-sample of 4724 men and women was characterized by sex, age, race, BMI, smoking status, vitamin D supplement use and sampling season. Data previously collected were completed with dosages of urinary phthalate metabolites, BPA and creatinine and serum 25(OH)D. Results of the study showed that the vitamin D level is lower in all BMI categories compared to subjects with normal weight. Phthalate metabolites were persistently inversely correlated with total 25(OH)D in the overall study population. Stratified analysis shows a stronger association in women than in men. This is plausible presuming that women used personal care products that are rich in phthalates more than men (52).

Conclusion

The information derived from a growing amount of literature on the associations between vitamin D and endocrine disrupting compounds, in itself promising, is not, however, matched by the results obtained in interventional studies. To prove that there is a causal relationship between vitamin D and EDCs, more trials are needed to demonstrate that maintaining 25 (OH)D levels within a certain range may be useful and safe for both the prevention and treatment of diseases caused by endocrine disrupting compounds.
Furthermore, future prospective studies are needed to support and investigate the potential causal associations between vitamin D levels and EDCs, answering important questions, such as the long-term effects of EDCs on vitamin D and how the phenotypic characteristics of EDCs may alter the response to vitamin D.

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