or synthetic. Natural EDs are phytoestrogens and fungal estrogens. Synthetics are hormones, pesticides, industrial agents, drugs and organic pollutants. The most common EDCs are estrogens, anti-estrogens, anti-androgens, progesterone, thyrotoxic agents, metals, aryl hydrocarbon receptor agonists and retinoids. They can be classified as polychlorinated biphenyls and organochlorine pesticides, pesticides, (organophosphates, carbamates, pyrethroids), plasticers (phthalates), bisphenol A, parabens, organic solvents, phytoestrogens, diethylstilbestrol, detergents and brominated flame-retardants. The main sources of those chemicals are food chain, contaminated household dust, insecticides, cosmetics, as well as industrial and occupational agents. The examples for those sources are polycarbonate plastics, including beverage and food storage containers, epoxy resins in the interior of metal cans, the ink used for thermal paper receipts, textiles which contain contaminants, such as flame-retardants, including tetrabromobisphenol A and polybrominated diphenyl ethers, medical (diethylstilbestrol), dental (diglycidyl methacrylate) or dietary (phytoestrogens) interventions and synthetic estrogens from anticonceptional pills, such as ethynilestradiol. In conclusion, all those chemicals should be screened for their adverse effects for human and wildlife. The studies, screening programs and standard approach for EDs should include toxicogenomics, which encompasses genomics, proteomics, metabolomics, neurotoxicology and neuroinformatics and insilico studies. This needs collaborations between countries, development of better screening approaches, improved methods of risk assessment and naturally reducing the exposures to well-known EDC.

Key words: Endocrine disrupting chemicals, endocrine disrupter, genetics, epigenetics, chemicals

Vitamin D in Sickness and Health

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Vitamin D is a secosteroid hormone, which is soluble in lipid. It is the oldest hormone produced by phytoplankton for more than 500 million years. The function of the hormone was thought to be protection of macromolecules sensitive to ultraviolet (UV) light such as DNA, RNA and proteins when they are exposed to sun for photosynthesis on the first forms of life. With the evolution, as vertebrates developed, it was a major physiologic problem to maintain the homeostasis of calcium when they started to live in land coming from the calcium-rich ocean. Vitamin D was necessary for the development and maintenance of the skeleton.

Important portion of vitamin D is synthesized in the skin with the effect of UVB. Limited portion of it is taken from food. A few contains vitamin D (the liver of codfish, fungi that has been exposed to UV light, salmon, fat-rich fish like tuna etc.).

7-dehydrocholesterol, found in skin, turns into pre-vitamin D3 when exposed to UV light with 290-315 nm wavelengths. The factors like angle of sunlight, latitude, seasons, the hour of the day, sun protectors, dressing style and aging affect this transformation and the amount of vitamin D synthesized in the skin. 7-dehydrocholesterol is found in every layer of the skin, besides almost 65% is found in the epidermis and more than 95% of pre-vitamin D is made in the epidermis. Pre-vitamin D3 quickly turns into vitamin D3 (cholecalciferol) with thermal and membrane dependent operations. The pre-vitamin D3 and vitamin D3 are converted into inactive photoproducts (tachysterol and lumisterol) when exposed to sun for long period of time and thus the vitamin D intoxication induced by sun is being prevented. The orally taken 20000 IU dose of vitamin D can be synthesized in the skin in summer when the whole body (while wearing a swimming suit) is exposed to sun in a way that the sun generates minimal erythema dose (MED) (forming a slight reddening on the skin; ~1 MED). If only the hands, arms and face are exposed to sun (~0.5 MED), nearly 3000 IU dose of vitamin D is being synthesized in the skin. Vitamin D2 and D3 taken with foods are incorporated to chylomicrons and transported into venous system via lymphatic system. Vitamin D (D2 and D3) synthesized in the skin and taken orally is stored in the adipose tissue and in need, it is being secreted from the adipose cells. In circulation, vitamin D binds to vitamin D-binding protein (VDBP) and is transported to the liver via this protein. In the liver, vitamin D is transformed into 25-hydroxyl vitamin D [25(OH)D] (calcidiol) using a microsomal enzyme 25-hydroxylase (CYP2R1). 25(OH)D is the major circulated form of vitamin D and the best indicator of vitamin D levels. This form synthesized by the liver is biologically inactive. It gets into the circulation, binds to VDBP and is transported to kidneys. 25(OH)D-VDBP complex is filtrated from the renal tubules and is taken back into the cell via receptor-mediated endocytosis. During this process, two proteins-tubulin and

megalin-play a role. Both of them are expressed in the proximal tubule and they are multiligand receptors. Even in deficiency of one of them, vitamin D is excreted with the urine resulting in 1,25 dihydroxy-vitamin D [1,25(OH)(2)D] deficiency. 25(OH)D splits from VDBP in the tubular cell and is transformed into its biological active form [1,25(OH)(2)D] via 1-alpha hydroxylase (CYP27B1). Renal 1-alpha hydroxylation is regulated powerfully. Hypophosphatemia, hypocalcaemia and increased parathyroid hormone (PTH) associated with hypocalcaemia increase the synthesis of 1,25(OH)(2)D. Hyperphosphatemia, the fibroblast growth factor-23 secreted from osteocytes (FGF-23) and 1,25(OH)(2)D itself inhibit the renal 1-alpha hydroxylase enzyme. FGF-23 inhibits the synthesis of 1,25(OH)(2)D by suppressing the gene expression of 1-alpha hydroxylase and the increased PTH. In addition, it leads to the transformation of active vitamin D into inactive metabolite, 24.25 dihydroxyvitamin D, via increasing the expression of 24-alpha hydroxylase (CYP24A1) enzyme. 1,25(OH)(2)D also regulates its synthesis by decreasing the synthesis and secretion of PTH and increasing the expression of 24-alpha hydroxylase enzyme.

1-alpha hydroxylase enzyme is expressed in many tissues other than kidney such as bone, placenta, prostate, keratinocytes, macrophages, T-lymphocytes, dendritic cells, parathyroid cells and many cancer cells. 1,25(OH)(2)D synthesized in these tissues is active and has autocrine and paracrine effects.

Active vitamin D shows its effects either on nuclear vitamin D receptor (VDR) with genomic or on membrane-dependent VDR with non-genomic pathways. The 1,25(OH)(2)D, either synthesized in kidneys or in other tissues, is a ligand of VDR. VDR is expressed in all nucleated cells and found in many different tissues. Circulating 1,25(OH)(2)D reaches the nucleus of target cell by passing cell membrane and cytoplasm and binds to VDR. After binding active vitamin D, nuclear VDR generates a heterodimeric complex by binding to retinoid X receptors. Then, it binds to specific nucleotide sequences known as 'vitamin D response elements' on DNA. 1,25(OH)(2)D works as a transcription factor and directly or indirectly regulates the expression of nearly 2000 genes. 3% of human genome is under the control of 1,25(OH)(2)D. Previously, it was thought that kidneys, intestines and bones were the only target organs of active vitamin D and that vitamin D regulated the mineral metabolism only by affecting these organs and it kept the track of calcium and phosphorus homeostasis. Today, other than calcium/bone homeostasis, 1,25(OH)(2)D has many effects such as suppressing cell proliferation, angiogenesis, rennin production and inducing terminal differentiation, apoptosis, as well as production of insulin from pancreatic cells and catelicidin from macrophages.

The best parameter showing the vitamin D condition is 25(OH)D. Even though there is still no consensus on the optimal values for the serum levels of 25(OH)D, many authors accept values above 30 ng/mL (75 nmol/L) as sufficient, values between 20 and 29 ng/mL (50-75 nmol/L) as insufficient and values below 20 ng/mL (50 nmol/L) as deficient. The situation is thought to be intoxication when the levels of 25(OH)D are above 150 ng/mL.

Causes for vitamin D deficiency:

1. Impaired/insufficient vitamin D intake and synthesis-insufficient exposure to sun, insufficient intake with food, lipid malabsorption
2. Impaired hydroxylation in liver
3. Impaired hydroxylation in kidney
4. Target organ resistance to vitamin D metabolites (hereditary VDR resistance, vitamin D-dependent rickets type 2).

Almost 1 billion people in the world have been thought to have vitamin D deficiency. Vitamin D deficiency has become a pandemic. When we look at the literature, vitamin D status differs among the countries and even in different regions of the same country. In Europe and the US, it has been reported that 40-100% of older women and men living in the society (not in care houses) has vitamin D deficiency. Studies in Turkey also show that vitamin D deficiency is very common in Turkey.

The insufficient exposure to sun, female gender, living in a care house, aging, multiparity (>3 births), living in higher latitudes, increased BMI, low education levels, low social-economic status, insufficient vitamin D intake, winter season, closed dressing style and period are found to be associated with low vitamin D levels. 25(OH)D level measurements are suggested for only risky groups (elderly, people with dark skin, usage of a drug accelerating the metabolism of vitamin D, insufficient exposure to sun, osteoporosis and malabsorption) in terms of vitamin D deficiency. It is recommended that whole population should be screened and all pregnant women should be tested for vitamin D levels routinely.

The treatment dose for vitamin D changes according to the reason of vitamin D deficiency and the severity of the deficiency. For cases with 25(OH)D levels <10-20 ng/mL, the treatment dose is 50000 IU/week and the treatment is given for 6-8 weeks and it is suggested that the serum 25(OH)D needs to reach a value >30 ng/mL after the treatment. After reaching the targeted levels of serum vitamin D, the daily maintenance dose should be continued. If the targeted levels cannot be reached, the vitamin D treatment with same dose (50000 IU/week) can be continued for 3-6 weeks. For patients with malabsorption, higher doses should be given (10000-50000 IU/day). For patients having 25(OH)D levels between 20-30 ng/mL, 800-1000 IU/day vitamin D is suggested.

Vitamin D deficiency results in rickets in children and osteomalacia in adults. Vitamin D is being used for the treatment of osteomalacia and rickets. In addition to these, studies have shown that vitamin D deficiency is associated with many autoimmune, infectious and other types of diseases such as cardiovascular diseases, metabolic syndrome, hypertension, depression, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases. There is insufficient data in the literature to support the usage of vitamin D for prevention and treatment of these diseases.

Key words: Vitamin D, sickness, health