Vitamin D Deficiency, Prevention and Treatment

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Clinical Practice

CASE

A 35 year female born and residing in Esfahan presents to the physician due to fatigue and sense of weakness. The patient refers that she has been having bilateral low back pain accompanied by throbbing bone pain in the lower extremities since 5 months ago.

In past history menses is regular and 3 pregnancy followed by lactating the newborns. The patient denies use of any medication, except regular use of sunscreen. She also denies history of DM.

In the physical examination:

BP: 120/80

BMI: 30 Kg/M^2

Cranial nerves are intact

Examination of nerves system is within normal limit

There is no proximal myopathy.

Laboratory examination revealed:

- TSH and T4 within normal limits
- Serum calcium 9.5 mg/dl (8.5-10.5)
- Phosphate: 3.5 mg/d (2.5-4)
- Albumin: 4 g/dl
- 25(OH) D: 4 ng/ml
- PTH: 84 Pg/ml (8-51).

WHAT IS THE RECOMMENDED TREATMENT FOR THIS PATIENT?

The clinical problem

Source of vitamin D In humans the main source of vitamin D is sunlight exposure.[1] In the nature there are not plenty of food sources containing vitamin D. As a result almost all vitamin D obtained from exposure to sunlight.[2]

Ultraviolet B (UVB) In the skin produces vitamin D through a nonenzymatic pathway. The 7-dehydrocholesterol converts into pre vitamin D3 and then through the thermal reaction turns into vitamin D3, which enters the systemic blood flow and in the liver converts to 25 (OH) D. In the kidney the 25 (OH) D (through 1 Alfa hydroxylation) becomes the end product called 1.25 (OH) 2D.[3]

In different investigations it is demonstrated that the following factors result in decrease vitamin D production: skin pigmentation, aging, seasonal variation, sunscreen usage and obesity.[4-6]

Epidemiology

At the present time vitamin D deficiency is one of the most common health problems in the world. As a matter of fact vitamin D deficiency is pandemic worldwide.[7]

It is estimated that 30-50% of pediatric age group as well as adults in the United States, Canada and Europe are vitamin D deficient. There has been report of vitamin D deficiency in places, where the sun is almost present all the time, in the Arabic peninsula such as Saudi Arabia and Qatar.[8,9]

Isfahan endocrine and metabolism Research center performed a survey on high school students in the city of Isfahan in 2005. It was determined that vitamin D deficiency was 46.2% prevalent among the students based on the value of 25 (OH) D<20 ng/ml.[10]

In addition, a study performed at Tehran Endocrine and metabolism Research Center on 522 pregnant female in 2002. This study revealed that 66.8% of patients had vitamin D deficiency in their blood and consequently 93.3% of them presented with the vitamin D deficiency in the umbilical cord.[11]

The main reason for the vitamin D deficiency epidemic in the world is that there in not sufficient amount of vitamin D in the food consumed on a daily bases. The estimated amount in adult is between 3000 and 5000 IU per day.[2] As a result the main source of vitamin D, almost entirely, depends on sun exposure. When an adult is exposed to 1 minimal erythmal dose of UV (MED), a slight pinkness to the skin 24 h after exposure, this amount of exposure produces almost 10,000-25,000 vitamin D.[7]

On the other hand in the absence of sunlight exposure at least 2000-3000 IU of vitamin D is necessary for children and adults to maintain a 30 ng/ml vitamin D in their blood.[7]

Vitamin D insufficiency/deficiency

At the present time the definition of vitamin D sufficiency, insufficiency and deficiency depends on the metabolism of calcium which by itself estimated based on the graph of PTH and 25 (OH) D in general population. Based on this method the vitamin D deficiency is defined as serum 25 (OH) D <20 ng/ml. A serum level between 21 and 29 ng/ml is insufficient and a 25 (OH) D greater than 30 ng/ml is considered sufficient.[1]

The gold standard to measure 25 (OH) D in serum is immunoassay.[12]

Vitamin D deficiency side effects

Musculoskeletal system

Low 25 (OH) D in the serum significantly correlates with low BMD and increases the risk of hip fracture.[13]

In women Health initiative study it is observed that a decrease of 10 ng/ml of 25 (OH) D in the serum increases the risk of Hip fracture significantly.[12] In addition decreases in vitamin D in pregnant female result in skeletal changes in the fetus that may be detected by 19 week of gestation.

In a study Mahon and his colleagues determined that there is correlation between rickets of the femur in the fetus and the decrease in vitamin D in the serum of the mother.[14]

Microbial disease

Recent studies have shown that vitamin D is important in the regulation of immune system. In a study performed by Ginde and his colleagues, they found out that there is a relationship between upper respiratory tract infections and low vitamin D in the blood.[15]

In NHANCE III study, patients with active tuberculosis present with significantly lower serum vitamin D levels. In recent studies it has been shown that vitamin D acts as an intermediate in the Monokine system.

In addition, vitamin D plays a role in the production of antimicrobial peptides by monocyte and macrophages.[12]

Cardiovascular mortality

NHANCE III study in the United States shows that there is an increase in all case mortality among general population, especially among women, when the 25 (OH) D<30 ng/ml. On the other hand a serum 25 (OH) D between 35 and 40 ng/ml has the highest mortality protective values. Death due to cardiovascular complications was the highest reported mortality among individuals with vitamin D deficiency.

The prevalence of coronary heart disease, heart failure and peripheral artery disease increases significantly when the level of vitamin D decreases in the serum.[16]

Metabolic disease

The recent studies have shown that there is a reverse relation between the level of 25 (OH) D and Hypertension, obesity, insulin resistance and glucose intolerance. Based on NHANCE III study the decrease rate of 25 (OH) D level in the serum associated with increase in the body mass index (BMI).[17]

Prevention and treatment in adults

Majority of middle age adults are at increased risk of vitamin D deficiency due to decrease sun exposure and increase use of sun screens. Therefore, studies show that in order to reach a serum level of 25 (OH) D above 30 ng/ml a minimum of 1000 IU or probably 1500-2000 IU/day is necessary.

The main reason for Vitamin D deficiency is insufficient consumption of vitamin D in combination to inadequate sun exposure. Individuals with fat mal absorption have higher rate of vitamin D deficiency since the vitamin D absorption from diet and supplementation is incomplete in this patients.

Patients with Celiac disease also present with vitamin D deficiency. In these patients in spite of pharmacologic doses of daily oral vitamin D, level of serum vitamin D does not increase.

The treatment of vitamin D Insufficiency/deficiency except in rickets and osteomalacia and without hypocalcaemia composed of 2 steps:

- Replenishing vitamin D store more than 30 ng/ml
- Maintenance treatment

In Iran the pharmacologic forms of vitamin D are 50000 IU Pearl vitamin D3 and the 300000 IU injection form. Multivitamins usually contain less than 400 IU in each tablet. The Calcium-D contains 200 IU vitamin D. Therefore, the tablet of calcium-D is not sufficient for treatment and maintenance treatment in patients who need to therapy.

It is only permissible to use the injection form of vitamin D in fat malabsorbtion syndrome. It is recommended to measure the level of 25 (OH) D, PTH and serum calcium and phosphate to evaluate the severity of vitamin D deficiency before the treatment is initiated.

Also, it is advisable to evaluate the patient for severity of secondary hyperparathyroidism. Physicians may also need to rule out other etiologies that might contribute to hyperparathyroidism. Hypercalcemia due to primary hyperparathyroidism, and familial hypocalciuric hypercalcemia (FHH) should be considered as differential diagnosis.[12]

There are two common protocols for the treatment of patients.

- Holick protocol: Weekly Pearl 50000 IU of vitamin D3 for a period of 8 weeks given to the patient to replenish the deficient vitamin D. In the maintenance phase 50000 IU vitamin D3 is administered every 2 weeks. It is recommended to measure the serum level of 25 (OH D) after 2-3 months of treatment; and if the level is above 30 ng/ml the maintenance therapy should continue.[7]
- The patient receives 500,000-1000,0000 IU of vitamin D3 in divided doses with oral pearl of 50,000 IU vitamin D3 in a period of 4-5 weeks (for instance the patient takes 1 pearl every 2-3 days). There is no any pearl given to the patient for the following 4-5 weeks. In this protocol after the end of the second 4-5 weeks the serum level of 25 (OH) D is measured and if it is above 30 ng/ml receives the maintenance therapy. The maintenance therapy composed of 50000 IU oral vitamin D3 on a monthly base. The level of serum PTH is measured during the treatment in order to make sure that the level of Parathyroid hormone has not increased from the base line value. In case of increase in serum PTH level during treatment the physician should suspect concurrent Primary Hyperparathyroidism which is not rare in case of vitamin D deficiency, since the vitamin D deficiency is epidemic.[12]

If the serum level of vitamin D during the 10-12 weeks of treatment does not increase to above 30 ng/ml, it is recommended to repeat the replacement protocol. However, if the level of serum vitamin D after 2 periods of treatment was low and the patient compliance to treatment is assured; the physician should suspect intestinal fat malabsorption as a differential diagnosis (for example celiac disease).

If the celiac disease was confirmed the injectable form of vitamin D is recommended.[12]

CONCLUSION

The vitamin D deficiency is a worldwide epidemic. In Iran the only source of vitamin D is sun exposure.

In order to prevent the vitamin D deficiency in

Iran, the food sources such as milk or cheese should be fortified with vitamin D or the vitamin D deficiency should be prevented by oral pearls supplements.

In Iran, the fortification of food sources with vitamin D is not widely performed. Therefore, it is recommended to take advantage of oral supplements for the prevention, as well as, treatment and maintenance of vitamin D deficiency.

The concomitant primary hyperparathyroidism in patients with vitamin D deficiency who are going under treatment should always be considered. The low serum vitamin D may prevent the increase in serum calcium. However, when the treatment with vitamin D initiated it leads to increase in serum calcium and consequent hypercalciuria. If there is suspicion of presence of vitamin D deficiency and primary hyperparathyroidism at the same time, the level of serum calcium, PTH and 24 hour urine calcium should be monitored.

In regard to this case the weekly treatment with Pearl 50000 IU vitamin D3 initiated and continued for a period of 8 weeks. Then the Pearl 50000 IU vitamin D3 continued every 2 weeks. The serum level of PTH and 25 (OH) D were evaluated after 3 months of treatment.

The serum of 25 (OH) D was 42 ng/ml and the PTH was 70 Pg/ml. As it is known, the secondary hyperparathyroidism due to vitamin D deficiency improves after 6-12 months of treatment with vitamin D. Therefore, the serum PTH level in this patient is not worrisome. Therefore, the maintenance therapy in this patient continued and after 3 months of the treatment the patient reported sense of wellbeing and the low back pain and the throbbing bone pain totally resolved.

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