Vitamin D and Anaesthesia

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Vitamin D is a vitamin not only associated with calcium-phosphorus metabolism but also affects many organ systems. Because of its effect on the immune system in recent years, it has attracted much attention. Vitamin D deficiency is a clinical condition that can be widely observed in the society. Thus, patients with vitamin D deficiency are often seen in anaesthesia practice. In the absence of vitamin D, prolongation of intensive care unit stay, increase in mortality and morbidity and also association of chronic diseases further increase the importance of vitamin D deficiency. The results obtained from studies have led to the question of whether poor surgical outcome is associated with vitamin D deficiency. We assessed the vitamin D deficiency and its negative consequences for the anaesthesiologist.

Keywords: Vitamin D, anaesthesia, intensive care, pain

Introduction

Vitamin D deficiency has become a frequently questioned situation, and the likelihood of encountering vitamin D deficiency in medical practice has increased. As anaesthesiologists, we encounter vitamin D deficiency in many settings, such as preoperative assessments, anaesthesia, intensive care units (ICUs), and pain management. Vitamin D is responsible for mineral balance. By affecting absorption and metabolism, it regulates the levels of serum calcium and phosphorus (1). Vitamin D deficiency may result in rickets in children and osteoporosis and osteomalacia in adults (2). However, with the recent discovery of vitamin D receptors in most body tissues and cells, other functions of vitamin D have been brought up for discussion.

Vitamin D Deficiency

Vitamin D deficiency is seen in the general population with a frequency of 30%–50% (3). Approximately one million people in the world are considered to be suffering from vitamin D deficiency or insufficiency (4). In a study conducted in the United States with 4495 volunteers, vitamin D deficiency was found in 41.6% of the volunteers. In the same study, the highest rate of vitamin D deficiency was 82.1% in the black race. It was followed by the Latin race at 69.2% (5). In our country, of the 513 patients aged between 18 and 69 years who were admitted to a hospital, 51.8% had vitamin D deficiency, and 20.7% had vitamin D insufficiency (6). In a study conducted on anaesthesia clinic personnel in Iceland and Wisconsin at the end of winter, the average serum 25(OH)D levels were below 25 nmol L⁻¹ among 4.7% and 4.0% of the personnel, and 34.9% and 50% of the personnel had levels below 50 nmol L⁻¹. In 56.6% and 61.3% of the participants, vitamin D levels were below 75 nmol L⁻¹ (7). Vitamin D level below 20 ng mL⁻¹ is considered to be a deficiency, between 20 ng mL⁻¹ and 30 ng mL⁻¹ is considered to be an insufficiency, between 40 ng mL⁻¹ and 50 ng mL⁻¹ is considered to be optimal and over 150 ng mL⁻¹ is considered to be toxic. The optimal serum vitamin D level is 30 ng mL⁻¹ (8, 9).

General Information about Vitamin D

Vitamin D can be both endogenously synthesized and taken with the diet. Vitamin D consists of two forms: cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂). Majority of vitamin D in the body is vitamin D₃. Vitamin D₂ is produced in plants and yeast. Vitamin D₂ and activated vitamin D obtained from vitamin D₃ appear to be similar in terms of biological activity, although their binding to transport proteins and their metabolism differ (10). The vitamin D precursor 7-dehydrocholesterol, which is endogenously found in keratinocytes of the epidermis, is activated by ultraviolet B (UVB)

and forms pre-vitamin D₃. Previtamin D₃ is transported to the liver via a vitamin D binding protein and is hydroxylated to 25-dehydroxy vitamin D there. This active hormone reaches the target tissues with the vitamin D binding protein and fulfils its functions (11). 1,25(OH)₂D regulates approximately 200 genes such as rennin in the kidney, insulin production in the pancreas, cytokine release from lymphocytes, cathelicidin production and cardiomyocyte and proliferation of vascular smooth muscle cells in macrophages (4, 12). Although in the proximal renal tubules mainly there is 1 α hydroxylase, keratinocytes, macrophages and enterocytes can also be found. Both 25(OH)D and 1,25(OH)₂D are inactivated by 24-hydroxylase. Vitamin D is excreted in urine and bile. Vitamin D metabolites, on the other hand, are reabsorbed from the renal tubules. 1,25(OH)₂D increases the absorption of calcium from the duodenum and phosphorus from the ileum. In the absence of vitamin D, 10–15% of calcium and 60% of phosphorous can be absorbed (13). In the presence of vitamin D, calcium absorption increases by up to 30–40%, and phosphorus absorption increases up to 80% (4). 1,25(OH)₂D also increases bone resorption, decreases parathormone synthesis and secretion, increases insulin production, decreases the synthesis of rennin and improves myocardial contractility.

Vitamin D Deficiency and its Comorbidities

Musculoskeletal diseases

We now know that vitamin D deficiency definitely causes growth retardation and rickets in children. In adults, it can cause increases in osteopenia, osteoporosis and bone fractures (14-16). Many multiple sclerosis (MS) patients have vitamin D deficiency or insufficiency. In addition, it has been shown that serum 25(OH)D levels are lower in the acute exacerbation stage of MS than in the remission stage. It is also known that as the severity of MS increases, serum 25(OH)D levels decrease (17-21).

Cardiovascular diseases

Vitamin D deficiency is a predisposing factor for hypertension, diabetes, left ventricular hypertrophy, congestive heart failure and chronic vascular inflammation (4, 22). There are studies showing an increasing correlation between vitamin D deficiency and pulmonary, cardiovascular diseases and cancer (22-25). It has also been shown that vitamin D supplements reduce the incidence and mortality rates of these diseases (26-29). The best known metabolism of antiatherogenic effect of vitamin D is the regulation of inflammatory response. It regulates endothelial functions, stimulates nitric oxide production and reduces oxidative stress (30, 31). There are studies showing that vitamin D does not increase morbidity and mortality in cardiac surgeries (32).

In a study conducted by Krishnan et al. (33), in 19 patients who underwent cardiopulmonary bypass, serum 25(OH)D₃; 1 α ,25(OH)₂D₃; parathyroid hormone; C-reactive protein (CRP) and ionised calcium [i(Ca)] levels were measured,

and a 35% decrease in acute fluid loading on serum 25(OH)D₃ level, 45% decrease in 1 α ,25(OH)₂D₃ and i(Ca) and an increase in parathyroid hormone levels were observed.

While serum 25(OH)D₃ levels had been above the 1 α ,25(OH)₂D₃ basal level, only on the fifth day it decreased to the initial level. The CRP levels were significantly high at the 24th hour and 5th day of measurements and were not associated with the decrease in vitamin D level. In this study, it was shown that acute fluid loading significantly reduces 25(OH)D₃ and 1 α , 25(OH)₂D₃ levels in critical diseases. However, Turan et al stated in their retrospective study they conducted by means of the data they obtained from cardiac anaesthesia records that perioperative vitamin D levels were not associated with cardiac, neurological morbidity and mortality and the duration of stay in intensive care.

Diabetes mellitus

Type 2 diabetes mellitus (DM) is a progressive disease that shows both insulin resistance and β -cell dysfunction (34, 35). Vitamin D deficiency may be effective in insulin resistance and type 2 DM pathogenesis by affecting both β -cell function and insulin sensitivity (36, 37).

Renal diseases

A study showed that vitamin D deficiency in patients undergoing haemodialysis is frequently observed and is associated with increased early mortality (38). Vitamin D deficiency is an expected result of chronic kidney diseases (39, 40). Treatment of vitamin D deficiency in patients with renal failure increases survival (41-43).

Respiratory diseases

Many studies have shown that there is a clear relationship between a decrease in 25(OH)D levels and respiratory tract infections (44-47). In epidemiological studies, an association between asthma and vitamin D deficiency has been detected, and there are prospective studies indicating that vitamin D deficiency is also present in children with asthma (48-51). In a comprehensive study conducted by Camargo et al. (52) in the cord blood of 922 neonates, the relationship between 25(OH)D levels and respiratory infections, wheezing and asthma were investigated, and while no relationship with asthma incidence was detected, it was found that it was inversely related to respiratory infections and childhood wheezing.

Obesity and ageing

Because vitamin D is oil soluble, it is quickly absorbed by fat cells. Due to the sequestration of vitamin D to the large fat mass, vitamin D deficiency can be observed in obesity (53). Thus, low serum 25(OH)D levels are known to be present in obesity (54). This is thought to be due to an increase in the immunoreactive parathyroid hormone (55, 56). On ageing, the level of 7-dehydrocholesterol in the skin decreases, and vitamin D₃-forming capacity of the skin also decreases (57).

Cancer and immunomodulation

Today, the role of vitamin D in immunomodulation is becoming increasingly important. Vitamin D is associated with many autoimmune diseases such as MS, type 1 DM, systemic lupus erythematosus, vasculitis and rheumatoid arthritis, in addition to cancer and cardiovascular diseases. It has been shown that $1,25(\text{OH})\text{D}_3$ suppresses the growth of cancer cells, induces apoptosis and reduces angiogenesis (12, 58).

It is also known that $1,25(\text{OH})\text{D}_3$ has an immunomodulatory effect on monocytes and activates T and B lymphocytes (59, 60). In many inflammatory diseases, high serum $25(\text{OH})\text{D}$ levels or vitamin D supplementation is known to reduce CRP and inflammatory cytokines levels and the erythrocyte sedimentation rate (61, 62).

Neurological and Psychiatric Diseases

Studies showing the neuroprotective effects of vitamin D are also available. In an animal study conducted by Baldi et al. (63), it was detected that in rats that had been fed with a vitamin D-deficient diet for 8 weeks, cortical and striatal infarct volumes were larger in a stroke created after cerebral artery occlusion. It was also noted that vitamin D deficiency increases the incidence of schizophrenia (64).

Pain

Vitamin D deficiency, as a cause of skeletal mineralization defects, can lead to widespread or regional joint and muscle pains. These symptoms can be confused with other diseases, such as degenerative joint diseases, fibromyalgia, chronic fatigue syndrome (4, 65). Fibromyalgia and chronic fatigue syndrome are among the most common diseases seen in pain clinics. Vitamin D deficiency is observed among bone metastases in cancer patients due to oral intake restriction and hormonal effects.

Intensive care

The role of vitamin D among intensive care patients has been frequently discussed in recent years. This is not only due to the immunomodulatory effect but also its relationship with chronic diseases such as DM, hypertension and chronic obstructive pulmonary disease. In a study conducted on intensive care patients whose $25(\text{OH})\text{D}$ vitamin levels were investigated, prolonged hospital stay, ICU re-admission within 90 days or the risk of 90-day mortality were evaluated, and a positive correlation was observed between serum $25(\text{OH})\text{D}$ level and prolonged hospitalization, ICU re-admission within 90 days and mortality (66).

In a retrospective study, sepsis and/or septic shock diagnosis and vitamin D levels of ICU patients when they were admitted to ICU and mortality rates within 30 days were compared between 2006 and 2011. In total, 65 (54%) out of 121 patients were found to have vitamin D deficiency, and the mortality rates of these patients were significantly higher (67). In a retrospective study, Turan et al. (68) evaluated the mortality rates of 3509 patients who underwent non-cardiac

surgery and their vitamin D levels and reported that high vitamin D levels significantly reduce mortality rates. It was deduced that vitamin D levels are associated with hospital deaths, serious infections and serious cardiovascular events. There are studies indicating that ICU patients with vitamin D deficiency and those patients who need ventilators show higher mortality (69).

All diseases mentioned above are conditions that can be encountered in every day anaesthesia practice. Although the effects of vitamin D deficiency were separately examined, there is no clear consensus on what the level of pre-anaesthesia blood values should be.

Conclusion

As anaesthetists, we might encounter patients having vitamin D deficiency or insufficiency before or during anaesthesia or those admitted to ICUs or algology units. In this article, we discussed the effects of vitamin D deficiency or insufficiency on many diseases. Perhaps, the determination of vitamin D levels in the pre-anaesthesia stage, in critical patients in particular, may have importance. Nevertheless, more studies that emphasize the importance of vitamin D in anaesthesia practice are required.

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