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Review

Assessment of Vitamin D in Sickle Cell Anaemia Patients

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Abstract

Background: Sickle Cell Disease (SCD) is a group of disorders of haemoglobin (Haemoglobinopathies) arising from inheritance of abnormal haemoglobin S (HbS) with consequent clinical presentation. It arises from a single-base change in the DNA where adenine is replaced by thymine this lead to the substitution of glutamic acid by valine at position 6 of the β-globin chain which leads to the production of a defective form of haemoglobin (Hb) and HbS.

Methods: Literature search was conducted from recognized online databases and libraries.

Results: Sickle Cell Anaemia (SCA) is the prototype and severe form of Sickle cell disease, a major public health problem in sub saharan Africa with high morbidities like bony alterations and bone fragility especially in those with vitamin D deficiency. Vitamin D (VD) is one of the nutritional concern for individuals with SCA, the outcomes of vitamin D deficiency are ricket and osteoporosis, in addition, VD enhances innate immunity and suppressing the excessive expression of proinflammatory cytokines a correlation between COVID-19 susceptibility.

Conclusion: Sickle cell anaemia patients have hypocalcaemic tendency associated with supranormal parathyroid hormone (PTH) and alkaline phosphatase (ALP), and imply impaired intestinal absorption of calcium and vitamin D leading to disturbed calcium metabolism which might contribute to the skeletal changes seen in sickle cell anaemia. This review article focuses on assessment of vitamin D in sickle cell anaemia patients.

Keywords: sickle cell anaemia, vitamin D, COVID-19, Alkaline phosphatase.

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Introduction

Sickle Cell Disease (SCD) is a group of disorders of haemoglobin (Haemoglobinopathies) arising from inheritance of abnormal haemoglobin S (HbS) with consequent clinical presentation (1). An autosomal recessive inherited genetic disorder that arises from mutation of β-globin gene caused by substitution of nitrogenous base adenine A by thymine T (GAG - GTG) at position 6 of the β globin chain in the shortarm of chromosome 11 (2). Sickle cell anaemia (SCA) is the prototype and severe form of SCD (1,3). SCD is the commonest single gene disorder worldwide (4). In Nigeria, the prevalence of SCA is about 1-3% in a population of over 160 million peoples (5,6). Highest frequency of SCA was found in tropical regions, particularly Sub Saharan Africa, India and the Middle East (7), SubSaharan Africa has the maximum burden of SCA, where 75% of the affected babies live, and the estimate suggested that 50-80% of these babies will die before adulthood (8).Vitamin D is a fat soluble lipophilic secosteroids molecule, in its active form responsible for intestinal absorption of calcium, synthesized in the skin from 7-dehydrocholesterol following exposure to UVB rays (spectrum 280-320nm) radiation from the sun (9). Various studies have shown that almost one billion people worldwide are vitamin D deficient (7), being recognized as significant health problem worldwide, even in regions with year–long adequate sunlight (7). The nutrient of concern for individuals with Sickle cell anaemia is vitamin D, vitamin D plays a key role in cell growth and differentiation, as well as, musculoskeletal health in SCA patients (10). Various studies have reported that, SCA patients have lower concentrations of 25-hydroxyvitamin D and an increased prevalence of vitamin D deficiency (11,12), which may be worsened by increased erythropoiesis and basal metabolic rate (11), inadequate dietary intake and decreased nutrient absorption due to inflammatory damage of the intestinal mucosa (13). Similarly, age, race, body mass index, latitude, diet, sunlight exposure, and skin pigmentation are all factors influencing vitamin D status (14). Vitamin D and calcium are required for optimal bone health with 90% of required vitamin D synthesis coming from exposure to sunlight, due to complications of this chronic inflammatory disease associated with chronic haemolysis, vaso-occlusion, and tissue hypoxia, bone metabolism is adversely affected in SCA patients (15). Painful Vaso-occlusive crises or osteomyelitis are the acute clinical manifestations of SCD, while osteonecrosis, osteoporosis and osteopenia and progressive organ damage can be seen in long term complications which constitutes major health challenges in the management of the disease (9). Other factors that play role in bone health are parathyroid

hormone PTH and alkaline phosphatases ALP (16). Vitamin D promotes calcium absorption from the gut and facilitates mineralization of bone (17), thus, in condition like SCA associated with deficiency of vitamin D, calcium absorption from the gut is impaired and bone mineralization is compromised (18). Alteration in calcium homeostasis lead to bone mineral diseases (19) and in SCA bone mineral disease have been linked to low level of vitamin D (20), The aim of this article is to assess vitamin D Level in SCA patients.

Vitamin D production and metabolism

Most related compounds of vitamin D are D2 (ergocalceferol) and D3 (cholecalciferol). Certain plants and fungi produce vitamin D2, while vitamin D3 is synthesized by animals (e.g., fish, birds, vertebrates) and within the human skin from 7-dehydrocholesterol (7-DHC) following exposure to UVB rays (spectrum 280-320nm) radiation from the sun (9). Together vitamins D2 and D3 are inactive prohormones that binds to vitamin D-binding protein, transported to the liver and converted to 25-hydroxyvitamin D (25(OH)D) by an enzyme 25-hydroxylase or CYP 2R1 located in the endoplasmic reticulum which undergoes further hydroxylation by another enzyme 1,25-dihydroxylase/ 1α- hydroxylase /CYP 27B1 a mitochondrial enzyme in the kidney to form active metabolite 1,25-dihydroxyvitamin D (1,25(OH)D), this step is regulated by calcium and phosphate concentrations through parathyroid hormone (PTH) (7) and is the active metabolite that is involved in many physiological processes. The whole of the (25(OH)D) 2or 3 in the serum or plasma is referred to as total 25- hydroxyvitamin D (calcidiol) which is the inactive form of vitamin D (28) is the best indicator of total body vitamin D storage because of its half-life (2-3 weeks), more than 1,25(OH)D (calcitriol) and is the active form of vitamin D with half –life (8-12 hours), similarly, actions of 25OHD and 1,25 (OH)D are catabolized by CYP 24A1.

Vitamin D Mechanism of Action

There are two fundamental mechanisms by which active vitamin D regulates the process of intestinal calcium absorption this are the genomic and non genomic actions (21). active vitamin D is a ligand for vitamin D receptors which are nearly found in every tissue, has ability to influence VDR transcriptonal activity through effects on retinoid X receptor (RXR) heterodimerization and /or co-modulator recruitment (21) which binds with vitamin D response element (VDRE) located on the regulatory sequence of the target gene and brings about transcription of transient receptor potential cation channel super family V member 6 (TRPV6) of the intestinal cell leading to formation of critical calcium transport channel which help in calcium absorption in the intestine (Genomic). Nongenomic actions involves the biological response of transcaltachia (rapid hormonal stimulation of intestinal calcium transport), the study of transcaltachia involves the vascular perfusion of the duodenum of vitamin D-replete chicks (22). Calcium moves through the brush border membrane and become localized in lysosomal vesicles by a process that may involve endocytosis. After uptake into the cell and movement of the calcium across the cell in the lysosomal vesicles, the transported calcium exits across the basal lateral membrane by an exocytosis process.

Vitamin D deficiency and COVID-19 susceptibility

Hypovitaminosis D (insufficiency & deficiency of vitamin D) as 25OHD less than 75nmol/L or 30ng/mL as insufficiency, deficiency of vitamin D as less than 50nmol/ L or 20ng/mL and severe vitamin D deficiency as less than 25nmol/L or 10ngmL (23). Mostly, vitamin D decreases the risk of microbial infection by immuno-modulating innate and adaptive immunity through production of several antimicrobial peptides (cathelicidins, defensivins and IL-37) and suppresses the excessive expression of proinflammatory cytokines (eg IL-6, TNF-alpha, and interferon gamma) and controlling the response mediated by Th1 lymphocytes (24), which is less effective in vitamin D deficiency. Vitamin D has a vital effect on enhancing the expression of Angiotensin – converting enzyme 2 (ACE-2) an important receptor facilitating the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (25), also enhance the expression of antioxidation-related genes. Hypovitaminosis D is associated with cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome, cancer, increased death rates, depression, decrease cognitive functions, preeclampsia, tuberculosis and HIV (25). Vitamin D deficiency is prevalent among those living at higher latitudes or with inadequate sun exposure, advanced age, obese individuals, and vegans (26). There is no presently scientific consensus about the optimal dose of vitamin D supplementation for COVID-19. However, the Institute of Medicine has placed the recommended daily allowance (RDA) for vitamin D at 600 IU per day up to 70 years of age, thereafter 800 IU per day for those older than 70 years (27), but this was reference for bone health (conversion: 1µg = 40 IU and 0.025 µg = 1 IU, 100 IU of D2 or D3 raises serum 25OHD by only 1ng/mL = 2.5 nmol/L).

Laboratory evaluation of vitamin D

There are two main circulating forms of vitamin D: 25-hydroxyvitamin D (25-OHD) and 1,25-dihydroxyvitamin D (1,25 $(OH)_2D$) in the serum measured in nanogram per milliliter/nanomol per liter (1ng/mL = 2.5 nmol/L) (29). When assessing vitamin D status, measure serum 25- hydroxyvitamin D

concentration as this reflects total body vitamin D reserves hence the barometer for vitamin D status (28,29). 25-OHD is the only vitamin D metabolite that is used to determine whether a patient is vitamin D deficient, sufficient, or intoxicated (28), and is the major circulating form of vitamin D that has a half-life of approximately 2-3 weeks (30), hence is the summation of both vitamin D intake and vitamin D produced from sun exposure (28). The circulating concentration of 25-OHD is almost 1000-fold higher than the concentrations of 1,25- $(OH)_2D$. Serum 1,25-dihydroxyvitamin D provides no information about vitamin D status and is often normal or even elevated due to secondary hyperparathyroidism associated with vitamin D deficiency (29), as such is not useful marker for vitamin D intake and cutaneous synthesis or for correlation with health outcomes due to its short serum half-life 8-12 hours (30) and not regulated by vitamin D intake but by other factors such as parathyroid hormone (PTH). PTH regulates calcium metabolism by increasing tubular reabsorption of calcium in the kidney, increasing mobilization of calcium from the skeleton and by increasing the renal production of 1,25 $(OH)_2D$ (28). Vitamin D binding protein (DBP) is used to measure circulating levels of 25-(OH)D and 1,25 (OH)D in the circulation (30), similarly, various methods were introduced(31). Initial methods for measuring 25-OHD such as, liquid chromatography or composite protein binding/radioimmunoassay (RIA) were burdensome and also recognized other polar metabolites to the same extent as such typically overestimated 25 (OH)D levels by approximately 10-20% and not suited to routine laboratory analysis (31). To remove interfering vitamin D metabolites, simple preparetive chromatography was developed to separate 25-(OH)D from more polar metabolites that interfered with the assay. In the mid-1970`s, high- performance liquid chromatography (HPLC) was applied to the 25- (OH)D assay (31), HPLC was considered to be the gold standard but was cumbersome assay, thus not routinely used by reference laboratories for clinical samples, however, liquid chromatography tandem mass spectroscopy (LC-MS) was applied for the direct measurement of 25-(OH)D which quantitatively measured both 25-(OH)D2 and 25-(OH)D3 respectively (32).

Conclusion

Bone diseases are commonly reported in SCA patients and have been increasingly associated with VDD. Hypovitaminosis D has been described as an epidemic in recent years and its association with higher risk of COVID-19 infection and cardiometabolic alterations such as dyslipidemia, obesity, metabolic syndrome, arterial hypertension and diabetes. Therefore, keeping appropriate blood levels of Vitamin D through supplementation or through sunshine exposure is recommended for the public to be able to cope with the pandemic. There is need for periodic serum VD evaluation in healthcare management of skeletal disorders and nutritional review status of the SCA, this may provide additional information for pathogenesis of bone loss in SCA, and will help in diagnosis and treatment thereby improving the quality of life.

Conflict of interest

None declared.

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