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Mini-Review

Parathyroid hormone abnormities in sickle cell anemia patients

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Abstract

Sickle cell anemia (SCA) is an inherited autosomal recessive blood disorder, characterized by the presence of sickle hemoglobin (HbS) that imparts sickle shape to RBC under low oxygen tension. SCA is a fatal multisystem disorder that exhibits extraordinary degree of phenotypic variability. Despite the high mortality and morbidity associated with complication in SCA patients, there is limited information on the abnormalities of parathyroid hormone (PTH). Therefore, the purpose of this study was to describe the abnormalities of PTH in SCA patients. We searched Medline, Embase, the Cochrane Library, and observational studies relating to the parathyroid hormone, PTH, hyperparathyroidism and SCA. The hypocalcemia found in SCA patient is thought to be a reflection of parathyroid gland abnormalities and failure to activate vitamin D. This information will help future research and eventually will improve diagnosis, prognosis, and management of PTH abnormities in SCA patients.

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Introduction

Sickle cell anemia (SCA) is an inherited autosomal recessive blood disorder, caused by A>T transversion in sixth codon of HBB gene. SCA is characterized by the presence of sickle hemoglobin (HbS) in red blood cells (RBCs) that assume sickle shape under low oxygen tension (1). Patients with SCA experience more frequent pain crises, which contributes to high morbidity and healthcare expenditure (2). SCA is a fatal multisystem disorder that exhibits complications in a number of organs including the spleen, liver, skin, eyes, lungs, kidney cardiovascular system, central nervous system, genitourinary system and skeletal system (3). Patients with SCA show an extraordinary degree of phenotypic variability and differ in the involvement of organ systems and in complications (4). However, early detection, preventive measures, and disease-modifying therapies made once-fatal SCA as a chronic disease. Acute hemolysis with oxidant stress is one the most common manifestation of SCA. Several lines of research suggest that oxidative stress is responsible for the secondary dysfunctions in SCA patients (4). Different population studies showed that more than 65% of adult patients with SCA have low bone mineral density (BMD) (5). Local hypoxia and oxidative stress leads to the increased osteoclast activity and osteoblast impairment in SCA patients with osteopenia and osteoporosis (6).

Bone metabolism and serum mineral homeostasis are regulated by parathyroid hormone (PTH) in coordination with intestine and kidney. Further, the anabolic effect of PTH in bone metabolism was demonstrated in several studies (7-9). Classical actions of PTH in maintaining the extracellular calcium homeostasis are depicted in Figure 1. PTH is involved in maintaining ionized calcium and excessive secretion of PTH is called hyperparathyroidism which increase in blood calcium levels. This occurs either as primary (due to cancer or gland cell hyperplasia), or secondary hyperparathyroidism (SHPTH) (other conditions that increase PTH production).

Methods and Materials

Despite the high mortality and morbidity associated with complication in patients, there is limited information on the abnormalities of PTH. Therefore, the purpose of this study was to describe the abnormalities of PTH in SCA patients. We searched Medline/PubMed, Embase, the Cochrane Library, Scopus, and observational studies relating to the parathyroid hormone, PTH, hyperparathyroidism and SCA.

Parathyroid disorders in sickle cell disease

A random case of primary hyperparathyroidism (PHPTH) due to left parathyroid adenoma was documented in a patient with sickle cell disease (10). Decrease in pain episodes upon treatment of PHPTH in SCA patient

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Implication for health policy/practice/research/ medical education

This study helps in understanding the extent of parathyroid hormone abnormalities in sickle cell anemia patients. Hypocalcemia and hyperparathyroidism are commonly seen in sickle cell anemia patients. The complications of hyperparathyroidism overlap with symptoms of vaso-occlusive crises in sickle cell anemia patients.

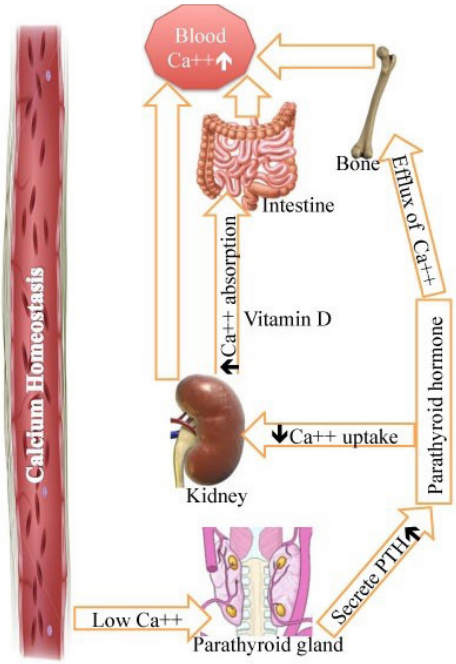

Figure 1. Schematic representation of the classical actions of PTH to maintain extracellular calcium homeostasis

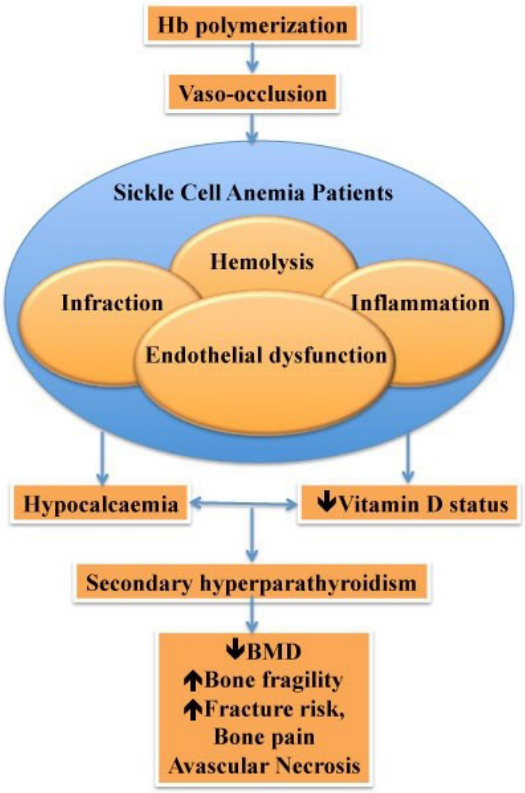

Figure 2. Schematic representation of the causes and manifestations SHPTH in sickle cell anemia.

indicating that the PHPTH mimics the vaso-occlusive crisis in SCA (10). Significant improvement in experience of pain after parathyroidectomy in SCA patients, demonstrated the role of PTH in pain modulation (11). SHPTH in SCA patients can occur due to any condition that causes chronic hypocalcaemia. Lower serum calcium level in SCA patients was documented in several studies (12-15). In Saudi Arabian HbSS patients, hypocalcaemia and SHPTH are linked to poor vitamin D status (13). However, no such relationship between hypocalcaemia and PTH or vitamin D status in SCA patients living in the tropical island of curacao was observed (12). SHPTH in SCA patients can occur due to any condition that causes chronic hypocalcemia. Further, a persistent or intermittent hyperphosphatemia was found in adult SCA patients (16,17). SHPTH in SCA patients is mainly due to vitamin D deficiency (Figure 2) and the symptoms are mainly bone fragility with increased fracture risk, myopathy and some patients may have bone pain (18,19).

High blood levels of PTH increase the influx of calcium into RBC and affect their survival by altering the osmatic fragility (20). Repeated sickling and unsickling cycles results in the decreased osmatic fragility of the erythrocytes that leads to anemia (21). Further analysis of osmatic fragility curves of both fresh and incubated RBC of SCA patients revealed a leftward shift in osmotic fragiligram compared to Hb-AA and Hb-AS RBCs (22). SHPTH might be one of the possible causes of anemia in SCA patients. In support of this, a significant increase of mean point perivascular fibrosis was noted in the arterial vessels of the bone marrow in SCA patients (23). In addition to this, ineffective erythropoiesis in SCA patients was demonstrated using molecular analysis of chimerism in peripheral blood and bone marrow (24).

As bone remodeling is a crucial process for calcium regulation, hyperparathyroidism in SCA patients can stimulate bone demineralization. More than 65% of adult patients with SCA suffer from low BMD due to erythropoietic stress and subsequent bone marrow hyperplasia (25). Children receiving hydroxyurea for at least 6 months were more likely to have an abnormal BMD, which is independent of gender, age and menopause (26). Evaluation of risk factors for poor bone mineralization in children with SCA revealed significant deficits in dietary calcium and circulating vitamin D levels (5,27). In contrast to this BMD was not related to calcium intake, vitamin D status in sickle cell disease patients (28). However, vitamin D deficiency and SHPTH was found in 72% and 38% respectively in these patients (28). Further, low

BMD in SCA contribute to the development of avascular necrosis (29). Adult SCA patients showed decreased PTH compared to controls and this PTH correlated positively with BMD (30). In addition to the hyperparathyroidism, adult SCA patients of Bahrain showed several endocrine dysfunctions such as *in vivo* hypoadrenalism, hypogonadism and hypothyroidism (31).

Management of PTH abnormalities in SCA

Imaging studies are not routinely used in the assessment of SHPTH. Serum intact PTH, 25-hydroxyvitamin D, calcium and phosphate level should be determined to monitor SHPTH. Vitamin D sufficiency can be achieved using various forms of vitamin D formulations such as calcitriol, doxercalciferol and paricalcitol (32). To achieve the prescribed target levels serum phosphate, dietary inorganic phosphate restriction and phosphate binders such as calcium carbonate and calcium acetate can be used (33). Lower leukocyte vitamin C levels indicated vitamin C deficiency in SCA patients (34,35). As vitamin C interacts with the calcium sensing receptors on parathyroid cells, there exists a relationship between high plasma vitamin C and low level of PTH (36). However, SHPTH treatment with vitamin C supplementation warrants further discussion. SCA patients with extremely high serum PTH levels fail to respond to above treatment options, needs partial or total parathyroidectomy (11).

Conclusion

SCA commonly encountered with several bone disorders such as dactylitis, avascular necrosis of the head of the femur, osteomyelitis and most often with bone pain. Hypocalcemia found in SCA patient is thought to be a reflection of parathyroid gland suppression and failure to activate vitamin D. Consultation with a pediatric or adult endocrinologist is often essential for long-term management of hyperparathyroidism and to improve the quality of life in SCA patients.

Authors' contribution

Both BVKSL and AN contributed equally. All authors read and signed the final paper.

Conflicts of interest

There are no conflicts of interests.

Ethical considerations

The authors of this manuscript declare that they have completely observed the ethical requirements for this communication.

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