Effect of Vitamin D Supplementation on Clinical Outcomes of Sickle Cell Disease

Thesis

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List of Abbreviations

Abb.	Full term
BMI	*Body mass index*
CBC	*Complete blood count*
CT	*Computed tomography*
FDA	*Food and Drug Administration*
HbS	*Hemoglobin S*
HbSC	*Sickle cell hemoglobin C disease*
HbSE	*Sickle cell hemoglobin E disease*
HbSβ	*Hemoglobin S beta thalassemia*
HPLC	*High performance liquid chromatography*
HPLC	*High–performance liquid chromatography*
LDH	*Lactate dehydrogenase*
MARRS	*Membrane-associated rapid response steroid binding protein*
NO	*Nitric oxide*
PCV	*Packed cell volume*
PTH	*Parathyroid gland*
ROS	*Reactive oxygen species*
SCA	*Sickle cell anemia*
SCD	*Sickle cell disease*
VDD	*Vitamin D deficiency*

INTRODUCTION

Sickle cell disease (SCD) is caused by a mutation at the sixth codon of the beta-globulin hemoglobin gene, generating abnormal hemoglobin called hemoglobin S (HbS). The manifestations of SCD are due to the presence of HbS, of which molecules are organized into polymeric beams when deoxygenated and give the RBC an elongated and rigid sickle-shaped red blood cell ***(Zago et al., 2007).***

Vaso-occlusive crises are the most common type of crisis. It may be precipitated by cold, infection, dehydration, exertion or ischemia. Occlusion of small vessels by sickled erythrocytes causes pain that is variable from mild to severe. Patients may present with swollen painful joints, signs of lung involvement, neurological signs, acute abdominal distension and pain, loin pain (renal papillary necrosis), priapism and retinal occlusion ***(Brousse et al., 2014).***

Children with sickle cell anemia have a higher risk of developing nutritional deficiencies due to reduced appetite ***(Mitchell et al., 2004).*** Poor dietary intake of nutrients and infectious complications demand greater attention from health professionals. Among the vitamins, vitamin D must be carefully evaluated in children with sickle-cell anemia ***(Kawchak et al., 2007).***

Vitamin D (25-hydroxyvitamin D) deficiency has emerged as a public health focus in recent years for its contribution to adverse skeletal and extra-skeletal manifestations. Moreover, individuals living with SCD reportedly have a high prevalence of vitamin D deficiency, but data are limited with respect to possible associations between low vitamin D and acute vaso-occlusive complications ***(Lee et al., 2015).***

AIM OF THE WORK

The current study is a follow-up prospective study aimed to:

1. Assess the level of vitamin D in SCD patients
2. Assess the effect of vitamin D supplementation on the clinical outcome of SCD including; frequency of vaso-occlusive crisis and hospital admission and rate of infections.

SICKLE CELL DISEASE

Sickle cell disease (SCD) is a hereditary hemoglobinopathy characterized by a single point mutation in the 6th codon leads to substitution of glutamic acid for valine, resulting in the formation of hemoglobin S (HbS) production ***(Schnog et al., 2004)*** leading to hemolytic anemia and intermittent occlusion of small vessels, chronic organ damage, and organ dysfunction ***(Smiley et al., 2008).***

The term SCD refers to all hematological sickling disorders including sickle cell trait (SCT) (HbAS), sickle cell anemia (SCA) (HbSS), sickle cell hemoglobin C disease (HbSC), sickle cell hemoglobin E disease (HbSE) and hemoglobin S beta thalassemia (HbSβ) ***(Stuart and Nagel, 2004).*** The clinical manifestations of SCD may fall into two partially overlapping sub-phenotypes characterized chronic hemolytic anemia and vaso-occlusive complications ***(Kato et al., 2007)***. The type and severity of complications vary significantly between individuals from mild symptoms to serious life threatening complications ***(Stuart and Nagel, 2004).***

Incidence and geographic distribution:

These inherited disorders of hemoglobin are the most common gene disorders, and it is estimated that 7% of the world's population are carriers. Approximately 300.000

children world wide are born with documented SCD every year. Sickling disorders are found frequently in the Afro-Caribbean populations and sporadically throughout the Mediterranean regions, India, and the Middle East ***(Jeremiah, 2006).***

Four region-specific African haplotypes (the Senegal, Benign, Bantu, and Cameron haplotypes) and one Asian haplotype (the Arab-India haplotype) have been defined ***(Rees et al., 2010).***

In Egypt, along the Nile Valley, the HbS gene is almost non existent, but in the western desert near the Libyan border variable rates of 0.38 per cent in the coastal areas to 9.0 per cent in the New Valley oases have been reported. HbS carrier rates vary from 9 to 22 per cent in some regions ***(Jeremiah, 2006).***

Pathophysiology:

A) HbS Polymerization:

Polymerization of HbS and cell sickling are the prime pathophysiological events in SCD. So; Oxygen tension and intracellular HbS concentration are the primary molecular drivers of this process ***(Archer et al., 2015).*** The rate and extent of HbS polymerization is proportionate to the extent and duration of hemoglobin deoxygenation that is affected by co inheritance of genetic factors which modify the intracellular

HbS or HbF concentration for example; the co-inherited of α-thalassemia or hereditary persistence of HbF ***(Rees et al., 2010).***

B) Vaso-occlusion "Cell Sickling":

Sickle cell adhesion

It is generally believed that vaso-occlusion develops from adhesion of sticky sickle cell RBCs to endothelium followed by trapping and polymerization of rigid less deformable cells as intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1 and selectins. All interact with endothelial cells, RBCs and variety of soluble proteins within plasma, such as; thrombospondin (from platelets) and Von Willebrand factor from endothelial cells to mediate vasoocclusion within macro-and microvasculature ***(Kato et al., 2006).***

Role of Inflammation

It enhances the expression of adhesion molecules, further increasing the tendency of sickled erythrocytes to adhere to the vascular endothelium and worsen vaso-occlusion ***(Rees et al., 2010).*** Ischemia-reperfusion injury release free hemoglobin and heme secondary to RBCs lysis and increased placental growth factor (PLGF) production, all may be contributing to the inflammatory vasculopathy. Reperfusion of ischemic tissue promotes chronic inflammation by increased oxidative damage and adhesion of leukocytes (mainly neutrophils) to the

endothelium followed by extravasation into the tissues and damage tissues ***(Manawani and Frenette, 2013).***

Oxidative stress

The cycles of ischemia-perfusion injury causing activation of xanthine-xanthine oxidase system that disturbs normal redox state promoting intravascular oxidant stress and disrupting nitric oxide (NO) homeostasis. So; the oxidation that is mediated by oxidants and free radicals which is called reactive oxygen species (ROS) are formed as a byproduct of oxygen metabolism and nitric oxide. The increase in the normal redox state of a cell because toxic effects resulting in cell and tissue damage ***(Rees et al., 2010).***

C) Hemolysis:

It is caused by HbS polymerization and it is evidenced by its development of progressive vasculopathy ***(Kato et al., 2006).*** Hemolysis results in the release of Hb and arginase from erythrocytes increasing the consumption and decreasing production of NO respectively ***(Rees et al., 2010).***

Clinical Features and Complications

The major features are related to hemolytic anemia and vaso-occlusion, which can lead to acute & chronic pain and tissue ischemia or infarction ***(Vichinsky, 2016).***