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Editorial Open Access

# Supplementation of Vitamin D in Patients with Sickle Cell Bone Disease: A D-bate or a Combate?

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## Editorial

After its discovery as a genetically inherited hemoglobinopathy one hundred years ago, finding a widely available cure for sickle cell anemia (SCA, HbSS) still remains a challenge and the disease requires multi-disciplinary theranostic approaches (Menaa et al., 2013; Menaa, 2014). Indeed, more effort and resources to promptly find alternative therapeutics and/or adjuvants (e.g. nutraceutics) to HU, the orphan Food and Drug Administration (FDA)-approved drug, are mandatory as a means of decreasing mortality, morbidity and improving quality of life among SCA patients (Hyacinth et al., 2010; Jackson et al. 2012; Menaa et al., 2013; Ozen et al., 2013; Menaa, 2014).

Importantly, since over three decades, a growing body of studies (Curcic et al., 1977; Mohammed et al., 1993; van der Dijs et al., 1997; Buison et al., 2004; Lal et al., 2006; Adewoye et al., 2008; Rovner et al., 2008; Chapelon et al., 2009a, 2009b; Sadat-Ali et al., 2011, Osunkwo et al., 2012; Garrido et al., 2012; Arlet et al., 2013; Ozen et al., 2013; Adams-Graves et al., 2014; Kaza and Moulton, 2014; Wykes et al., 2014) have reported links between deficiency in vitamin D (25-hydroxy vitamin D; 25-OHD, de facto a hormone), an endocrine organ dysfunction commonly detected in SCA patients, and its health consequences. Thereby, it has been globally showed that children, adolescents or adults patients with SCA (up to 65%) have higher susceptibility/prevalence (i.e. about 3-4 times) of more profound deficiency in vitamin D (i.e. serum level < 15 ng/mL) than healthy individuals (i.e. up to 90% with serum levels < 30 ng/mL) (Rovner et al., 2008; Chapelon et al., 2009a, 2009b; Osunkwo et al., 2011; Jackson et al., 2012). Nevertheless, genetics, social, geographical, seasonal, nutritional and physiological influences, among others, are interconnected and contribute to the life adaptation, specie evolution, chronic diseases epidemiology and their clinical complexity (Russel and Russel, 1983; Donovan, 1984; Buison et al., 2004). Hence, one should always avoid any generalization considering that sometimes HbSS patients matched with HbAA control patients may elicit no significant differences in vitamin D levels (van der Dijs et al., 1997), and a slight bone mineral density (BMD) decrease could be found in SCA pre-adolescent female children independently of disease severity, vitamin D deficiency, low calcium intake or bone hyper-resorption but maybe due to abnormal bone formation (Chapelon et al., 2009b).

In general, the etiologies of vitamin D deficiency are poorly defined in SCA patients (e.g. often attributed to increased skin melanin concentrations, lower dietary intake, reduced levels of physical activity, highly prevalent bone resorption markers), but often result in bony changes and bone fragility (e.g. rickets, osteomalacia, incomplete ossification, low BMD, osteoporosis, osteonecrosis, fracture risk, chronic musculoskeletal pain and weakness, low BMD associated-vasoocclusive crises, hyperparathyroidism) (Chapelon et al., 2009b; Garrido et al., 2012; Menaa et al., 2013; Ozen et al. 2013; Arlet 2013; Wykes et al., 2014). Although vitamin D is essential for normal absorption of calcium, for calcium and bone mass homeostasis, the significance and optimal means of correction of vitamin D deficiency were poorly studied. Hence, it is worth to note that due to the lack of prospective and randomized studies in these patient populations, there are currently not enough recommendations for macro- or micronutrients (e.g. calcium and vitamin D) supplementation (e.g. ergocalciferol aka vitamin D2 which is found in vegetables, cholecalciferol alias vitamin D3 which is present in some fishes and meats) in this population. Interestingly, a recent study (Wykes et al., 2014) showed that: (i) 91% of children had vitamin D levels lower than 20 ng/mL; (ii) intramuscular ergocalciferol (7729 IU/Kg) and oral cholecalciferol (5234 IU/Kg) supplementations resulted in significant increases (2.82 versus 6.44 ng/L/IU/Kg, respectively) of vitamin D blood concentration to normal levels during 4 months when administrated for about 4 days, suggesting a much better increment with oral cholecalciferol compared to intramuscular ergocalciferol. This study is in line with another recent clinical investigation (Osunkwo et al., 2012) which compared a 6-week course of oral high-dose cholecalciferol (4000-100 000 IU per week) with a placebo, and showed that cholecalciferol achieved higher serum vitamin D level in SCA subjects that subsequently experienced fewer pain days per week and had higher physical activity quality-of-life scores. Besides, other pertinent studies show that treatment of adult SCD with vitamin D and calcium can restore vitamin D levels to normal and improve BMD, albeit markers of bone resorption remained unchanged (Adewoye et al., 2008). Also and consistently, treatment with high-dose vitamin D resulted in complete resolution of chronic pain symptoms and improvement in BMD (Osunkwo, 2011; Arya and Agarwal, 2012).

Eventually, clinical recommendations contribute to the creation of many opportunities for possible therapeutic and chemopreventive applications. These shall include early interventions and routine check-ups in SCA patients, such as: (i) blood levels monitoring of parathyroid hormone (PTH) which serum concentrations are expected to be supranormal, 25 Hydroxyvitamin D (25OHD) synthetized in liver from skin or Vitamin D2/D3 supplementation and 1,25 Dihydroxyvitamin D (1,25(OH)2D) subsequently generated in liver, calmodulin (CaM) and calcium (Ca2+) due to hypocalcaemic tendency, as well as markers of bone resorption and formation (e.g. C-terminal telopeptides of pro-collagen type I, type I-collagen, bone-specific alkaline phosphatase, osteocalcin); (ii) BMD estimation by dual-energy X-ray absorptiometry (DXA) at lumbar spine and proximal femur/femoral neck, lumbar spine, and distal third of the ulna plus radius; (iii) determination of each patient´s habits (e.g. solar exposition which should be about 20-30 minutes daily without anti-UV cream; nutrition including vitamin D supplementation (≥ 10.000 UI cholecalciferol every week, although the optimal dosing remains to

be determined in spite of its wide safety window). In this regard, it is important to keep in mind that the presence of pro-drugs (e.g. butyrate, phenylbutyrate) can enhance vitamin D systemic bioavailability (Newmark and Young, 1995), and so, shall be vitamin D dosing shall be tailored in a personalized fashion according to blood vitamin D concentrations of each patient in order to avoid any adverse-effects ("hypervitaminose D"); Physical activity (e.g. running or walking about 30 minutes per day); Social life considerations (e.g. stimulation/coaching the SCA patients for better social interactions).

Further studies in SCA patients are warranted to evaluate the effects of vitamin D repletion on clinical outcomes such as bone density, chronic musculoskeletal pain, and functional status. In addition to randomized and prospective studies, genomic and epidemiological investigations as well as meta-analyses shall be of a great help to better prevent SCA complications, efficiently and safely manage patients with sickle cell bone disease in a personalized manner…

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