Vitamin D deficiency and chronic pain in sickle cell disease

Recent studies report a high prevalence of vitamin D deficiency (VDD) among patients with sickle cell disease (SCD), with rates as high as 65–100% depending on the season (Buison *et al*, 2004; Lal *et al*, 2006; Adewoye *et al*, 2008; Rovner *et al*, 2008; Chapelon *et al*, 2009). Despite this evidence, VDD remains both under-recognized and under-treated in patients with SCD.

There appears to be substantial overlap between the symptoms of chronic pain seen in SCD and VDD. In both conditions, pain is commonly localized to the lower spine, pelvis and extremity bones and described as a dull, aching pain exacerbated by activity and weight bearing (Gloth & Greenough, 2004; Holick, 2007; Lofti *et al*, 2007; Straube *et al*, 2009). Both conditions are associated with an increased risk of low bone mineral density (BMD). Additional symptoms of VDD include muscle weakness, increased risk of falls and a predisposition to micro- or macro fractures (Holick, 2007).

Though the relationship between vitamin D and chronic pain has yet to be fully understood, supplementation of vitamin D may serve a dual role in SCD patients by helping to improve both bone health and the chronic pain experience. Several studies have shown that the treatment of VDD led to improvement in pain symptoms and decreased the use of pain medications in non-sickle cell subjects with chronic pain (Gloth & Greenough, 2004; Straube *et al*, 2010). However, there has been no evidence to date implicating VDD to the adverse bone health outcomes seen in SCD. We therefore sought to determine the role, if any, of VDD in shaping the chronic pain experience of children and adolescents with SCD.

Between January 2008 and January 2010, we evaluated 25-hydroxy vitamin D (25OHD) levels among 53 patients with SCD. All patients were in their steady state and were not experiencing an acute vaso-occlusive crisis (VOC) at the time of evaluation. Patients were selected because of frequent clinic visits due to the presence of either chronic pain, suspected or confirmed bone fragility, or other complications of SCD. In this study, chronic pain was defined as self-reported pain on

Table I. Summary of subject characteristics for all subjects and subjects with and without chronic pain respectively.

$n = 53$	All subjects $n = 53$ (%)	Chronic pain $n = 17$ (%)	No chronic pain $n = 36$ (%)	P value
Age distribution (years)	1–19	15·8 ± 0·6	10·3 ± 0·9	0·0003
Female sex	30 (57)	12 (71)	18 (50)	0·1642
Genotype				
Hb SS	40 (75)	14 (82)	25 (72)	NS
Hb SC	11 (21)	2 (12)	9 (25)	NS
Hb SB+	2 (4)	1 (6)	1 (3)	NS
Haemoglobin g/l	97 ± 14	94 ± 14	98 ± 14	NS
Reticulocyte count	10·2 ± 5·2	10·29 ± 5·71	10·18 ± 4·98	NS
On hydroxycarbamide (%)	27 (51)	14 (82)	13 (36)	0·0028
25OHD levels (nmol/l)	30·9 ± 16·55	21·2 ± 8·2	37·1 ± 18·8	0·0021
Insufficient (52·5–75 nmol/l)	8 (15)			
Deficient (30–50 nmol/l)	17 (32)			
Severely deficient (15–27·5 nmol/l)	21 (40)			
Profoundly deficient (≤12·5 nmol/l)	7 (13)			
Radiographic bone fragility	22 (42)	14 (82)	8 (22)	<0·0001
Avascular necrosis	16 (30)			
Compression spine fractures	6 (11)			
Frequent vaso-occlusive crisis	22 (42)			
Bone mineral density (DEXA)	13			
Normal	5 (38)	4 (80)	1 (20)	NS
Low (osteopenia/osteoporosis)	8 (62)	7 (88)	1 (12)	NS

DEXA, dual energy X-ray absorptiometry; NS, not significant.

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50% or more days per month with or without daily use of analgesics. We excluded any subject with chronic renal disease and other chronic pain syndromes, such as juvenile rheumatoid arthritis. Vitamin D insufficiency was defined as serum 25OHD <75 nmol/l; vitamin D deficiency (VDD) was defined as serum 25OHD 30–50 nmol/l; severe VDD was defined as serum 25OHD 15–27·5 nmol/l; and profound VDD was defined as serum 25OHD <12·5 nmol/l (Holick, 2007). Bone fragility refers to radiographic evidence of either avascular Necrosis of joint(s) or vertebral compression fractures. BMD was assessed by dual energy X-ray absorptiometry (DEXA) for whole body (WB) and lumbo-sacral spine (LS) using the LUNAR Prodigy model. Low BMD was defined as a *z*-score ≤−2.

The mean age of the subjects was 12 ± 5·5 (range 1–19) years; 57% were female and 75% were homozygous SS (Table I). Thirty-two per cent of subjects had chronic pain, nearly half of subjects (42%) had radiographic evidence of bone fragility, and 52% were on hydroxycarbamide disease-modifying therapy. Of the 13 subjects who underwent DEXA scans, eight had a low BMD. All subjects had abnormally low levels of 25OHD; the mean 25OHD level was 31 ± 16·5 nmo/l. Fifteen per cent of patients were vitamin D insufficient, 32% were deficient, 40% were severely deficient and 13% were profoundly deficient. These findings were consistent with those of other studies (Lal *et al*, 2006; Adewoye *et al*, 2008; Rovner *et al*, 2008; Chapelon *et al*, 2009).

Chronic pain was associated with significantly lower 25OHD levels when compared to those without chronic pain (21·2 ± 8·2 vs. 36 ± 17·5 nmol/l; $P = 0{\cdot}0021$, Table I). Bone fragility was also associated with lower 25OHD levels (23·7 ± 11·5 vs. 36·7 ± 17·7 nmol/l; $P = 0{\cdot}0045$). Among patients with chronic pain, none had chronic leg ulcers. There was no difference in 25OHD levels between subjects who were or were not taking hydroxycarbamide. Furthermore, 25OHD levels did not correlate with haemoglobin, reticulocyte count, genotype, or BMD. Subjects with chronic pain were more likely to be older, taking hydroxycarbamide, and have evidence of bone fragility (Table I). We did not evaluate the effect of acute illness on 25OHD levels but there was no significant correlation between number of VOC and 25OHD levels ($P = 0{\cdot}728$).

This is the first study to associate VDD with clinical features of poor musculoskeletal health (chronic pain, avascular necrosis, spine compression fractures) in patients with SCD. Our population had a higher rate of chronic pain (32%) and use of hydroxycarbamide (52%) compared to most pediatric SCD cohorts. This is due at least in part to the selection of patients who were seen frequently in clinic because of recurrent acute pain, chronic pain and/or other sickle related complications. Presence or absence of sickle cell nephropathy, which could significantly contribute to the development of VDD, was not evaluated, but would certainly warrant further study. We also did not determine the prevalence of lactose intolerance, or evaluate the dietary intake of vitamin D or other lifestyle factors which could affect the development of VDD in this population.

This study was limited by the small sample size and the inclusion criteria, which favours inclusion of patients with very severe manifestations of SCD. The overlap between the symptoms of VDD and chronic pain and the association between the degree of VDD and the presence of chronic pain in this population of severely affected SCD patients is striking. Our findings confirm that individuals with SCD are particularly prone to VDD and also suggest a link between VDD and bone fragility in SCD. Although VDD is unlikely to be the sole source of chronic pain in SCD, the extremely high prevalence of VDD in these patients suggests the need for further investigation of this link between VDD and SCD chronic pain, as well as the potential therapeutic benefits of vitamin D supplementation in this highly symptomatic population.

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