Bone involvement is the commonest clinical manifestation of sickle cell disease both in the acute setting such as painful vaso-occlusive crises, and as a source of chronic, progressive disability such as avascular necrosis. Management of these problems is often difficult because of the diagnostic imprecision of most laboratory and imaging investigations and because of the lack of evidence for most surgical procedures in sickle cell disease. This review first discusses the acute problems related to bone involvement in sickle cell disease, with particular reference to differentiating infection from infarction, and then describes the long-term effects of sickle cell disease on bone mineral density, growth, and chronic bone and joint damage.

Keywords: sickle cell disease, bone, vaso-occlusion, osteomyelitis, osteonecrosis.

Acute bone problems in sickle cell disease

The most frequent complications requiring hospital admissions for patients with sickle cell disease are painful vaso-occlusive crises and osteomyelitis (Platt et al, 1991; Bailey et al, 1992; Neonato et al, 2000) (Table I). Other acute bony problems that have been described in sickle cell disease are stress fractures (Bahebeck et al, 2002), orbital compression syndrome because of orbital bone infarction (Ganesh et al, 2001; Naran & Fontana, 2001), dental problems (Demirbas et al, 2004), vertebral collapse (Emodi & Okoye, 2001) and bone marrow necrosis (Ataga & Orringer, 2000).

Vaso-occlusive crises

Vaso-occlusive crises affect virtually all patients with sickle cell disease, often beginning in late infancy and recurring throughout life. The pathogenesis of the microvascular occlusion, the hallmark of the painful sickle cell crisis, is complex involving activation and adhesion of leucocytes, platelets and endothelial cells as well as haemoglobin S-containing erythrocytes (Frenette, 2004). While this process can occur in virtually any organ, it is particularly common in the bone marrow, resulting in bone marrow infarction typically in the medullary cavity or epiphyses (Lonergan et al, 2001; Kim & Miller, 2002). The reasons for the vulnerability of the bone marrow to microvascular occlusion are unclear but may be partly because of marrow hypercellularity leading to impaired blood flow and regional hypoxia (Smith, 1996). Clinically, patients complain of intense pain localized to one or more areas of their skeleton. This may be accompanied by localized tenderness, swelling and erythema over the site of infarction; fever and leucocytosis are also common (Smith, 1996). Most patients recover from vaso-occlusive crises with no further complications. However, when marrow infarction involves the epiphyses, this may give rise to joint effusions that are clinically similar to septic arthritis (Smith, 1996; Kim & Miller, 2002), or where there is infarction of vertebral bone marrow, to collapse of the vertebrae with a typical ‘fish mouth’ appearance (Lonergan et al, 2001).

Dactylitis

In children under the age of 7 years, particularly those aged 1–2 years, vaso-occlusive crises frequently occur in the small bone of the hands and feet (dactylitis), which still contain haemopoietic bone marrow at this age in children with sickle cell disease (Kim & Miller, 2002). Clinically, dactylitis presents with acute, painful swelling of one or more of the digits. Histologically, there is extensive infarction of the marrow, medullary trabeculae and inner layer of the cortical bone, together with subperiosteal new bone formation (Weinberg & Currarino, 1972). Most episodes resolve within 2 weeks, by which time new bone formation is evident radiologically and there may be a ‘moth eaten’ appearance of the involved digits because of cortical thinning and irregular attenuation of the medullary spaces (Lonergan et al, 2001); rarely, involvement and infarction of the epiphyses leads to premature fusion and shortened fingers (Babulkar et al, 1995).
Table I. Acute bone problems in sickle cell disease.

<table>
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<th>Condition</th>
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<tr>
<td>Painful (vaso-occlusive) crisis</td>
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<tr>
<td>Osteomyelitis</td>
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<tr>
<td>Stress fracture</td>
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<td>Orbital compression</td>
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<td>Dental complications</td>
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<td>Vertebral collapse</td>
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<td>Bone marrow necrosis</td>
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**Imaging during acute vaso-occlusive crises**

The diagnosis of a painful crisis is predominantly a clinical one. Standard radiographs are generally not helpful in confirming the diagnosis of bone marrow infarction as they are usually normal during the acute phase of a vaso-occlusive crisis; although over the ensuing months radiographs often show areas of ill-defined translucency followed by arc-like subchondral and intramedullary lucent areas and patchy sclerosis (Lonergan et al., 2001).

By contrast, radioisotope bone scanning using a combination of 99mtechnecium (Tc)-labelled sulphur colloid (to measure bone marrow uptake) and 99mTc-diphosphonate (to measure bone uptake) can reliably detect areas of infarction in the acute phase (Amundsen et al., 1984; Skaggs et al., 2001; Kim & Miller, 2002). This approach was used to show that infarcts in sickle cell disease can occur in every bone in the body (Kim & Miller, 2002). It also shows that the commonest sites for acute infarcts are the tibia/fibula (30%), the femur (25%) and the radius, ulna and humerus (21%), consistent with clinical data showing a predilection for the long bones (Keeley & Buchanan, 1982). Unfortunately, despite its sensitivity, radioisotope bone scanning has proved unreliable in distinguishing infarction from other complications such as osteomyelitis (see below) (Amundsen et al., 1984; Rao et al., 1985; Kim & Miller, 2002), and it is therefore not useful as a routine diagnostic investigation in sickle cell disease.

Magnetic resonance imaging (MRI) is also a very sensitive imaging technique for detecting bone and bone marrow infarction (Mankad et al., 1988; van Zanten et al., 1989; Mankad et al., 1990; Bonnerot et al., 1994; Deely & Schweitzer, 1997; Frush et al., 1999). Abnormal periosteal signal intensity and soft tissue changes are frequently seen in the first few days of a vaso-occlusive crisis; however, as with scintigraphy, these changes are often difficult to distinguish from those seen in osteomyelitis (Bonnerot et al., 1994; Frush et al., 1999). At present, therefore, MRI is not useful routinely in the management of patients with vaso-occlusive crises and should be reserved for investigating those patients whose symptoms fail to settle with conventional management and/or where there is a high suspicion of osteomyelitis. Similarly, as discussed below, there are difficulties both with MRI and scintigraphy in distinguishing between infarction/infection and infarction/increased marrow haemopoiesis in sickle cell disease (Keeley & Buchanan, 1982; Deely & Schweitzer, 1997).

**Osteomyelitis**

The increased susceptibility of sickle cell disease patients to infections, including osteomyelitis, has long been recognized with several mechanisms postulated including hyposplenism, impaired complement activity and the presence of infarcted or necrotic bone. A recent French study of a cohort of 299 patients followed in four Parisian centres, found a prevalence of osteomyelitis of 12%. Interestingly, the prevalence was significantly lower in those patients with the Bantu haplotype (Neonato et al., 2000). This finding is in keeping with other studies where it was found that patients with more severe haemoglobinopathies such as Benin and Senegal, not only have more severe organ damage because of sickling, but also have increased incidence of infectious complications (Palmos et al., 1991).

The most common cause of osteomyelitis in sickle cell disease is Salmonella (especially the non-typical serotypes Salmonella typhimurium, Salmonella enteritidis, Salmonella choleraesuis and Salmonella paratyphi B), followed by Staphylococcus aureus and Gram-negative enteric bacilli (Atkins et al., 1997; Burnett et al., 1998), perhaps because intravascular sickling of the bowel leads to patchy ischaemic infarction (Table II). Osteomyelitis in sickle cell disease has also been reported in association with tuberculosis (Kooy et al., 1996) and systemic spread of Mycobacterium ulcerans from a Buruli skin ulcer (Pszolla et al., 2003).

**Diagnosis of osteomyelitis in sickle cell disease**

Diagnosis of osteomyelitis can be one of the most common management dilemmas in sickle cell disease: failure to identify it may result in severe bone damage and life-threatening infection while an erroneous diagnosis subjects the patient to at least 6 weeks of unnecessary intravenous and oral antibiotics. Osteomyelitis usually presents with pain, swelling and tenderness over the affected area. The most common sites are the femur, tibia or humerus (Stark et al., 1991). Most patients also have fever and elevated inflammatory markers (Chambers et al., 2000; Skaggs et al., 2001) but the fever may be modest (Bennett, 1992). These signs and symptoms are similar to those found in vaso-occlusive crises, making the distinction between a painful crisis and osteomyelitis extremely difficult on clinical grounds; indeed osteomyelitis may not be suspected until the

Table II. Causes of osteomyelitis in sickle cell disease.

<table>
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<th>Organism</th>
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<tr>
<td>Salmonella typhimurium</td>
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<tr>
<td>Salmonella enteritidis</td>
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<tr>
<td>Salmonella choleraesuis</td>
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<tr>
<td>Salmonella paratyphi B</td>
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<tr>
<td>Staphylococcus aureus</td>
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<tr>
<td>Haemophilus influenzae</td>
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<tr>
<td>Escherichia coli</td>
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<td>Enterobacter spp.</td>
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signs and symptoms of a typical painful crisis have failed to resolve after 1–2 weeks of standard therapy (Jean-Baptiste & De Ceulaer, 2000). Blood cultures are often sterile when taken at this stage, as it is common practice to treat patients with vaso-occlusive crises with broad-spectrum antibiotics upon admission, especially if they are febrile. Thus, confident diagnosis of osteomyelitis in such patients tends to rely on various imaging techniques. However, in some cases, osteomyelitis presents late, as a more indolent process often with abscess formation, in which case there is usually little diagnostic difficulty (Barrett-Connor, 1971; Dirschl, 1994).

On plain radiographs, the changes seen at the early stages of osteomyelitis, namely periostitis and osteopenia, are non-specific and also seen in vaso-occlusion and therefore of limited value (Lonergan et al., 2001). Lucent areas are not seen until much later in the natural history of the infection (Fig 1). Ultrasonography shows the extraosseous pathology in acute osteomyelitis and may show periosteal elevation (William et al., 2000). It has also the advantage of being rapid, non-invasive and fairly simple to target to the area(s) of maximum pain (Sidhu & Rich, 1999). The sensitivity of ultrasonography in diagnosing osteomyelitis in sickle cell disease has been reported to be as high as 74% (Rifai & Nyman, 1997; Sadat-Ali et al., 1999; Kim & Miller, 2002). A combination of 99mTc-sulphur colloid and 99mTc-diphosphonate (Buchanan, 1996; Skaggs et al., 2001; Kim & Miller, 2002) or 99mTc with gallium seems to improve accuracy (Amundsen et al., 1984), as marrow uptake tends to be normal in osteomyelitis while it is usually increased in infarction; however, as both false positives and false negatives still occur, we no longer use this approach. Radiolabelled leucocyte scans similarly fail to reliably discriminate between osteomyelitis and infarction (Buchanan, 1996).

The MRI is increasingly being used to help diagnose osteomyelitis (Lonergan et al., 2001). As with other imaging modalities, there is overlap between the changes seen in infection and infarction: in both situations MRI shows reactive marrow oedema together with surrounding hyperaemia (Bonnerot et al., 1994; Umans et al., 2000). The accuracy of MRI is greater when gadolinium enhancement is used (Deely et al., 1994; Umans et al., 2000) but even this is not 100% specific for differentiating osteomyelitis from infarction (Frush et al., 1999; Lonergan et al., 2001). However, once osteomyelitis was confirmed by culture results, it is very useful for accurate localization of the lesion and for monitoring for response to treatment once antibiotic therapy has been initiated (Bonnerot et al., 1994).

Therefore, despite the progress made in the development and use of imaging techniques, a definitive diagnosis of osteomyelitis in sickle cell disease still relies more upon clinical assessment together with positive cultures from blood or bone obtained by aspiration or biopsy, than upon any single imaging modality. It is also useful to remember that bone pain in sickle cell disease is much more likely (in one series (Keely & Buchanan, 1982) it was 50 times more likely), because of a vaso-occlusive crisis than to osteomyelitis.

Treatment of osteomyelitis in sickle cell disease

The choice of antibiotics is generally dictated by the microorganism detected. Our first line treatment for confirmed or suspected osteomyelitis is a third line cephalosporin such as ceftriaxone, in order to make sure Salmonella infections are covered. Ciprofloxacin is a useful alternative for older children with Salmonella osteomyelitis, having the advantage of excellent oral bioavailability. In adults, other species such as Staphylococcus, should also be covered by empirical antibiotic therapy (Sadat-Ali, 1998). Treatment of confirmed cases should continue for at least 6 weeks.

When there is radiological evidence of accumulation of fluid at the site of infection, drainage is recommended (Sadat-Ali, 1998). However, there is no firm consensus...
regarding when to drill or drain and these invasive procedures tend to be reserved for those who are not responding to antibiotic therapy or those who have localized encapsulated septic collections (Syrogiannopoulos et al, 1986; Atkins et al, 1997; Sadat-Ali, 1998).

**Septic arthritis**

Septic arthritis is also seen in sickle cell disease and is generally caused by the same organisms as osteomyelitis (Ebong, 1987). It rarely develops in isolation; instead, it tends to occur in association with a painful vaso-occlusive crisis (Jean-Baptiste & De Ceulaer, 2000). Early diagnosis to prevent irreversible joint damage is essential but usually not problematic because of the ease with which diagnostic synovial fluid can be obtained. It is, however, important to be cautious as vaso-occlusion affecting the articular surfaces may lead to a similar clinical picture as infectious arthritis (Jean-Baptiste & De Ceulaer, 2000).

**Other acute bone problems in sickle cell disease**

Bone involvement in sickle cell disease may also contribute to other sickle-related complications. In acute chest syndrome, both rib infarcts, leading to hypoventilation because of pain and fat embolism, secondary to bone marrow infarction, are important contributory factors in the pathogenesis of the syndrome (Rucknagel, 2001; Salzman, 2002). Other acute bony problems that have been described in sickle cell disease include stress fractures (Bahebeck et al, 2002), vertebral collapse (Emodi & Okoye, 2001) and orbital compression syndrome because of orbital bone infarction, which may present with acute periorbital swelling (Ganesh et al, 2001; Naran & Fontana, 2001). Dental problems are particularly prevalent in patients with sickle cell disease. There is an increased incidence of dental caries (Laurence et al, 2002), pulpal necrosis (O’Rourke & Hawley, 1998; Demirbas et al, 2004; Kavadiatsatala et al, 2004) and abnormal radiographic and morphological findings (Taylor et al, 1995). Compounded with the relatively poor blood supply to the mandible, it is not surprising to find an increased incidence of mandibular osteomyelitis in sickle cell disease secondary to dental infections (Adekeye & Cornah, 1985; Olaitan et al, 1997).

**Chronic bone problems in sickle cell disease**

Chronic skeletal problems are common in sickle cell disease (Table III). Many patients suffer from chronic pain because of avascular necrosis (AVN), vertebral collapse and/or chronic arthritis. In addition, hyperplasia of the bone marrow may cause osteopenia and growth disturbance (Claster & Vichinsky, 2003).

**Avascular necrosis**

Osteonecrosis or AVN, occurs when vaso-occlusion results in the infarction of the articular surfaces and heads of the long bones. The true prevalence of osteonecrosis in sickle cell disease is difficult to judge because of the small number of prospective studies using sensitive methods of detection such as MRI (Ware et al, 1991; Adekile et al, 2001; Gupta & Adekile, 2004). However, by using MRI, Ware et al (1991) found osteonecrosis in the epiphyses of almost 41% of adults with sickle cell disease. Adekile et al (2001), also using MRI, found a slightly lower prevalence in children (27%). These studies both showed a much higher frequency of osteonecrosis than previously reported in studies based on plain X-rays. Milner et al (1991) studied 2590 patients and found radiological evidence of osteonecrosis of the femoral head in only 9.8% of patients with sickle cell disease, with the highest frequency in adults, in those with homozygous sickle cell disease and in those with co-existing alpha-thalassaemia trait. That this is an underestimate of the true prevalence of osteonecrosis is also suggested by the finding that 47% of patients with hip disease and 79% of those with shoulder disease were asymptomatic at the time the radiological diagnosis was made (Milner et al, 1991).

A recent cohort study over four decades in 284 patients with sickle cell disease found that osteonecrosis was present in 15% of the cohort (Powars et al, 2002). The mean age of onset was 35 years and it was rare in the first decade of life (Powars et al, 2002). However, as the authors acknowledged, this study probably underestimated the true frequency of osteonecrosis in sickle cell disease, as there was no systematic screening of asymptomatic patients and a higher frequency of osteonecrosis was found in the more recent decades when MRI became available (Powars et al, 2002). This study also found a lower frequency of osteonecrosis in those patients who had co-inherited alpha-thalassaemia trait (17% vs 32% patients without alpha-thalassaemia trait) although this was not found in other studies in sickle cell disease (Steinberg et al, 1983) or sickle cell disease in general (Ballas et al, 1989; Milner et al, 1991).

The pathophysiology of osteonecrosis in sickle cell disease seems to differ from osteonecrosis because of other aetiologies. When MRI is used to quantify lesions in AVN of the femoral head, the lesions seen in sickle cell disease are larger than those seen in osteonecrosis because of other aetiologies (Malizos et al, 2001). Whereas in osteonecrosis not because of sickle cell disease, the localization and size of the lesions is directly related to the mechanical stresses on the femoral head, the larger size and wider distribution of the lesion in sickle cell disease point to the fact that a much larger variety of independent factors result in vascular occlusion in sickle arthropathy.

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**Table III. Chronic bone problems in sickle cell disease**

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<th>Disease</th>
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<tr>
<td>Osteonecrosis</td>
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<tr>
<td>Chronic arthritis</td>
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<tr>
<td>Osteoporosis</td>
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<tr>
<td>Impaired growth</td>
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The most common sites of osteonecrosis are the femoral heads followed by the head of the humerus, knee and small joints of the hands and feet (Jean-Baptiste & De Ceulaer, 2000; Lonergan et al, 2001). It is common to have multiple joints affected: >50% of patients with an affected hip have bilateral disease and 74% of those with an affected shoulder will also have AVN of the femoral head (Milner et al, 1991; Milner et al, 1993).

Symptomatic patients complain of painful, limited motion of the affected joint, occasionally with pain at rest. Advanced disease may be easily diagnosed with plain radiographs, which show mottled attenuation of the epiphysis, subchondral lucent areas and flattening/collapse of the articular surfaces (Fig 2). This may be followed by narrowing of the joint space, articular sclerosis and osteophyte formation (Lonergan et al, 2001). Early disease is best diagnosed by MRI as mentioned above, plain X-rays may not detect early disease (Milner et al, 1991; Gupta & Adekile, 2004). Untreated, 87% of affected femoral heads will collapse within 5 years of diagnosis (Hernigou et al, 2003).

The treatment options for AVN of the hip in sickle cell disease are difficult to assess as no controlled trials comparing the different approaches are published. One of the most effective methods of preventing progression of joint damage is bed rest, in order to avoid weight bearing (Hernigou et al, 2003), however, this has such drastic implications for patients’ lives that it is usually an unacceptable option. In addition, the long-term symptomatic treatment is ineffective and the majority of joints require surgery for pain relief and functional improvement. Early disease may improve with coring and osteotomy (Styles & Vichinsky, 1996); however, failure rates in some studies are as high as 50% at 5 years (Bishop et al, 1988; Clarke et al, 1989; Milner et al, 1991) and a randomized controlled trial is currently in progress to determine whether decompression coring procedures can prevent progression of AVN (Claster & Vichinsky, 2003). Late disease requires joint replacement. Such patients must be cared for in specialized centres with expertise in sickle cell disease as they have a very high incidence of perioperative complications (compared with general orthopaedic patients), including excessive blood loss, acute chest syndrome, infection and failure of prostheses (Vichinsky et al, 1999). Other surgical techniques (Hernigou et al, 1993) are being used in an attempt to overcome these problems but none have yet produced satisfactory results.

**Osteopenia and osteoporosis**

Several studies have shown an overall reduction in bone mineral density, attributed to marrow hyperplasia, in patients with sickle cell disease (Brinker et al, 1998; Soliman et al, 1998; VanderJagt et al, 2002; Nelson et al, 2003). Compared with normal subjects from the general population, Brinker et al (1998) found that the patients with sickle cell disease had lower bone mineral density values in all scan regions (c. 6–21% lower than expected). In particular, vertebral osteoporosis is common in patients with sickle cell disease (Brinker et al, 1998). Radiologically, this shows as increased radiolucency of the vertebral bodies, prominence of vertebral trabeculae and a smooth, biconcave deformity of the vertebrae known as ‘fish-mouth’ vertebrae, which forms as a result of compression by the adjacent intervertebral discs (Williams et al, 2004a). Patients may go on to develop vertebral collapse either from the osteoporosis or as a result of vertebral infarction. Vertebral collapse is often asymptomatic but may cause acute and/or long-term pain requiring analgesia and mechanical support such as a brace.

**Growth**

Impaired growth is a well recognized complication of sickle cell disease in children (Platt et al, 1984; Stevens et al, 1986; Leonard et al, 1998; Barden et al, 2002); at least some of this impairment in growth seems to be because of marrow hyperplasia (Claster & Vichinsky, 2003). Marrow hyperplasia can cause ischaemia of the central portion of the vertebral growth plate, leading to disturbance of vertebral growth and resulting in the characteristic ‘H’ shaped vertebrae because of squared-off depression of the vertebral end plates (Reynolds,
1987; Williams et al, 2004a). Alternatively, some female patients with sickle cell disease develop ‘tOWER’ vertebrae in which there is an increase in the height of the vertebral bodies without an associated increase in the width, again postulated to be a consequence of chronic marrow hyperplasia (Marlow et al, 1998). In addition to marrow hyperplasia, local anoxic events may lead to premature closure of epiphyses and impaired or even asymmetrical growth of the long bones of the limbs (Collett-Solberg et al, 2002).

In addition to these marked skeletal abnormalities in the spine, there is also evidence of more subtle abnormalities as a common feature of sickle cell disease. A recent study carried out a detailed assessment of growth, nutritional status and body composition in 36 children with homozygous sickle cell disease (Barden et al, 2002). There was no significant difference in their height or bone age between the children with sickle cell disease and their age, sex and ethnically matched controls. However, the sickle cell disease group had significantly delayed skeletal maturation and had marked deficits in z-scores for weight-for-age, height, elbow breadth, skin fold thickness and mid upper arm circumference, consistent with global deficits in growth and energy reserves (Barden et al, 2002). Growth hormone deficiency is a reversible cause of impaired growth but not commonly seen in these children (Nunlee-Bland et al, 2004). Several studies have shown that children with sickle cell disease have lower levels of vitamins A, B6 and D than their ethnically matched peers and that these levels were related to these children’s morbidity (Nelson et al, 2002; Schall et al, 2004). In addition, vitamin deficiencies in sickle cell disease do not seem to be related to malnutrition per se (Kennedy et al, 2001) but to a high resting energy expenditure, which also seems to be related to the degree of impaired growth in these children (Odonkor, 1983; Williams et al, 2004b).

Conclusion
The vast majority of complications affecting patients with sickle cell disease are musculoskeletal in origin and, although they do not contribute significantly to mortality, they are the major source of acute and chronic morbidity. Despite their significant clinical and socioeconomic impact, the resources available to diagnose and treat bone disease in sickle cell disease remain limited. The use of hydroxyurea has significantly altered the quality of life of those with recurrent vaso-occlusive crises but the treatment of acute crises remains largely supportive (Amrolia et al, 2003). Similarly, the management of osteomyelitis remains problematic, as current imaging techniques fail to confidently distinguish between osteomyelitis and vaso-occlusion often leading to long hospital stays and invasive investigations before a definitive diagnosis can be made. Of the chronic bone disorders, the most disabling is osteonecrosis. Management of this condition is generally unsatisfactory; despite the availability of early diagnosis, no strategy other than absolute bed rest has yet been shown to prevent progression of joint damage and surgery is associated with a high rate of postoperative complications. Finally, it is clear that most, if not all patients with homozygous sickle cell disease have abnormal skeletal growth and maturation; the mechanisms and implications of this for the health of children and adults with this disease remain to be explored.

Acknowledgements
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References


