Fracture healing in HIV-positive populations

Highly active anti-retroviral therapy has transformed HIV into a chronic disease with a long-term asymptomatic phase. As a result, emphasis is shifting to other effects of the virus, aside from immunosuppression and mortality. We have reviewed the current evidence for an association between HIV infection and poor fracture healing.

The increased prevalence of osteoporosis and fragility fractures in HIV patients is well recognised. The suggestion that this may be purely as a result of highly active anti-retroviral therapy has been largely rejected. Apart from directly impeding cellular function in bone remodelling, HIV infection is known to cause derangement in the levels of those cytokines involved in fracture healing (particularly tumour necrosis factor-α) and appears to impair the blood supply of bone.

Many other factors complicate this issue, including a reduced body mass index, suboptimal nutrition, the effects of anti-retroviral drugs and the avoidance of operative intervention because of high rates of wound infection. However, there are sound molecular and biochemical hypotheses for a direct relationship between HIV infection and impaired fracture healing, and the rewards for further knowledge in this area are extensive in terms of optimised fracture management, reduced patient morbidity and educated resource allocation. Further investigation in this area is overdue.

Anti-retroviral drugs have had considerable success in lengthening the asymptomatic phase of infection with HIV and prolonging the interval between clinically apparent AIDS and death. Although the availability of drug therapy worldwide remains problematic, many patients receiving highly active anti-retroviral treatment (HAART) now experience infection with HIV as a pharmacologically-mediated chronic disease.

In the early days of the HIV epidemic, infection was diagnosed late, treatment had minimal impact on survival and the acute manifestations of the illness were clearly of primary concern. However, an increase in the duration of apparently asymptomatic infection raises new questions about the longer term effects of the virus, its treatment and appropriate management strategies. While HIV infection is thought to affect soft-tissue healing, and both HIV and HAART have been linked to a reduced bone mineral density (BMD), which may predispose to fragility fracture, little is known about the effects of HIV and its current management paradigms on bone healing. Furthermore, there are few data on how the virus and its management may influence the development of maximal bone mass during childhood and the late sequelae of inadequate bone mineralisation. Since an estimated 2.5 million children live with HIV, adverse consequences arising from an HIV-limited peak bone mass would have potentially far-reaching effects.

The relationship between HIV infection and fracture healing is worthy of investigation, given the large number of people affected. HIV infection and trauma, the latter particularly as a result of road-traffic accidents, are concentrated in the developing world. Even in developed countries, those who are socio-economically deprived are particularly over-represented in both the HIV sero-positive population and as victims of trauma, whether accidental or forensic. Those living below the poverty threshold are also liable to encounter exaggerated morbidity and further social deprivation after traumatic injury. Early identification and targeted clinical management of patients who are vulnerable to the complications of fracture healing can improve outcomes. In addition, both HIV infection and trauma independently contribute considerable economic burdens to...
health systems worldwide. Their combined impact warrants the use of effective strategies for the control of financial escalation in health and social cost, particularly given their prevalence in resource-constrained countries.

The key factors involved in the relationship between fracture healing and HIV infection relate first to the likely effect of the retrovirus and its treatment on bone metabolism. Altered rates of bone formation and resorption, in a deranged metabolic and cytokine environment, not only have implications for the BMD and fracture risk, but also for remodelling in secondary bone healing. In addition, reports of osteonecrosis in HIV patients raise questions regarding the integrity of the blood supply for fracture healing in this group.16 Bone quality and immunosuppression are also critical factors in the choice of fixation methods (Fig. 1).17

We present a review of this emerging issue, highlighting areas of clinical concern and propose a model with which to build clinical understanding in this field. Finally, avenues for new collaborative research are suggested.

**Reduced BMD may increase the risk of fragility fracture in HIV-positive patients**

A number of cross-sectional studies have indicated that there is a higher prevalence of osteoporosis and osteopenia in those with HIV infection than among healthy control subjects.18-22 However, the scientific reasoning underpinning these observations remains unclear. A reduced BMD is a well-recognised cause of fragility fractures23 and, as such, HIV-related paucity of bone stock could potentially increase the risk of fracture and its related morbidities. Indeed, with increasing survival attributable to better anti-retroviral therapy, an HIV-related reduction in BMD would invariably compound age-related causes of altered bone density, such as the menopause, with clinical implications.24,25

Recently, there has been controversy as to whether a reduced BMD is related to the HIV infection itself, or to its treatment with anti-retroviral drugs.19,26 Protease inhibitors have been implicated in causing a reduced BMD27 and a recent meta-analysis found that there was a significant increase in osteoporosis in patients receiving HAART compared with both anti-retroviral-naïve (not previously exposed to anti-retroviral drugs) HIV-positive and seronegative patients.28 Research into HAART-naïve subjects and comparative studies of HAART-naïve and anti-retroviral-treated patients suggest that HIV itself is detrimental to BMD.18,19,29 Indeed, it was suggested in one study that the time from the initial infection was the only variable to correlate positively with a reduction in BMD.21 This cross-sectional study was robust in design and compared four groups as follows: HIV patients on protease inhibitors, those on other anti-retroviral drugs, those naïve to anti-retroviral treatment, and a healthy control group. It excluded candidates with other risk factors for low BMD. However, it was limited by small sample sizes and did not examine the level of cytokines or other serum markers which might have been useful in analysing the observed pattern. Furthermore, this association was not replicated in another similar study.19 As Singh and Moyle4 discuss in

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**Fig. 1**

Algorithm showing the factors affecting the union of fractures in HIV-positive patients (BMD, bone mineral density; ARV, anti-retroviral; HAART, highly active anti-retroviral therapy).
their review, several studies have shown a small decline in the BMD at the commencement of anti-retroviral treatment which was followed by recovery and further improvement above the baseline in due course. It has been suggested that HIV infection leads to disruption of the relationship between bone formation and resorption, with a net loss of BMD as the effects of the virus progress. A study by Aukrust et al showed that falling CD4 counts and rising viral loads were often the trigger for the commencement of HAART treatment, which then led to the re-coupling of bone formation and resorption mechanisms, albeit with a small time delay. However, they specifically examined serum markers of bone metabolism, and did not correlate changes in their levels with the BMD.

The mechanism by which HIV may interfere with bone metabolism has not been elucidated, and this represents an important issue in osteo-immunology. It is possible that such a mechanism is linked to the modulation of the tumour necrosis factor-α (TNF-α) superfamily, which includes the receptor activator NFκB ligand (RANKL) and osteoprotegerin (OPG). RANKL binds to its receptor, RANK, on osteoclasts to stimulate their activity, whereas OPG is produced by osteoblasts to act as a decoy ligand, preventing RANK-RANKL binding and reducing bone resorption. TNF-α, observed at high levels in HIV patients, may be able to stimulate both pathways, but the overall effect on bone turnover is complex and unproven, and there may be other more critical mechanisms to be elucidated. In addition, the Wnt/lipoprotein receptor-related protein 5 (LRP5) signalling pathway is being increasingly recognised as a critical determinant of bone formation. The circulating factor Wnt binds to LRP5 on osteoblast surface membranes to initiate intra-cellular signalling. This drives production of osteogenic molecules including bone morphogenetic protein and OPG, culminating in bone formation. It has recently been demonstrated that Dkk-1, a molecule which inhibits this pathway, and therefore bone formation, is induced by TNF-α (Fig. 2). The activity of this pathway in the context of the chronic up-regulation of TNF-α in HIV infection may be of interest in the future.

The biochemical evidence linking HIV infection to alterations in bone metabolism in part relates to observations that the protein osteocalcin circulates at reduced levels in the serum of HIV patients, compared with healthy subjects. However, this is thought to be a result of the down-regulation of calcitropic hormones (parathyroid hormone (PTH)) and 1,25 dihydroxycholecalciferol. Calcitropin is known to suppress T-cell activity. The precise function of osteocalcin is unknown, but is thought to relate to its structure, which allows it to align with calcium ions in hydroxyapatite. This apposition is thought to enable it to modulate bone growth, and thus the protein is used to indicate bone formation. Osteocalcin has been shown to correlate positively with the CD4 count, and negatively with both TNF-α and TNF receptor (R), while a low serum osteocalcin level is accompanied by increased C-telopeptide levels, suggestive of bone resorption. It has also been found that the magnitude of reduced bone formation, while correlating positively with the CD4 count, is independent of low levels of 1,25-dihydroxycholecalciferol. The suggestion is that advancing HIV infection may impede bone formation and increase resorption although, as previously noted, Aukrust et al failed to correlate these molecular markers with gross changes in the BMD. Other studies have shown low levels of both bone formation and resorption through surrogate markers in serum and urine, sug-
gesting that there is a universally reduced bone turnover. A cross-sectional study of bone biopsies from anti-retroviral-naïve subjects found reduced osteocalcin levels in those with the lowest CD4 counts, but no overall reduction in the BMD, and lower levels of osteoclasts than expected. Interpretation of such results should be approached with caution, however, given the uncertain significance of osteocalcin in bone formation.

A recent meta-analysis of studies claiming to demonstrate an association between HIV infection and reduced BMD showed that no significant difference remained if data were adjusted for weight differences between groups. While a proportion of the increased risk of fracture in HIV infection may be due to low body-weight, and efforts to optimise nutritional support should be rigorous, there is a plausible pathophysiological mechanism for deranged bone remodelling and, therefore, a more direct interaction cannot be excluded.

Bisphosphonates are the mainstay in the secondary prevention of fragility fractures in an HIV sero-negative population. However, a recent systematic review drew attention to the lack of high-level evidence in the context of HIV infection, but indicated that bisphosphonates were safe alternatives to calcium and vitamin D in the HIV-positive population and could improve the BMD. Alendronate has been identified as the drug of choice in this setting, being relatively well tolerated because it can be administered weekly. However, in the small study populations analysed, extrapolation from improvements in the BMD to a reduced fracture risk was not performed. Currently, routine BMD screening is not recommended for patients with HIV infection. Nevertheless, it seems reasonable to have a low threshold for investigating reduced BMD in sero-positive patients with fractures, particularly those with independent risk factors such as a low body mass index or a history of cigarette smoking, and to instigate secondary prevention when appropriate, as proposed in the algorithm prepared by Negredo et al.

An altered cytokine environment in HIV-positive subjects may impact on bone healing

It is well recognised that fracture healing is initiated by an inflammatory response to bone injury. The molecular aspects of bone healing have been reviewed in detail by Dimitriou, Tsiridis and Giannoudis. Local release of pro-inflammatory cytokines such as TNF-α, interleukin-1 (IL-1) and IL-6 activates cytokine cascades which trigger the recruitment and differentiation of cells involved in the formation of callus and bone repair. Inhibition of an inflammatory response by cyclo-oxygenase inhibitors is known to adversely affect the process of fracture healing. Although HIV infection is immunosuppressive, cross-sectional studies showing that serum TNF-α is often raised in HIV-positive subjects in comparison with healthy control groups, indicate that the production of inflammatory cytokines is possible in the context of HIV. Aukrust et al also found significantly raised serum levels of soluble TNF receptors (sTNFRs) and a correlation between positive sTNFRs and patient survival, which may make the level of serum sTNFRs a more useful measurement of TNF activity in patients with HIV infection than the serum concentration of TNF itself. The effects of chronically raised levels of TNF-α on fracture healing are speculative. Ongoing inflammation could prime the body for an inflammatory response to a fracture, resulting in a highly efficient up-regulation of cytokines. Alternatively, an increased baseline level of TNF-α could lead to desensitisation, preventing or decelerating the healing process to the detriment of the patient. Certainly, raised TNF-α activity is associated with a number of adverse outcomes in HIV-infected patients, including neurodegeneration and cardiomyopathy.

TNF-α is not the only cytokine which has been associated with bone-related changes in HIV-positive subjects. A study of perinatally-infected children found an association between low concentrations of insulin-like growth factor-1 (IGF-1) and reduced bone ultrasound attenuation, a correlate of BMD. An inverse correlation between IGF-1 and IL-6 was observed. In addition, IGFs have an anabolic function on the skeleton and IGF-1 is known to be the major effector of bone growth. Both IGF-1 and IL-6 are involved in fracture healing. The effects of deranged levels due to advanced HIV infection are unknown.

More work is required if these interactions are to be characterised better. At present, it seems prudent to take particular care to optimise bone healing in HIV-positive fracture patients by removing or minimising factors known to impede the relevant biochemical cascades, such as the use of non-steroidal anti-inflammatory drugs and cigarette smoking.

HIV infection may predispose to osteonecrosis

One of the factors known to affect fracture healing is local blood flow to the site of the injury. In experimental models, devascularised fracture sites have impaired healing. A further concern about the implications of HIV infection on fracture healing arises from reports of osteonecrosis in HIV-positive patients, predominantly of the femoral head. Although in many cases HAART is implicated as a cause of osteonecrosis, one case series identified HIV infection as the only risk factor in 60% of cases. This, however, only translated to three patients, making interpretation speculative. Osteonecrosis occurs as a result of a reduced arteriolar blood supply, but the manner in which HIV infection affects the blood flow is unclear, although there have been associations reported between retrovirus infection and the presence of both raised anti-phospholipid antibodies and protein-S deficiency. This suggests the possibility of a microvascular, possibly microthrombotic, origin for circulatory compromise.
Conditions which may jeopardise arterial flow to the site of primary bone healing are associated with higher rates of delayed and nonunion of fractures. The suggestion that HIV infection may have adverse effects on blood flow, as evidenced by its reported association with osteonecrosis, may further contribute to problems in fracture healing.

Reduced BMD may adversely affect bone formation and remodelling after fracture

In the absence of rigid fixation, fracture healing relies initially on the formation of callus. The development of woven bone and a subsequent extended remodelling period occur. As discussed above, it is possible that HIV-positive patients treated either with or without anti-retroviral drugs experience changes in the relative rates of bone formation and resorption. This may result in a lower overall rate of ossification and a longer time for fracture healing. In the HIV sero-negative population, there is a suggestion that a reduced BMD is associated with a reduced speed of fracture healing. This relationship may be expected to hold true in the context of HIV, so that patients with reduced BMD are at an increased risk of both fragility fracture and subsequent delayed union.

Of note, 3-hydroxy-3 methylglutaryl-coenzyme A reductase inhibitors, also known as statins, have been shown to improve BMD and, in a mouse model, to increase the strength of healed fracture sites. Statins may, therefore, have a future role in augmenting fracture healing in patients with reduced BMD, including those with HIV infection. The development of lipodystrophy has been associated with osteonecrosis, and the effects of statins on lipid handling may prove to be of additional benefit in patients experiencing dysregulation of metabolic processes as a result of HAART.

Infection risk and bone stock influence the choice of fixation method

The high incidence of post-operative infection in HIV patients undergoing surgery for trauma has been observed in a number of case series, in both patients with World Health Organisation (WHO) clinical disease stages 1 and 2 and in those with symptomatic HIV infection. While methods of internal fixation have been effective in stabilising fractures, their use in open fractures in HIV-positive patients has been reported to attract a rate of wound infection of between 42% and 72%, albeit before the use of HAART in sub-Saharan Africa. Furthermore, up to 71% of fractures from a similar group of patients were complicated by osteomyelitis. These rates of infection are of great concern. In the context of a reduced BMD, a situation relevant to many HIV sero-positive patients, the use of internal fixation and particularly locking plates has been shown to give consistently good results. It may be that future research will show that infection rates in internal fixation are reduced in patients who are receiving HAART.

A recent randomised, controlled trial comparing pin-track infection in HIV-positive and HIV-negative subjects with open fractures of long bones found that there were significantly more infections in the HIV-positive group despite equivalent injuries. However, in comparison with the rates of infection observed in internal fixation, external fixation was associated with a much lower rate of wound infection of approximately 7%, although stratification of the study group was not discussed. This promising finding suggests that external fixation, if indicated mechanically, may be more appropriate for stabilisation of a fracture in HIV-positive patients. Despite this, it remains important to balance the risks of infection against the risks of poor stabilisation in determining the choice of fixation.

HIV serotype may increase the incidence of delayed fracture healing and nonunion

While there is evidence to suggest that all the factors discussed above may prove to be detrimental to patients infected with HIV by increasing the risk of fracture and impeding their healing, there are few studies which have specifically investigated fracture healing in HIV-positive patients. Harrison et al found an increase in the incidence of nonunion of externally-stabilised tibial fractures in HIV sero-positive patients, compared with a sero-negative control group, albeit without statistical significance. This was potentially a function of the small sample size. More importantly, the tibial fractures in question were open and, therefore, more vulnerable to infection. They found that infected fractures were more vulnerable to delayed or nonunion than non-infected injuries. The observed association between HIV and nonunion may, therefore, be secondary to an increased infection rate which would not be surprising in the light of the immunosuppressive effects of the retrovirus.

These reservations notwithstanding, the observed difference in fracture union in HIV-positive patients may be an independent consequence of the disease process and warrants further investigation. Furthermore, if complications in fracture healing in the presence of HIV can be reliably attributed to infection, this provides a crucial insight in order to ensure that surgical practice is pursued which minimises the risk of infection and improves the time to fracture union.

Studying fracture healing in the context of HIV

There are a number of issues which complicate the study of the effect of the HIV status on the outcome of fracture healing. The unravelling of the effect of HIV infection from those of immune reconstitution after HAART treatment, drug side-effects, cachexia and secondary infections demands rigorous study design, which can become ethically prohibitive. Furthermore, researchers in other areas have highlighted problems with detecting the time to union based on clinical or radiological criteria when patients are followed up at infrequent intervals. Moreover, the use of
serum biochemical markers as surrogates for fracture union in HIV patients should be treated with caution. Serum cytokine levels are of limited use in understanding what is happening in a local environment such as around a fracture callus. Serum levels of osteocalcin and other ‘markers’ of bone formation and resorption have been found to correlate poorly with fracture union and there is a high level of intersubject variability.

However, these issues can be managed with appropriate study design and interpretation and should not be a deterrent to further work in this field.

Summary

There is a suggestion that HIV infection may be related to delayed and nonunion of fractures. The altered cytokine environment arising from HIV infection may modify the inflammatory response which triggers the process of bone healing, although the exact form of such modification has yet to be understood. There is increasing evidence to suggest that HIV sero-positivity alone affects bone turnover, and in particular, may inhibit bone formation, which could contribute to problems with union. Modulation of the TNF-superfamily appears to be one mechanism by which the virus exerts these effects. Furthermore, reports of osteonecrosis in HIV-positive patients without other risk factors poses the question as to whether HIV may compromise the reliability of the blood supply required for fracture healing.

While much of this evidence is tangential to the specific case of fracture healing in patients infected with HIV, the area appears to be worthy of further investigation. HIV infection is becoming increasingly controllable with the use of anti-retroviral drugs. As a result, the number of people with a chronically-altered cytokine physiology, and therefore at risk of previously unrecognised pathological processes, is growing substantially. If the HIV status positively predicts an increased risk of delayed or nonunion in trauma patients, fracture management could be tailored accordingly. The selection of appropriate fixation methods, the optimisation of the nutritional state and the use of statins are emerging as potential management adjuncts, among others. Indeed, the screening of high-risk fracture patients for HIV has been advocated in order to tailor management.

This evidence therefore identifies an area in which emergency physicians and orthopaedic surgeons with limited knowledge of specialist HIV medicine could start to improve outcome significantly in this group of patients.

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References


