ORTHOPEDIC COMPLICATIONS IN HIV PATIENTS

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ABSTRACT

The considerable increase of the life expectancy of HIV--infected patients in the age of highly-powerful antiretroviral treatment results in important metabolic and bone--joint changes resulting from a long-lasting viral infection time and from this treatment. The most common orthopaedic complications are bone mineralization changes, osteonecrosis, carpal tunnel syndrome and gleno-humeral adhesive capsulitis, with different clinical presentation features, natural disease progression and therapeutic response compared to the overall population. Literature reports are initial, and the experience of the multidisciplinary service of the University of São Paulo's Institute of Orthopaedics and Traumatology enables us a more in-depth knowledge about the various pathologies involved and the development of treatment protocols that are appropriate to these diagnoses.

Keywords – HIV; Orthopaedics; Diagnosis

INTRODUCTION

With the considerable increase in the life expectancy of HIV-infected patients in the era of high-activity antiretroviral therapy (ART), some of the consequences of prolonged viral infection and that treatment have been seen. The metabolic consequences occurring within this context are explored in several publications in the literature, especially the lipodystrophy syndrome. Currently, the increasing observation of osteoarticular changes in these patients is the subject of more detailed study, with the aim of detecting their possible causes and determining the most appropriate therapeutic approach.

Among the complex metabolic changes in chronic HIV infection and its treatment, there is a decrease of bone mineralization in a high proportion of patients resulting from various factors present in the host itself, in the virus, and in the antiretroviral drugs (ARV). Bone is continuously remodeled by the synchronization of its formation and resorption, which can be deregulated during HIV infection. Bone mineralization decreases, causing osteopenia, which can result in osteoporosis.

The osteoarticular changes most frequently reported in patients infected for a long period with HIV and using ART are osteopenia/osteoporosis, osteonecrosis, carpal tunnel syndrome, and adhesive capsulitis of the shoulders.

Osteopenia/osteoporosis

According to the World Health Organization, the definitions of osteopenia and osteoporosis are based on bone densitometry results[(1)]. Osteoporosis is defined as when this ratio is less than 2 times the standard deviation, and osteopenia when the result is between -1 and -2 times the standard deviation[(2)]. Osteoporosis can be considered severe when, in addition to this criterion, the patient has a fracture (Figure 1).

Several studies have shown a high prevalence of these abnormalities in patients infected with HIV, according to these criteria[(1-4,6-11)]. Multiple factors have been reported as causes of osteopenia, including the direct effects of the virus on osteogenic cells;

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persistent activation of proinflammatory cytokines, particularly TNFα and interleukin-1; changes in the metabolism of vitamin D, with a deficiency in 1,25-dihydroxyvitamin-D; and the participation of mitochondrial abnormalities related to lactic acidemia and the development of opportunistic infections[4,5] (Figure 2).

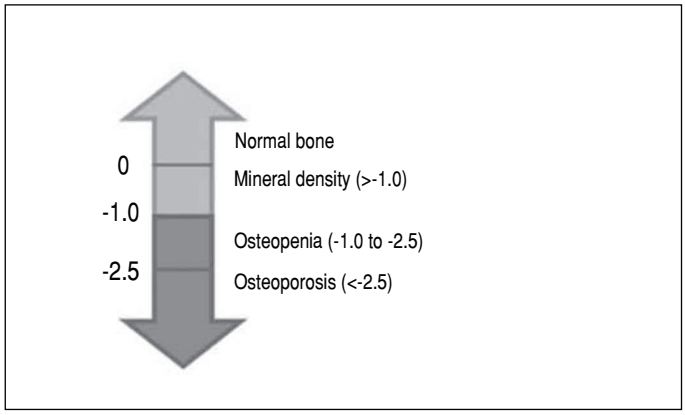

Figure 1 – Graphical representation of the normal ranges and changes in bone mineral density based on standard deviation from the general population.

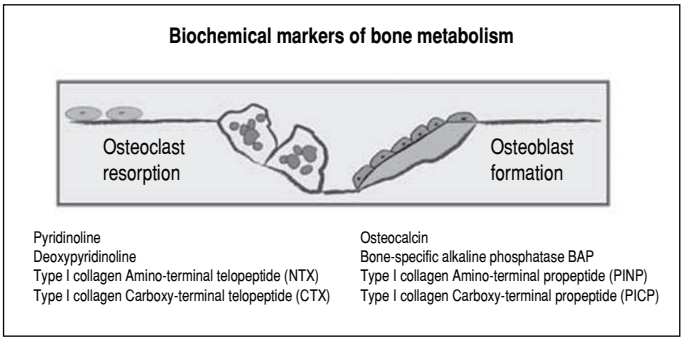

Figure 2 – Biochemical markers of bone metabolism.

There have been studies regarding the influence of antiretroviral therapy that show an increased risk when using protease inhibitors (PI), since indinavir is known to inhibit bone formation and ritonavir is known to inhibit osteoclast differentiation and function[1,6,7,9-11]. Recent reports on reverse transcriptase inhibitors have linked tenofovir to the occurrence of osteomalacia and Fanconi syndrome[12]. Still other factors may contribute to accelerated bone loss, such as nutritional deficiency, low serum calcium levels, immobilization, hypogonadism, hyperthyroidism, hyperparathyroidism, renal failure, use of opioids or heroin, use of corticosteroids, postmenopause in women, and alcohol consumption greater than 16g/day[1,8] (Figures 3 and 4).

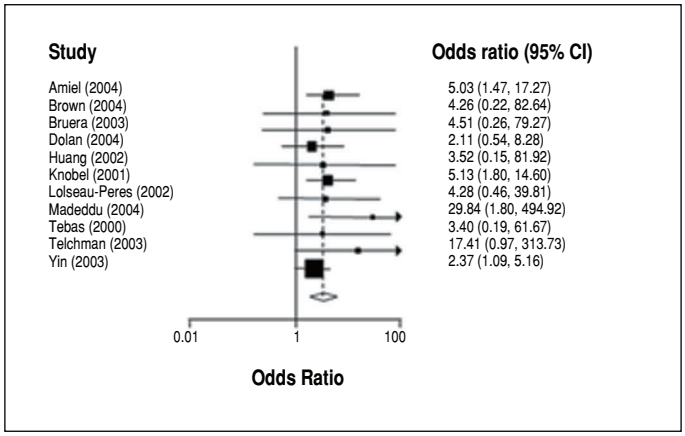

Figure 3 – Meta-analysis: risk of osteoporosis in HIV patients and control population.

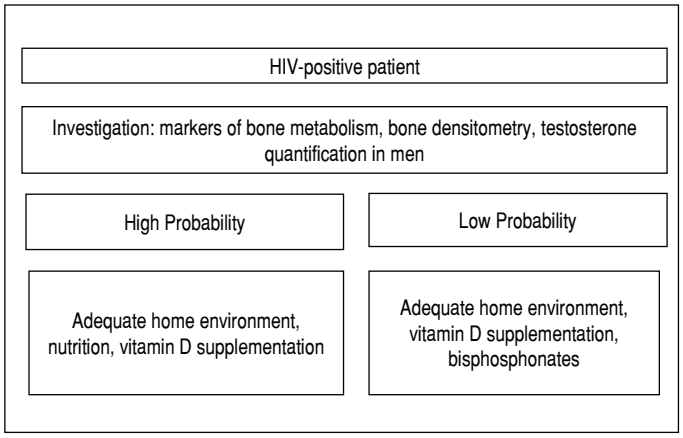

Figure 4 – Algorithm: investigation and prevention of complications of decreased bone mineral density.

The main form of osteoporosis treatment is prevention, conducted by encouraging physical activity and proper nutrition in the first three decades of life in order to reach maximum bone mass formation.

Calcium intake and supplementary vitamin D should be part of any therapeutic regimen for osteoporosis. In postmenopausal women, hormone replacement therapy is an important method of prevention of osteoporosis. As for drug therapy, there are basically two classes of medications: bone antiresorptive agents and bone formation-stimulating agents.

Osteonecrosis

The occurrence of osteonecrosis in patients with HIV has been reported since 1990, with incidences that are progressively increasing and higher than the general population[7,8]. The annual incidence of symptomatic osteonecrosis in the general population is estimated between 0.010 and 0.135%[13].

Recent studies using magnetic resonance imaging

(MRI) to detect osteonecrosis in patients with HIV have estimated its incidence to be approximately 4%. The incidence of bilaterality ranges from 35 to 80%[13].

In the general population, there some known risk factors and conditions associated with the development of osteonecrosis, such as the use of systemic corticosteroids, alcoholism, hyperlipidemia, sickle cell anemia, coagulopathies, Gaucher's disease, systemic lupus erythematosus, rheumatoid arthritis, hyperuricemia and gout, radiation therapy, obesity, pancreatitis, fracture sequelae, chemotherapy, vasculitis, and smoking. Besides these factors, in the development of osteonecrosis in patients infected with HIV, we also have dyslipidemia, the use of megestrol acetate and steroids, testosterone replacement, as well as the forms of vasculitis that predispose the patient to intraosseous thrombosis by the presence of anticardiolipin antibodies and by a deficiency of S protein. Moreover, the antiretroviral therapy itself may be related to the increasing development of osteonecrosis[7,8,13].

For the diagnosis of osteonecrosis, clinical signs should be observed, such as the presence of joint pain and limitations in the range of motion. The most frequently involved joints are the hips, unilaterally or bilaterally, the knees, ankles, elbows, and shoulders[14,15].

It should be noted that the interval between radiological changes and clinical symptoms can be long, ranging from three to eight years. Simple radiographs of the joint have low diagnostic sensitivity early in the disease. The radiological findings frequently indicating osteonecrosis include cystic sclerosis, subchondral radiolucency, bone collapse, and degenerative joint changes. Computed tomography without contrast adds little information to ordinary radiographs. MRI has 99% sensitivity and specificity for diagnosis from the earliest phase. Bone scintigraphy can be used to determine its stage and in the search for hidden asymptomatic foci, although it is not very specific[14,15].

Treatment varies with the stage of the disease. In patients with HIV, it is important to exclude or control other risk factors that are not part of the disease itself or the antiretroviral drug. In oligosymptomatic individuals, treatment may be based on the use of analgesics and non-hormonal anti-inflammatory drugs[6].

Decompression procedures can be used in the area of necrosis in the early stages, with or without free or pedicled cortico-spongious grafts. With disease progression, when changes in articular congruence begin, procedures such as osteotomies, unicompartmental arthroplasty or hemiarthroplasties may be indicated, and in more advanced cases, the solution is total arthroplasty[14].

Carpal tunnel syndrome

The incidence in the general population is around 3.8% with clinical examination and, when electroneuromyography is used, it is 2.7%. In the HIV-positive population, the incidence has remained very close to that of the general population[16,17].

This syndrome has been associated with the use of ART, especially protease inhibitors, and would result from known metabolic disorders and as myxedematous material is deposited in the carpal tunnel, with consequent nerve compression. Other factors such as professional activities, hypothyroidism, hyperglycemia, rheumatoid arthritis, obesity, and various metabolic disorders are associated with the development of this syndrome in patients with HIV/AIDS. Therefore, the direct correlation with the presence of HIV and antiretroviral therapy is still questionable[16,17].

Treatment is based on the stage of the compression syndrome. In the mild stage, treatment is conservative, with the use of nocturnal splints and the use of anti-inflammatory medications[18]. In the moderate and severe stages, surgical treatment is indicated. This can be performed conventionally or endoscopically[18]. In both procedures, the median nerve is decompressed through the opening of the flexor retinaculum.

Adhesive capsulitis

Adhesive capsulitis has been linked to HIV patients receiving an ART regimen with PIs[19]. The reported cases are limited to shoulder involvement, suggesting that other sites are rare[19,20]. The condition's characteristic symptoms include progressive unilateral or bilateral pain in the shoulders, with restricted active and passive ranges of motion. Classically, the onset of symptoms is insidious, occurring about 12 to 14 months after initiation of the use of PIs[19]. Simple radiographs may show bone rarefaction caused by disuse, however, magnetic resonance arthrography is the examination of choice for diagnosis. Symptoms tend to regress spontaneously after a period of six to

24 months with the institution of adequate treatment and interruption of ART[19,20].

The treatment of adhesive capsulitis depends on its time course and the severity of adhesions. In milder cases, conservative treatment with analgesics, anti-inflammatory drugs, and physical therapy is the most suitable[19,21]. In the most severe cases, which are unresponsive to conservative treatment, arthroscopic treatment is the most suitable, followed by early mobilization. We have avoided the indication of manipulation alone due to the higher incidence of proximal humerus fractures and its more painful postoperative period, which makes early mobilization difficult[21].

DISCUSSION

Given the prevalence and importance of osteoarticular changes, in March 2006 the IOT began caring for HIV/AIDS patients with orthopedic complaints who were referred from two referral centers for the treatment of patients infected with HIV.

From March 2006 to March 2008, of the 206 patients evaluated, 83 were enrolled in the clinic, with a total of 614 visits between initial consultations and returns.

The patients studied had prolonged HIV infection, with an average of 114 months since diagnosis. They also had prolonged exposure to ART, with a mean of 96 months of use. Among the most widely used drugs were lamivudine, zidovudine, and nelfinavir. There was a history of PI use in 72% of the sample (Figure 5).

At the time of evaluation, only 8% of patients had CD4 counts below 200 cells/mm^3 and 74% had an undetectable viral load.

The most prevalent orthopedic change in this population was osteonecrosis, with an incidence of 12%. The hip joint was the most affected, with findings of bilaterality in all cases. One hundred per cent bilaterality is easily explained for all cases by the origin being secondary, which raises this index (Figure 6 and Table 1).

The chief patient complaint initially consisted of only hip pain with limitation of motion and limping during evolution, following the classical clinical picture of the disease.

All patients diagnosed with osteonecrosis were in advanced stages of the disease.

This fact may indicate a disease with a more

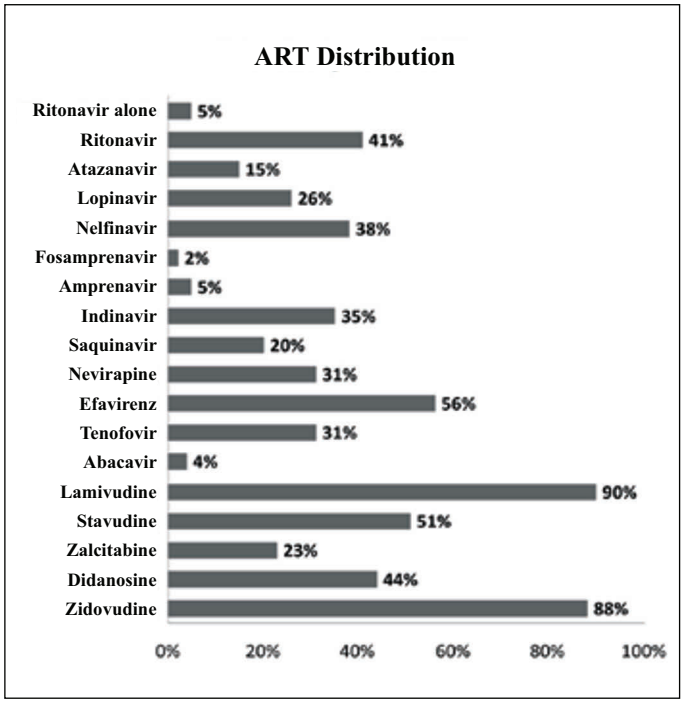

Figure 5 – Distribution of ART among HIV-infected patients monitored at the IOT outpatient clinic.

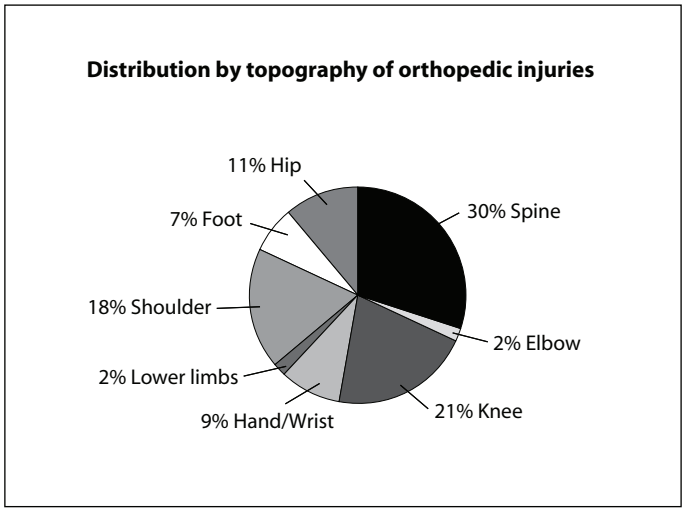

Figure 6 – Distribution by topography of orthopedic injuries in HIV-infected patients monitored at the IOT outpatient clinic.

Table 1 – Osteoarticular changes.

Upper limbs	Lower limbs	Degenerative	Axial skeleton
Osteonecrosis of the humeral head	Osteonecrosis of the femoral head	Tendinopathies	Mechanical back pain
Carpal tunnel syndrome	Osteonecrosis of the femoral condyle	Muscular injuries	Vertebral body collapse
Adhesive shoulder capsulitis	Metatarsalgia		
	Femoropatelar syndrome		

aggressive course or a longer delay in diagnosis, probably related to the abundant clinical manifestations of this population and little appreciation for secondary complaints. In addition, we observed a trend of more rapid clinical disease progression in this study, with more intense pain and a pattern of response to non-surgical treatment that is less favorable than that of the general population.

CONCLUSION

Osteoarticular complications show a significant prevalence in the population living with HIV receiving high-activity antiretroviral therapy, with a pattern of clinical presentation, natural disease course, and response to therapy that is different from those of the general population.

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