REABSORPTION IN BONE METABOLISM OF HIV-POSITIVE PATIENTS

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SUMMARY

Introduction: HIV-infected patients show osteoporosis or densitometric osteopenia at a rate of 28-50%. The objective of this study is to check the changes on reabsorption/ development rates on these patients. Materials and Methods: A systematic review was carried out with meta-analysis of controlled studies assessing the correlation between osteopenia and/ or bone metabolism changes with HIV infection. All studies including osteocalcin or NTX with corresponding markers of bone development and reabsorption were included. Five studies were classified as class-III evidence, and involved 456 HIV-positive individuals and 590 controls. NTX had a significant increase ($p < 0.00014$) on the HIV-positive group, while osteocalcin has shown to be unchanged. Conclusion: This study allows us to conclude that, during HIV infection, the NTX marker is significantly high, reflecting a high reabsorptive activity on the bone tissue. This suggests an important role on osteoclastic activity in bone loss for HIV-positive patients.

Keywords: *HIV. Bone diseases, metabolic. Bone resorption.*

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INTRODUCTION

HIV-infected patients show densitometric osteopenia or osteoporosis at a ratio ranging from 28 to 50%, against an expected percentage of 16% in the overall population.[1,2] It was also evidenced that HIV-positive patients show significant changes on biochemical markers of bone metabolic activity, such as pyridinolins, alkaline phosphatase, NTX, CTX, hydroxyprolin and osteocalcin, among others.

The immune response associated to HIV infection produces pro-inflammatory cytokines activation, such as interleukins and growth factors that change the inter-relationship of the bone metabolic unit (osteoblasts and osteoclasts).[3] A protein found in the virus itself (TAX viral protein), which contributes to its replication and to the development of immunodeficiency, is strictly related to these changes proteína.[4,5]

AIDS is also associated to multiple risk factors to osteopenia, producing various metabolic and endocrine changes that lead to appetite, body weight loss and reduced functional ability.[6] In addition, antiretroviral therapy has been pointed out as a factor to bone metabolism unbalance, and may importantly contribute to bone mass loss.[7]

Determining whether these changes are caused by an increased osteoclastic activity (reabsorption) or by the inhibited osteoblastic activity (formation) is essential for effective therapeutic strategies. Despite of that, most publications studying the activity of bone reabsorption and formation markers did not show enough statistical power to provide definitive conclusions. The objective of our study is to check for the existence of changes on bone reabsorption/ formation ratio on HIV-positive patients; for that, we used a meta-analysis of relevant studies assessing NTX (reabsorption marker) and osteocalcin (formation marker) levels in this group of patients.

METHODS

We conducted a systematic review with meta-analysis of controlled studies assessing the correlation between osteopenia and/ or changes on bone metabolism and HIV infection. All studies including osteocalcin as a bone formation marker and NTX as a reabsorption marker were assessed. The primary goal was to check if these markers were changed on HIV-positive patients, suggesting any bias on bone metabolism. Controlled studies involving HIV-positive patients were selected, regardless of being under therapy with Protease Inhibitor agents.

Literature search

In order to identify relevant studies, we made a search comprehending the last 20 years (1987 to 2007) on the following databases: MEDLINE, LILACS and EMBASE, assessing the correlation between HIV and Bone Metabolism Markers. The studies in every language were selected, and the following keywords (in English) were used in the search, either isolated or combined: HIV; bone; osteoporosis; osteopenia; osteocalcin, and; NTX> We also surveyed and selected publications listed on references of selected articles in order to supplement the search.

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INCLUSION AND EXCLUSION CRITERIA

The meta-analysis inclusion criteria were the following: studies assessing osteopenia and/or changes on bone metabolism of HIV-positive patients, controlled studies showing at least two comparison groups (e.g., HIV-positive vs. HIV-negative) and presenting as an analysis variable at least one of the markers being studied (osteocalcin or NTX).

The studies were classified according to their level of evidence, as suggested by the Centre for Evidence-Based Medicin.[8] From each selected article, the following data were withdrawn: data source, study design, inclusion and exclusion criteria for patients, mean osteocalcin and NTX levels, number of subjects on HIV + and – groups, number of subjects in treatment groups, with and without protease inhibitor agents.

STATISTICAL METHODS

All selected studies were distributed on descriptive statistics tables. A meta-analysis was performed by random effects method in view of the heterogeneous nature of the studies. The standardized mean difference (SMD) was employed as endpoint variable for each study. SMD is a continuous variable appropriate for meta-analyses where primary studies also use this kind of variable, such as in the case of osteocalcin and NTX dosages. The combined effect of these studies was assessed by Z test and heterogeneity was assessed by Cochram's Q-test, adopting a significance level of $p<0.05$ for both. The results of the meta-analysis were presented as tables.

RESULTS

Our search strategy produced 42 articles, but only five of these fully met the inclusion criteria, being selected for the meta-analysis. These studies involved 456 HIV-positive subjects and 590 control subjects, at total. We could not assess the results according to age, gender and severity of the disease. All selected studies were classified as class III evidence level (case-control type).

Despite of the different methods employed on laboratory analyses, the results were presented with the same measurement unit and, thus, can be regarded as equivalent and appropriate for statistical analysis. The results of the meta-analytic treatment are shown on Tables 1 and 2.

Table 1 – *Evaluation of NTX bone marker in HIV-positive patients*

Study	SMD	CI (upper)	CI (lower)	Weight (W)
Dolan	– 3.26736	– 3.01435	– 3.52038	60.00852
Teichmann	– 4.5759	– 4.31945	– 4.83236	58.40958
Mora	– 6.82527	– 6.5116	– 7.13894	39.04475

Overall SMD = -2.92219 (standard error = 0.76763), P = 0.00014, Q = 0.00000
SMD – standardized mean difference, CI – confidence interval.

Table 2 – *Evaluation of Osteocalcin bone marker in HIV-positive patients.*

Study	SMD	CI (upper)	CI (lower)	Weight (W)
Dolan	– 1.51907	– 1.22434	– 1.81379	44.22648
Teichmann	2.995975	3.455552	2.536399	18.18847
Amiel	0.032517	0.303915	0.23888	52.1555
Bruera	– 0.11863	0.277511	– 0.51477	24.48018

Overall SE = 0.280819 (SE = 0.7309), P = 0.70283, Q = 0.00000
SMD – standardized mean difference, CI – confidence interval.

Five studies were selected for analysis, namely: Mora et al 2004[9], Dolan et al 2004[10], Amiel et al 2003[11], Bruera et al 2003[12], Teichmann et al 2003.[13] Below, the main individual characteristics of each article are presented.

Mora et al[9] conducted a longitudinal study on 32 HIV-infected subjects exposed to HAART (highly-active antiretroviral agents), comparing them to 381 volunteers of the same age group. The variables of the study were: BMD (bone mineral density) assessed by DEXA, bone alkaline phosphatase and NTX, measured on serum and urine. Data confirmed the presence of low BMD and impaired bone metabolism on the HIV-positive group.

Dolan et al.[10] assessed 84 HIV-infected women and 63 healthy women with similar age, body weight and ethnicity. In addition to bone markers (OC and NTX), BMD was also assessed, enabling to conclude that HIV-infected women showed a reduced bone mass.

In a cross-sectional study, Amiel et al.[11] assessed 148 HIV-infected men stratified according with their antiretroviral treatment approach. BMD was assessed by bone densitometry, in addition to bone metabolism markers (OC and NTX). No treatment effect was found for bone metabolism, but bone mass loss was seen in HIV-infected patients, regardless of treatment approach. This low BMD was partially correlated to reduced body weight and increased bone reabsorption.

Bruera et al.[12] studied 142 individuals in the age group of 20-45 years, divided into 4 groups: A, 33 HIV-infected treatment-naive patients; B1, 36 HIV-positive subjects under treatment for more than one year (without protease inhibitors); B2, 42 HIV-positive subjects using antiretroviral therapy for over one year (protease inhibitor); B3, 15 healthy individuals (control). BMD was assessed by bone densitometry and by various markers of bone metabolism. BMD was significantly lower in HIV-infected subjects, but no difference was found between the therapy-naive group and the others.

Teichmann et al.[13] studied BMD and biochemical markers of bone metabolism in 50 HIV-infected subjects versus controls. No patient received reverse-transcriptase inhibitors or protease inhibitors, or vitamin D or calcium supplements. A correlation was found between low bone formation markers levels and increased bone reabsorption.

DISCUSSION

Osteopenia in HIV-positive patients is well established by scientific literature[1,2,6]; however, causes and associated factors that could explain the bone mass loss found on these individuals remains as a required challenge for preventing or minimize this important co-morbidity associated to HIV/ AIDS. Our results allowed us to conclude that the bone reabsorption marker (NTX) is shown to be significantly high in the HIV-positive group, while the bone formation marker (Osteocalcin) is found slightly reduced in the same group, but not with statistical significance.

The selected studies were heterogeneous (Cochram's Q-test); despite of this fact, we did not perform a classical analysis of sensitivity in light of the small number of studies meeting the inclusion criteria that were found in our literature search. In spite of that, we could assume that the main sources of heterogeneity were the small sample size, the lack of statistical power on the studies, and the heterogeneity of patients included on HIV-positive group in each individual study.

Our meta-analysis was constituted of Class-III evidence studies (basically, case-control studies) and those researches are not conceived to prove the etiology, but only an association between variables. A meta-analysis, however, may solve some of the individual problems in each study, improving the reliability and providing more powerful results; the five individual assessed studies tend to show that bone metabolism markers do not show differences when HIV-positive and negative groups are assessed. When a meta-analysis is made, the NTX reabsorption marker, as oppositely to what happened on individual studies, shows to be significantly higher ($p < 0.00014$) on HIV-positive group (Table 1). The heightened NTX level suggests that osteopenia (bone loss) seen in HIV-infected patients may be due to an increased osteoclastic activity related to viral infection.[14] Bone formation, however, measured by osteocalcin marker, did not show significant changes; a reduction on bone formation doesn't seem to contribute to osteopenia, as an increased formation is not associated as a protective factor. These findings may suggest that reabsorption increase, alone, is the main cause of bone mass loss in this group of patients.

There are many possible causes to explain the increased osteoclastic reabsorption in these individuals. HIV infection is associated to a number of co-morbidities leading to musculoskeletal system hypoactivity and also to metabolic and endocrine complications causing weight loss, hypogonadism, reduced organic capacity and increased catabolism; these complications are well-known risk factors associated to bone mass loss.[6] HIV infection may also influence, either directly or indirectly, the increase of osteoclastic activity by the interaction between immune response and bone homeostasis.

Many authors have demonstrated that cytokines released by inflammatory immune response, such as IL1, IL3, IL4, IL6, and IL11, TNF-α and several CSFs, including MCSF, are implicated on the control of osteoclastic differentiation and activation[15], increasing bone reabsorption.[16,17] Another suggested mechanism for explaining the increased osteoclastic activity involves the hyperexpression of cytokines and specific growth factors; increased IL4 or TGFb levels on the bone may result in bone mass loss, which is probably due to primary effects on osteoblasts.[6,15,16,17]

The activation of pro-inflammatory cytokines, such as IL-1 and TNF-α, plays an important role on AIDS pathogenesis.[3] This pro-inflammatory activation contributes to virus replication, to the development of immunodeficiency, and to the onset of some clinical manifestations, especially endocrine abnormalities seen in HIV-infected patients.[3,6,18]

Various cytokines and growth factors seem to be involved in the modulation of osteoblasts and osteoclasts.[6,18-20] TAX viral protein has been shown to play an important role in bone pathologies by inducing genes responsible for multiple cytokines, such as IL-6, IL2R TNF-alpha, as well as GM-CSF, which modulate osteoclasts and enhance bone reabsorption.[6,18-20] Indeed, the association between these cytokines and bone remodeling has been seen in many osteometabolic diseases, including post-menopausal osteoporosis.[4,5]

Our data provide an original contribution to the topic, suggesting that the increased osteoclastic activity might be responsible for BMD loss in this group of patients. The confirmation of these findings provides an important subside for justifying anti-reabsorptive therapies, such as the use of biphosphonates, for osteopenia in HIV-positive patients. We believe that many factors can contribute to increased osteoclastic bone reabsorption in these patients. Among these, we highlight the influence of co-morbidities that physically impair patients and the interaction of inflammatory immune response with bone homeostasis, by direct action on the osteoclast or by indirect action mediated by osteoblasts. Further studies clearly focusing all these physiopathological aspects are warranted to explain the real source of enhanced osteoclastic reabsorptive activity in HIV-infected individuals.

CONCLUSION

Our data allow us to conclude that during the course of HIV infection, the bone reabsorption marker NTX was found significantly high, suggesting a highly reabsorptive activity of bone tissue. These data point out to an important role of osteoclastic activity on bone loss in HIV-positive patients.

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