Insulin Resistance and Its Association With Osteoporosis in People Living With HIV

Gabriela Caeran,1 Luciana L. de Almeida,1 Thales A.S.H. Ilha,1 José A.M. de Carvalho,2 Carolina Stein,1 Rafael N. Moresco,2 Carlos J.P. Haygert,1 Fabio V. Comim,3 and Melissa O. Premaor3

1Department of Clinical Medicine, Federal University of Santa Maria, Santa Maria, Rio Grande do Sul 97105-900, Brazil
2Department of Clinical and Toxicalogical Analysis, Federal University of Santa Maria, Santa Maria, Rio Grande do Sul 97105-900, Brazil
3Department of Clinical Medicine, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais 30130-100, Brazil

Correspondence: Melissa Orlandin Premaor, MD, PhD, Departamento de Clínica Médica, Universidade Federal de Minas Gerais, Avenida Professor Alfredo Balena, 190 – sala 246, Belo Horizonte/MG, Brazil. Email: premaor@medicina.ufmg.br.

Abstract

Background: Despite the gain in life expectancy that people living with HIV (PLHIV) have had in the past few years, the disease is accompanied by an increase in the prevalence of noninfectious chronic diseases. PLHIV have a higher prevalence of osteoporosis, fracture, diabetes mellitus, and insulin resistance than the general population. It is unknown if insulin resistance is associated with osteoporosis and fractures in PLHIV. Our study aimed to assess the association between insulin resistance and osteoporosis in PLHIV.

Methods: A cross-sectional study was carried out in southern Brazil. PLHIV ages 50 years or older on antiretroviral treatment were included. Insulin resistance was considered present when the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was higher than expected for the Brazilian population (>2.7). The triglyceride-glucose (TyG) index was also calculated.

Results: Of the 101 PLHIV who agreed to participate, 84 underwent insulin and bone mineral density measurements. The prevalence of osteoporosis was 19%. The frequency of insulin resistance calculated by HOMA-IR was 68.2%. Participants with osteoporosis had lower body mass index (BMI) and triglyceride values than those without it. HOMA-IR [4.8(6.6) vs 8.68(9.6), P=0.013] and TyG [5.0(0.3) vs 5.2 (0.4), P=0.029]. The association between the total femur t-score disappeared after correction for BMI in the linear regression model. There was no association between vertebral fractures and insulin resistance.

Conclusion: In our study, PLHIV with osteoporosis have lower insulin resistance than PLHIV without it. However, this finding appears to be related to lower BMI. The association between insulin resistance and bone in PLHIV appears to be somewhat similar to that of the general population.

Key Words: HIV, osteoporosis, insulin resistance, vertebral fracture

According to the World Health Organization (WHO), in 2020, 37.7 million people were living with the human immunodeficiency virus (PLHIV) worldwide [1]. Advances in antiretroviral therapy (ART) have led to an increase in the survival of these patients in recent years [2, 3]. Now, it is almost the same as the general population [2, 3]. Contrastingly, the prevalence of noninfectious chronic diseases appears to increase in PLHIV and occur at an earlier age than in the general population [2, 3]. PLHIV have a higher frequency of cardiovascular disease, diabetes mellitus (DM), osteoporosis, and fractures [3, 4].

Subjects with DM have a higher risk of fractures than the general population [5–7]. This higher risk is present in patients with type 2 DM, even though they had increased bone mineral density (BMD) compared to healthy controls [5–7]. Factors such as chronic inflammation, glucose toxicity, and insulin resistance have been suggested as possible explanations for the bone disease present in patients with type 2 DM [5–7].

PLHIV have an increased prevalence of DM and insulin resistance [8]. Further, the frequency of DM seems to be twice the frequency of the general population [4]. In a study carried out in Africa, Noumegni et al found a prevalence of insulin resistance of 47.3%, despite a prevalence of DM of 2% [9]. Insulin resistance and DM might be associated with bone diseases in PLHIV. Therefore, our study aimed to evaluate the association between insulin resistance and osteoporosis in PLHIV in southern Brazil. We also studied the association between vertebral fractures and insulin resistance in these subjects.

Methods

A cross-sectional study was carried out on PLHIV registered to receive ARVs at the pharmacy of University Hospital of Santa Maria, South Brazil, from 2016 to 2018 [10]. According to Brazilian legislation, all PLHIV on ARVs must be registered at a referral pharmacy to receive the medication.
Thus, this patient registry list covered all individuals with an indication for ART in our region. The study population consisted of men and women ages 50 years or older. All patients registered at the pharmacy to receive ART were invited to participate in the study by telephone. All recruited subjects signed informed consent. The study was approved by the Research Ethics Committee of the Federal University of Santa Maria (CAAE 50505015.7.0000.5346) and followed the norms of Resolution 466/12 of the National Health Council and the Declaration of Helsinki.

A standardized questionnaire containing demographic and clinical data was applied. All biochemical assays were performed on the Mindray BS 380® automated system (Shenzhen, China). The parameters total cholesterol, high-density lipoproteins, triglycerides, and glucose were measured using Bioclin® reagents (Belo Horizonte, Minas Gerais, Brazil) using enzymatic methods. Creatinine was measured using Bioclin® reagents (Belo Horizonte) using colorimetric methods. Insulin was measured by the electrochemiluminescence methodology in the Cobas 6000 equipment (Roche, Basel, Switzerland).

Weight and height were measured according to the WHO recommendations [11]. BMD was measured by dual-energy x-ray absorptiometry (Lunar iDXA, GE Healthcare, Chicago, IL, USA), following the recommendations of the International Society for Clinical Densitometry (2015) [12]. The diagnosis of osteoporosis followed the WHO recommendations of 1994. It was considered present when the t-score was ≤ −2.5 in any measured sites (total femur, femoral neck, or spine) [13].

Vertebral fractures were evaluated using the Genant semiquantitative assessment [14]. This method uses the following scores: 0, no deformity; 1, mild deformity (anterior, medial, or posterior reduction in vertebral body height >20%−<25%); 2, moderate deformity (reduction in vertebral body height 26%−40%); 3, severe deformity (>40% reduction in vertebral body) [14]. Scores above 1 were considered vertebral fractures.

The assessment of insulin resistance was performed by calculating the Homeostatic Model Assessment of Insulin Resistance [HOMA1-IR = (I × G)/22.5 and HOMA1-%Beta = (20 × I)/(G − 3.5)] [15]. I corresponded to insulin in mmol/L and G to glucose in mmol/L. Insulin resistance was considered present when HOMA-IR was above the Brazilian population cut-off point (>2.7) [15]. The triglyceride-glucose (TyG) index [log (triglycerides × glucose)]/2 was also calculated [16].

Statistical Analysis

The results were expressed as prevalence rate (percentage), mean (standard deviation), and median (minimum, maximum). Student’s t, Mann-Whitney, and Fisher’s exact tests were used to assess variables associated with osteoporosis. A sensitivity analysis was performed, repeating the analysis but including only subjects with a body mass index (BMI) below 25 kg/m². The association between total hip t-score and insulin resistance was evaluated in a multiple linear regression model that included noncollinear variables with a P-value <0.05. Associations were considered significant whenever the 2-tailed P-value was less than 0.05. Statistical analyses were performed using the IBM SPSS Statistics 18.0 (IBM, Armonk, NY, USA).

Results

A total of 480 patients were invited to participate in the study, of whom 101 completed the questionnaire and 84 underwent both insulin dosage and BMD measurement plus spine X-ray. The characteristics of the subjects included in the study are described in Table 1. The prevalence of osteoporosis was 19%. Individuals with osteoporosis had lower BMI and triglycerides than individuals without osteoporosis. Vertebral fractures occurred approximately twice as often in individuals with osteoporosis. Both the HOMA-IR index and the TyG index were higher in the group without osteoporosis when compared to the group with osteoporosis; the HOMA-Beta index was similar between the groups (Table 1).

After performing a sensitivity analysis, in which we included only subjects with a BMI less than 25, only BMI (osteoporosis 21.2 (SD 1.9) vs without osteoporosis 22.5 (SD 1.9), \( P = 0.049 \)) and vertebral fractures (osteoporosis 81.8% vs without osteoporosis 33.3%, \( P = 0.012 \)) remained associated with osteoporosis. There was a statistical trend toward a higher index of HOMA-IR (osteoporosis 3.8 (SD 5.1) vs without osteoporosis 6.72 [(SD 10.0), \( P = 0.068 \)] in the group without osteoporosis.

HOMA-IR values did not differ in individuals with or without morphometric fractures [9.3 (SD 11.9) vs 6.6 (SD 6.5), \( P = 0.827 \)]. In addition, there was no association between vertebral fractures and insulin resistance in univariate regression analysis (data not shown).

The final model to assess the association between total femur T-score and insulin resistance is shown in Table 2. In the multiple linear regression model, the association between HOMA-IR and total femur T-score and TyG index and total femur T-score disappeared. BMI remained independently associated with osteoporosis in this model.

The frequency of insulin resistance was 68.20%. The use of glucocorticoids, smoking, and BMI were associated with insulin resistance (Table 3). Furthermore, there was no association between viral load and CD4 count and insulin resistance (Table 3).

Discussion

Our study evaluated the prevalence of osteoporosis and its association with insulin resistance in PLHIV. In our study, patients without osteoporosis had greater insulin resistance assessed by HOMA and TyG indices. When we excluded overweight patients, only TyG tended to have higher scores in subjects without osteoporosis. Furthermore, in the multiple linear regression analysis, the association between insulin resistance and t-score disappeared after correction for BMI.

Our findings suggest that the effects of insulin resistance on PLHIV bone may be similar to the effects of insulin resistance in the general population. In a populational study carried out in South Korea that included 1008 postmenopausal women (mean age 57.3 years), the t-score showed a linear association with the quartiles of the HOMA-IR [17]. Similar to our study, this association disappeared after adjusting for weight and height [17]. Furthermore, the Health, Aging and Body Composition Prospective Cohort Study, which evaluated 2398 community-dwelling, older adults without diabetes, found a 0.104 g/cm² increase in total hip BMD in the fourth quartile compared to the first quartile (\( P < 0.001 \)) [7]. This association was also attenuated after adjusting for BMI.
On the other hand, another study carried out in Tunisia, also in postmenopausal women, compared BMD between women with insulin resistance and the same BMI and found a higher BMD in the femoral neck and the total femur women with insulin resistance [18].

As well as in people with diabetes, PLHIV have an increased risk of fractures compared to the general population. Thereby, we had hypothesized that insulin resistance could be a common mechanism for these 2 diseases to be associated with an increased risk of fractures. Nevertheless, in our study, morphometric spine fractures were not associated with insulin resistance in PLHIV. Similarly, recent data from the Health, Aging and Body Composition Prospective Cohort Study also did not find an association between insulin resistance and increased risk of fractures in postmenopausal women after adjusting for confounding variables [risk of the last quartile compared to the first 1.12 (95%CI 0.87-1.46, P for linear trend 0.215)] [7].

The literature has extensively described the association between increased BMI and increased BMD. However, it should

| Table 1. Clinical characteristics of the sample studied according to the presence or absence of osteoporosis |
|-------------------------------------------------|
| Clinical parameters                             | Without osteoporosis | With osteoporosis | P-value |
| Age [years (SD)]                                | 57.3 (6.6)            | 58.8 (5.0)         | 0.336^a |
| Women (%)                                       | 39.7                  | 56.3               | 0.269^b |
| Time of diagnosis [years (SD)]                 | 11.0 (7.3)            | 9.4 (5.9)          | 0.354^b |
| Hepatitis B (%)                                 | 2.9                   | 0                  | 1.0^b   |
| Hepatitis C (%)                                 | 8.8                   | 18.8               | 0.363^c |
| Comorbidity (%)                                 | 30.9                  | 13.3               | 0.216^d |
| Diabetes mellitus (%)                          | 11.8                  | 0                  | 0.343^d |
| Family history of fracture (%)                 | 3.2                   | 0                  | 1.0^b   |
| Previous fracture (%)                          | 30.9                  | 31.3               | 1.0^b   |
| Corticosteroid use (%)                         | 28.4                  | 20.0               | 0.748^b |
| Physical activity (%)                          | 33.3                  | 25.0               | 0.765^b |
| Smoking (%)                                     | 26.5                  | 37.5               | 0.375^b |
| Alcohol use (%)                                 | 39.7                  | 25.0               | 0.390^b |
| Use of drugs (%)                                | 20.9                  | 12.5               | 0.725^b |
| BMI [kg/m2 (SD)]                                | 26.4(4.5)             | 22.9(3.9)          | 0.005^a |
| Morphometric fracture of spine (%)             | 36.5                  | 73.3               | 0.018^b |

| Biochemical parameters                         |                      |                    |         |
| CD4 [cell/mm3 (SD)]                            | 604 (260)             | 542 (205)          | 0.317^a |
| Viral load [copies/mL (SD) median (min. max)]  | 264 (1443)            | 217 (830)          | 0.808^a |
| Creatinine [mg/dL (SD)]                        | 1.01(0.3)             | 1.06(0.2)          | 0.534^a |
| Glucose [mg/dL (SD)]                           | 161.8(72.7)           | 135.1(64)          | 0.172^a |
| Insulin [IU/mL (SD)]                           | 20.8(19.7)            | 13.7(14.7)         | 0.179^a |
| Total cholesterol [mg/dL (SD)]                 | 223.6(60.9)           | 224.3(69.9)        | 0.971^a |
| HDL [mg/dL (SD)]                               | 63.2(23.1)            | 73.9(30.9)         | 0.223^a |
| LDL [mg/dL (SD)]                               | 106.6(50.8)           | 114.5(53.3)        | 0.610^a |
| Triglycerides [mg/dL (SD)]                     | 269.2(185.4)          | 179.9(59.6)        | 0.002^a |

| Insulin resistance                              |                      |                    |         |
| HOMA-IR                                        | 8.68 (9.6)            | 4.8(6.6)           | 0.013^a |
| HOMA-B                                         | 121.2(166.9)          | −5.9(330.3)        | 0.087^a |
| TyG index                                      | 5.2 (0.4)             | 5.0 (0.3)          | 0.029^a |

Abbreviations: BMI, body mass index; CD4, T-CD4 lymphocytes; HDL, high-density lipoproteins; LDL, low-density lipoproteins; HOMA-B, Homeostatic Model Assessment Beta; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; TyG, triglyceride/glucose

^aStudent’s t-test.

^bMann-Whitney test.

Table 2. Multiple linear regression model evaluating the association between the t-score of total hip and insulin resistance

|                       | B   | SEB | Beta | P-value |
|-----------------------|-----|-----|------|---------|
| BMI                   | 0.157 | 0.026 | 0.608 | <0.0001 |
| HOMA-IR               | 0.001 | 0.013 | 0.012 | 0.906   |
| TyG                   | 0.193 | 0.306 | 0.630 | 0.531   |

Abbreviations: BMI, body mass index; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; TyG, triglyceride/glucose index

(adjusted mean difference 0.007 g/cm2; P = 0.371) [7].
Wandelger G, Johnson LF, Egger M. Trends in life expectancy of PLHIV and an increased risk of DM 
In conclusion, in our study, PLHIV with osteoporosis have less insulin resistance than PLHIV without osteoporosis. However, this finding appears to be related to lower BMI in patients with osteoporosis. This finding might be similar to that found in postmenopausal women, which suggests that the effect of insulin resistance on bone metabolism may be similar to that of the general population. More studies are needed to assess the effect of insulin resistance on fracture risk in PLHIV.

Acknowledgments
This study was supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, # 440789/2017-6 and # 405729/2018-9).

Conflict of Interest
The authors declare that they have no conflict of interest.

Data Availability
The data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References
1. World Health Organization. HIV/AIDS key facts. Vol. 2022. Accessed May 4, 2021. https://www.who.int/news-room/fact-sheets/detail/hiv-aids.
2. Palella FJ J, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr. 2006;43(1):27-34.
3. Wandelger G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. Curr Opin HIV AIDS. 2016;11(5):492-500.
4. Premaor MO, Compston JE. People living with HIV and fracture risk. Osteoporos Int. 2020;31(9):1633-1644.
5. Khosla S, Samakkarnthai P, Monroe DG, Farr JN. Update on the pathogenesis and treatment of skeletal fragility in type 2 diabetes mellitus. Nat Rev Endocrinol. 2021;17(11):685-697.
6. Van Hulten V, Rasmussen N, Driessen JHM, Burden AM, Kvist A, van den Bergh JP. Fracture patterns in type 1 and type 2 diabetes mellitus: a narrative review of recent literature. Curr Osteoporos Rep. 2021;19(6):644-655.
7. Napoli N, Conte C, Pedone C, et al. Effect of insulin resistance on BMD and fracture risk in older adults. J Clin Endocrinol Metab. 2019;104(8):3303-3310.
8. Pedro MN, Rocha GZ, Guadagnini D, et al. Insulin resistance in HIV-patients: causes and consequences. Front Endocrinol (Lausanne). 2018;9:514.
9. Noumegni SRN, Nansseu JR, Ama VJM, et al. Insulin resistance and associated factors among HIV-infected patients in Sub-Saharan Africa: a cross sectional study from Cameroon. *Lipids Health Dis.* 2017;16(1):148.
10. de Almeida LL, Ilha T, de Carvalho JAM, et al. Sarcopenia and its association with vertebral fractures in people living with HIV. *Calcif Tissue Int.* 2020;107(3):249-256.
11. World Health Organization. *WHO steps surveillance, part 3: training and practical guides, Section 3: guide to physical measurement.* World Health Organization; 2008.
12. Densitometry I-TISfC. 2019 ISCD official positions—adult. Vol. 2019. ISCD; 2019. https://www.iscd.org/official-positions/2019-iscd-official-positions-adult/.
13. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organization; 1994.
14. Griffith JF, Genant HK. Diagnosis and classification of vertebral fracture. In: Bilezikian JP, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* 9th ed. Wiley; 2018.
15. Geloneze B, Vasques ACJ, Stabe CFC, et al. HOMA1-IR And HOMA2-IR indexes in identifying insulin resistance and metabolic syndrome: Brazilian Metabolic Syndrome Study (BRAMS). *Arq Bras Endocrinol Metabol.* 2009;53(2):281-287.
16. Vasques AC, Novaes FS, de Oliveira Mda S, et al. TyG index performs better than HOMA in a Brazilian population: a hyperglycemic clamp validated study. *Diabetes Res Clin Pract.* 2011;93(3):e98-e100.
17. Yang J, Hong N, Shim JS, Rhee Y, Kim HC. Association of insulin resistance with lower bone volume and strength index of the proximal femur in nondiabetic postmenopausal women. *J Bone Metab.* 2018;25(2):123-132.
18. Cherif R, Mahjoub F, Sahli H, et al. Positive association of obesity and insulin resistance with bone mineral density in Tunisian postmenopausal women. *J Clin Densitom.* 2018;21(2):163-171.
19. Ma L, Oei L, Jiang L, et al. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. *Eur J Epidemiol.* 2012;27(5):319-332.
20. Lui DTW, Lee CH, Chan YH, et al. HbA1c variability, in addition to mean HbA1c, predicts incident hip fractures in Chinese people with type 2 diabetes. *Osteoporos Int.* 2020;31(10):1955-1964.