

# Is hand-grip another culprit for the risk of fractures in HIV-positive patients?

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## SUMMARY

Risk of bone fractures in patients with HIV infection is greater than in the general population, particularly in those co-infected with hepatitis viruses. We compared bone mineral density (BMD) and muscular strength, measured by hand grip test (HG), in HIV mono-infected and co-infected patients. T-score values were lower in HIV patients co-infected with hepatitis viruses vs. mono-infected individuals. Since no significant correlations between HG and T-scores were found, we hypothesize that these factors belong, at least in part, to independent pathways, so both should be taken into account as risks for fragility fractures. Larger prospective studies are needed to confirm this hypothesis.

**KEY WORDS:** HIV, HCV, Bone mineral density, Hand grip, Osteoporosis, Bone fractures.

Received February 17, 2015

Accepted December 6, 2015

Previous studies reported that the risk of bone fractures is greater in HIV-positive patients than in the general population (Torti *et al.*, 2012). Although reduction of bone mineral density (BMD) may be the main culprit, it did not justify any fractures occurring in these patients (Porcelli *et al.*, 2014). To further complicate this issue, an additional significant risk of bone fractures was reported in HIV-positive patients co-infected with hepatitis viruses (HCV or HBV). A recent meta-analysis reported more frequent osteopenia/osteoporosis in HIV/HCV-co-infected patients and the risk of bone fractures was greater in HIV/HCV-co-infected patients than in HIV-mono-infected individuals (O'Neill *et al.*, 2014). In a large cohort study, the annual incidence of hip fractures was higher in patients with HIV or HCV than in the general population, in particular in subjects with

HIV/HCV co-infection (Lo Re *et al.*, 2012). In HIV-negative patients, muscular strength reduction (measured by hand-grip -HG- strength test) was also associated with low BMD and with an increased risk of fractures (Lan *et al.*, 2010, Marin *et al.*, 2010). In a recent longitudinal study, impaired physical performance (measured as grip strength and walking time) and joint pain were reported as risk factors for multiple fractures (Muraki *et al.*, 2013). Also, in HIV-positive patients, lipodystrophy and reduction of muscular mass were associated with decreased muscular strength and low BMD (Crawford *et al.*, 2013). This association was not studied in HIV/HCV-co-infected patients, while it may well explain the incomplete justification provided by low BMD for the risk of fractures (Porcelli *et al.*, 2014) or the greater incidence of fractures in these patients (either due to possible incomplete reconstitution of muscular strength or an increased risk of falling since these patients are predominantly intravenous drug users).

We aimed at comparing HIV-mono-infected with HIV/HBV/HCV-co-infected patients for BMD and several anthropometric and metabolic parameters, exploring in particular wheth-

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er HG is correlated with BMD. Since we were interested in any potential effect of chronic hepatitis associated with either HCV or HBV (Schiefke *et al.*, 2005), both patients infected by HCV and HBsAg chronic carriers with HIV infection were studied.

A cross-sectional study was performed enrolling all HIV-infected patients, either mono-infected with HIV or co-infected with HCV and/or HBsAg chronic carriers, followed at our centre. All patients underwent T-score evaluation (measured by ultrasound heel mineralometry, MOC QUS, Hologic Sahara®), HG strength test (by JAMAR® dynamometer), and body impedance assessment (BIA, AKERN®, bodygram plus® software). HG test was used to measure muscular isometric strength of hand flexors muscles. Muscular strength evaluation was performed on dominant hand. Dynamometer was composed of a hydraulic gauge, a handle (adjustable according to hand size) and a display showing peak force (in kg) achieved during the test. BIA vectorial analysis estimated some parameters of body composition (either in percentages or in kg): total body water (TBW), extra cellular water (ECW), intra cellular water (ICW), body cellular mass (BCM), fat-free mass (FFM), fat mass (FM), muscular mass (MM).

Non-parametric statistical analysis was performed for quantitative variables expressed as median values (Mann-Whitney test). Chi-square test was performed to compare qualitative variables. Relationships among variables (CD4+ T cell count, HG, T-score) was assessed through linear regression analysis. P-value <0.05 was considered for statistical significance.

Twenty HIV-positive adults (75% males; median age 47 years, range 25-80) were evaluated. Median CD4+ T-cell count was 652/mm<sup>3</sup> [range: 219/mm<sup>3</sup> to 1,223/mm<sup>3</sup>] with the lowest value (nadir) of 242/mm<sup>3</sup> [range: 11/mm<sup>3</sup> to 885/mm<sup>3</sup>]. Five patients (25%) had a detectable HIV-RNA. All patients received highly active antiretroviral therapy (HAART), the majority including tenofovir (TDF, 85% patients). Patients were ranked into two groups: HIV-mono-infected (n=12) and co-infected (n=6 with HCV -one of them being a HBsAg carrier-, and 2 HIV/HBV-co-infected). HIV-mono-infected and co-infected patients did not differ significantly for the main anthropometric, metabolic, epidemiological and clinical

parameters, except from T-score (standard deviation, SD) that was lower in the latter group (median: -0.9 in mono-infected [range: -1.8 to 1.7] vs -1.5 [range: -2.4 to -0.8]; p=0.024). Even though differences were not statistically significant, HIV patients co-infected with hepatitis viruses were older (median age: 47 years [range: 38 to 80] vs 44.5 years [range: 25 to 64]), had higher percentages of osteopenia/osteoporosis (i.e., <1 SD:50% vs 33%), more frequently had low levels of serum vitamin D (<30 ng/ml, 37.5% vs 33%), and lower HG (median: 33.85 Kg [range: 26 to 53] vs 36 kg [range: 28 to 53]) than HIV mono-infected subjects. Also, MM was lower in co-infected patients than in HIV-mono-infected subjects (median: 32.95 kg [range: 30 to 42.1] vs 39.55 kg [range: 23.6 to 52.5 kg]).

No statistically significant correlations were found although signs of different relationships between T-score and HG were suggested in HIV-mono-infected with respect to co-infected patients (Figure 1). In fact, in mono-infected subjects a tendency toward a direct linear correlation between HG and T-score was observed, while in co-infected subjects this correlation displayed an inverse trend, meaning that they were more likely to have lower HG even though T-score was higher (Figure 1A). In other terms, not only co-infected patients displayed more impaired BMD, but also those with better BMD were disadvantaged by worse HG. By contrast, HIV-mono-infected subjects were favoured not only because BMD was greater, but also because BMD and HG appeared to be consistently better in some patients.

Since CD4+ T-cell counts can influence the study variables (Grant *et al.*, 2013), we explored relationships between T-score and HG by CD4+ T-cell count either at nadir or at current determinations. T-score was always lower in co-infected patients at any CD4+ T-cell count either at nadir (Figure 1B) or at actual determinations (Figure 1C). For HG, value distribution did not show a similar pattern (Figure 1D/E) but, interestingly, a trend toward higher HG with greater CD4+ T-cell count was observed (Figure 1E).

Altogether, our data confirm, for the first time through heel MOC QUS, that BMD is reduced in HIV patients co-infected with hepatitis viruses with respect to mono-infected individuals. This evidence supports the role of MOC QUS and it is

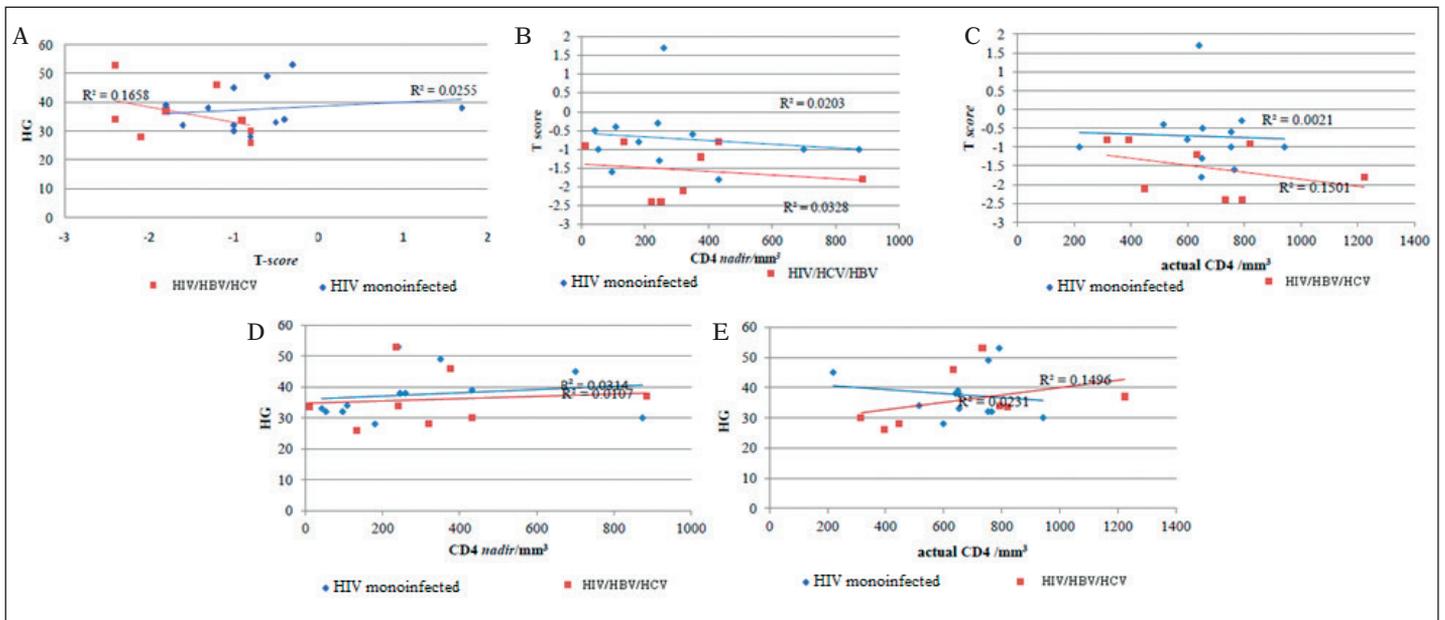


FIGURE 1A, 1B, 1C, 1D, 1E - HG, CD4 T cell count and T-score correlations in HIV-mono-infected (HIV, blue line and diamonds) and in co-infected (HIV/HBV/HCV, red line and squares) patients. P values not significant for any of R2. HG: hand grip (kg).

consistent with an increased risk of pathological fractures in HIV co-infected patients (Bedimo *et al.*, 2012, Bedimo and Tebas 2013, Maalouf *et al.*, 2013, Lo Re *et al.*, 2015). A recent study showed moderate correlation between MOC QUS and DXA parameters in HIV positive patients, particularly in HIV-positive females. MOC QUS was more accurate than DXA to predict risk of vertebral fractures (Clò *et al.*, 2015).

The actual predictive factors for fragility fractures in HIV positive patients are not fully known. Gender and co-infection with hepatitis viruses may have an important role in risk of bone fractures. In a recent study, HIV/HCV-co-infected women showed a significant bone deficit when compared with healthy patients (Lo Re *et al.*, 2015). Reduced HG (Lan *et al.*, 2010, Marin *et al.*, 2010, Muraki *et al.*, 2013) and lean mass (Iolascon *et al.*, 2013) were associated with (or predictive of) fractures in HIV-negative individuals. Antiretroviral therapy and HIV infection itself may influence risk of fractures, bone loss and muscular strength (Hoy, 2011). Indeed, in HIV-positive patients disability and bone fragility were associated with reduced lean mass and reduced BMD (Erlandson *et al.*, 2013).

Our data suggest that co-infected patients have reduced HG and MM with respect to HIV mono-infected patients. Since no significant correlations between HG and T-scores were found in either populations, we hypothesize that these factors belong, at least in part, to independent causal pathways, so both should be taken into account as potential risks of fragility fractures.

HIV/HCV co-infection is frequently associated with late (nadir CD4+ T-cell count <350 mm<sup>3</sup>) and very late presentation (nadir CD4+ T-cell count <200 mm<sup>3</sup>), reported as independent risk factors of low BMD (Li Vecchi *et al.*, 2012). In our study, the impact of HCV on BMD was suggested to be irrespective from CD4+ T-cell count, however. Furthermore, HIV/HCV-co-infected patients have more frequently intravenous drug use (IVDU) as a risk factor for HIV acquisition. As reported in a large cohort (Maalouf *et al.*, 2013), patients with osteoporotic fractures were more likely to be IVDUs and to have HIV/HCV co-infection, although alcohol consumption and drug abuse may interfere, either increasing the risk of traumatic fractures or increasing the risk of pathological fractures (Collin *et al.*, 2009).

Given the fact that both BMD and muscular strength are strongly linked to several factors other than the presence of chronic infections (e.g., gender, age, recreational drug use, vitamin intake, use of specific antiviral drugs) and considering the cross-sectional nature of the study design, it is hard to draw any significant conclusion from the small number of patients included in this analysis. However, our results suggest that these factors should be taken into consideration in further longitudinal studies for the risk of fractures. Particularly in HIV/HCV co-infected patients, HG could justify some fractures occurring in those with conserved BMD.

## REFERENCES

- BEDIMO R., MAALOUF N.M., ZHANG S., DRECHSLER H., TEBAS P. (2012). Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS*. **26**, 825-831.
- BEDIMO R., TEBAS P. (2013). Increased fracture risk with HIV infection—a growing concern. *Nat. Rev. Endocrinol.* **9**, 260-261.
- CLOÀ A., GIBELLINI D., DAMIANO D., VESCINI F., PONTI C., MORINI S., ET AL. (2015). Calcaneal quantitative ultrasound (QUS) and dual X-ray absorptiometry (DXA) bone analysis in adult HIV-positive patients. *New Microbiol.* **38**, 345-356.
- COLLIN F., DUVAL X., LE MOING V., PIROTH L., AL KAIED F., MASSIP P., VILLES V., ET AL. AND A. C.A.-C. S. GROUP. (2009). Ten-year incidence and risk factors of bone fractures in a cohort of treated HIV1-infected adults. *AIDS*. **23**, 1021-1024.
- CRAWFORD K.W., LI X., XU X., ABRAHAM A.G., DOBS A.S., MARGOLICK J.B., PALELLA F.J., ET AL. (2013). Lipodystrophy and inflammation predict later grip strength in HIV-infected men: the MACS Body Composition substudy. *AIDS Res. Hum. Retroviruses*. **29**, 1138-1145.
- ERLANDSON K.M., ALLSHOUSE A.A., JANKOWSKI C.M., MAWHINNEY S., KOHRT W.M., T. B. CAMPBELL (2013). Functional impairment is associated with low bone and muscle mass among persons aging with HIV infection. *J. Acquir. Immune Defic. Syndr.* **63**, 209-215.
- GRANT P.M., KITCH D., MCCOMSEY G.A., DUBE M.P., HAUBRICH R., HUANG J., ET AL. (2013). Low baseline CD4+ count is associated with greater bone mineral density loss after antiretroviral therapy initiation. *Clin. Infect. Dis.* **57**, 1483-1488.
- HOY J. (2011). Bone, fracture and frailty. *Curr. Opin. HIV AIDS*. **6**, 309-314.
- IOLASCON G., GIAMATTEI M.T., MORETTI A., DI PIETRO G., GIMIGLIANO F., ET AL. (2013). Sarcopenia in women with vertebral fragility fractures. *Aging. Clin. Exp. Res.* **25** (Suppl. 1), S129-131.
- LAN T.Y., M S. HOU, CHEN C.Y., CHANG W.C., LIN J., LIN C.C., ET AL. (2010). Risk factors for hip fracture in older adults: a case-control study in Taiwan. *Osteoporos. Int.* **21**, 773-784.
- LI VECCHI V., SORESI M., GIANNITRAPANI L., MAZZOLA G., LA SALA S., TRAMUTO F., ET AL. (2012). Dairy calcium intake and lifestyle risk factors for bone loss in hiv-infected and uninfected Mediterranean subjects. *BMC Infect. Dis.* **12**, 192.
- LO RE V., LYNN K., STUMM E.R., LONG J., NEZAMZADEH M.S., BAKER J.F., ET AL. (2015). Structural Bone Deficits in HIV/HCV-Coinfected, HCV-Monoinfected, and HIV-Monoinfected Women. *J. Infect. Dis.* **212**, 924-933.
- LO RE V., VOLK J., NEWCOMB C.W., YANG Y.X., FREEMAN C.P., HENNESSY S., ET AL. (2012). Risk of hip fracture associated with hepatitis C virus infection and hepatitis C/human immunodeficiency virus coinfection. *Hepatology*. **56**, 1688-1698.
- MAALOUF N.M., ZHANG S., DRECHSLER H., BROWN G.R., TEBAS P., BEDIMO R. (2013). Hepatitis C co-infection and severity of liver disease as risk factors for osteoporotic fractures among HIV-infected patients. *J. Bone Miner. Res.* **28**, 2577-2583.
- MARIN R.V., PEDROSA M.A., MOREIRA-PFRIMER L.D., MATSUDO S.M., LAZARETTI-CASTRO M. (2010). Association between lean mass and handgrip strength with bone mineral density in physically active postmenopausal women. *J. Clin. Densitom.* **13**, 96-101.
- MURAKI S., AKUNE T., ISHIMOTO Y., NAGATA K., YOSHIDA M., TANAKA S., ET AL. (2013). Risk factors for falls in a longitudinal population-based cohort study of Japanese men and women: the ROAD Study. *Bone*. **52**, 16-523.
- O'NEILL T.J., RIVERA L., STRUCKOV V., ZAHEEN A., THEIN H.H. (2014). The effect of HIV-hepatitis C co-infection on bone mineral density and fracture: a meta-analysis. *PLoS One*. **9**, e101493.
- PORCELLI T., GOTTI D., CRISTIANO A., MAFFEZZONI F., MAZZIOTTI G., FOCÀ E., ET AL. (2014). Role of bone mineral density in predicting morphometric vertebral fractures in patients with HIV infection. *Osteoporos. Int.* **25**, 2263-2269.
- SCHIEFKE I., FACH A., WIEDMANN M., ARETIN A.V., SCHENKER E., BORTE G.M., ET AL. (2005). Reduced bone mineral density and altered bone turnover markers in patients with non-cirrhotic chronic hepatitis B or C infection. *World J. Gastroenterol.* **11**, 1843-1847.
- TORTI C., MAZZIOTTI G., SOLDINI P.A., FOCÀ E., MAROLDI R., GOTTI D., ET AL. (2012). High prevalence of radiological vertebral fractures in HIV-infected males. *Endocrine*. **41**, 512-517.