PO-28

Effects of Eradication of HCV on Bone Mineral Density in HIV/HCV-Coinfected Patients

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Background

- Established cirrhosis is generally associated with osteoporosis; however, there is still some debate about the association between non-cirrhotic chronic HCV infection and osteoporosis.
- HCV infection has been associated with an increased risk of bone loss and fracture in HIV-infected persons. The mechanism is not well understood and may involve severity of liver disease, a reduction in bone mineral density (BMD), or microstructural abnormalities associated with HCV infection [1-3]. Nevertheless, unmeasured confounders, including behavioral and nutritional factors, have not been completely ruled out.

1. Maalouf NM, et al. J Bone Miner Res 2013; 28(12): 2577-83.
2. Bedimo R, et al. AIDS 2016; 30(4): 601-8.
3. Bedimo RJ, et al. Clin Infect Dis 2018; 66(9): 1442-7.

Aims

1. To assess the association between liver fibrosis and BMD in HIV/HCV-coinfected persons.
2. To assess the effects of eradication of HCV on BMD in HIV/HCV-coinfected persons in order.

Methods

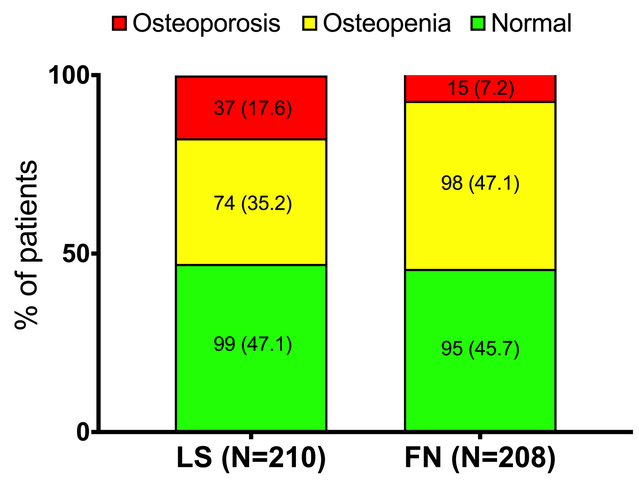
Design	• We prospectively analyzed BMD at baseline and 96 wk after initiation of anti-HCV therapy (Rx) in HIV/HCV-coinfected patients. • Patients were recruited during 2012 – 2016 in 14 centers
Variables	• Demographics, BMI, variables related to HIV, HCV, comorbidities, smoking and substance abuse, laboratory parameters. • BMD was assessed using dual-energy X-ray absorptiometry (DXA) at the lumbar spine and femoral neck. • As different densitometers were used (Hologic® [n=8], Lunar® [n=3], and Norland® [n=2]), standardized BMD (sBMD) was also calculated based on published equations[1,2]. • Liver stiffness (LS) was determined using transient elastography (TE) with FibroScan®, EchoSens, Paris, France and FIB-4 score • Biomarkers of bone remodeling: soluble receptor activator of nuclear factor-κappaβ ligand (sRANKL) and osteoprotegerin (OPG) were determined in plasma taken at baseline and 96 weeks
Definitions	• Osteoporosis, T score ≤−2.5 SD (WHO criteria) • Osteopenia, T score between −1 and −2.5 SD (WHO criteria) • Cirrhosis, LS >12.5 kPa

Hui SL, et al. J Bone Miner Res 1997; 12(9): 1463-70.
Lu Y, et al. Osteoporos Int 2001; 12(6): 438-44.

Characteristics of the Study Population

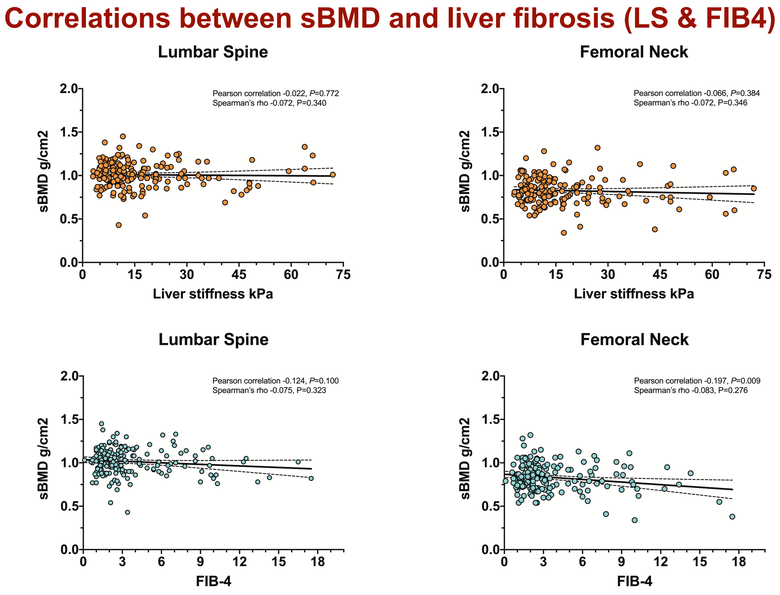
Characteristic	No SVR (n=93)	SVR (n=145)	P	TOTAL (n=238)
Male sex, No. (%)	66 (71)	116 (80)	0.109	182 (76.5)
Age, y, median (IQR) (baseline)	49.1 (46.6 - 52.6)	49.7 (46.3 - 53.2)	0.629	49.5 (46.4 - 53)
BMI (n=153), median (IQR)	24.1 (22.1 - 26.1)	24.4 (21.5 - 27.3)	0.460	24.2 (21.8 - 26.6)
Prior injection drug use, No. (%)	73 (78.5)	107 (73.8)	0.410	180 (75.6)
Methadone therapy, No. (%)	13 (14)	16 (11)	0.707	29 (12.2)
Current alcohol intake > 50 g/d, No. (%)	1 (1.1)	4 (2.8)	0.560	5 (2.1)
Diabetes mellitus	9 (9.7)	11 (7.6)	0.570	20 (8.4)
Current smoking	65 (69.9)	97 (66.9)	0.910	162 (68.1)
Arterial hypertension	14 (15.1)	17 (11.7)	0.456	31 (13)
CDC disease category C, No. (%)[a]	31 (33.3)	34 (23.4)	0.229	65 (27.3)
CD4+, nadir, cells/mm^3, median (IQR)	160 (69 - 253)	162 (84 - 246)	0.901	160 (72 - 250)
cART during anti-HCV treatment, No. (%)	92 (98.9)	142 (97.9)	0.708	234 (98.3)
CD4+, baseline, cells/mm^3, median (IQR)	550 (372 - 822)	518 (385 - 772)	0.556	527 (380 - 803)
Undetectable HIV RNA load at baseline, No. (%)	77 (82.8)	129 (89)	0.230	206 (86.6)
Prior anti-HCV therapy, No. (%)	9 (9.7)	18 (12.4)	0.516	27 (11.3)
HCV genotype, No. (%)				
1	55 (59.1)	94 (64.9)	0.334	149 (62.6)
2	3 (3.2)	2 (1.4)		5 (2.1)
3	19 (20.4)	24 (16.6)		43 (18.1)
4	10 (10.8)	10 (6.9)		20 (8.4)
Other/mixed	6 (6.5)	14 (9.7)		20 (8.4)
Unknown	0 (0)	1 (0.7)		1 (0.4)
HCV-RNA, Log_{10} IU/mL, median (IQR)	6.5 (6.1 - 6.9)	6.3 (5.8 - 6.6)	0.001	6.4 (5.9 - 6.7)
HBsAg positivity, No. (%)	3 (3.2)	5 (3.4)	0.655	8 (3.4)
Liver cirrhosis, No. (%) (METAVIR 4 or TE>12.5)	41 (44.1)	74 (51)	0.295	115 (48.3)
Anti-HCV therapy			0.003	
Peg-IFN + RBV	29 (31.2)	53 (36.6)		82 (34.5)
Peg-IFN + RBV + HCV protease inhibitor	36 (38.7)	77 (53.1)		113 (47.5)
Peg-IFN + RBV + daclatasvir	6 (6.5)	8 (5.5)		14 (5.9)
Sofosbuvir + RBV	22 (23.7)	7 (4.8)		29 (12.2)

WHO BMD categories at baseline



WHO, World Health Organization; **BMD**, bone mineral density

Correlations between sBMD and liver fibrosis (LS & FIB4)



sBMD, standardized bone mineral density; **LS**, liver stiffness

Variables associated with osteoporosis

In univariate analysis the following variables were associated with osteoporosis*: **Lumbar spine**: age, BMI, CD4+/CD8+ ratio, and methadone. **Femoral neck**: IDU, methadone use, and HBsAg positivity. Cirrhosis was not associated with osteoporosis at any site.

Multivariate logistic regression analysis
The models included variables associated with osteoporosis in univariate analysis and other variables of clinical relevance.

Lumbar Spine

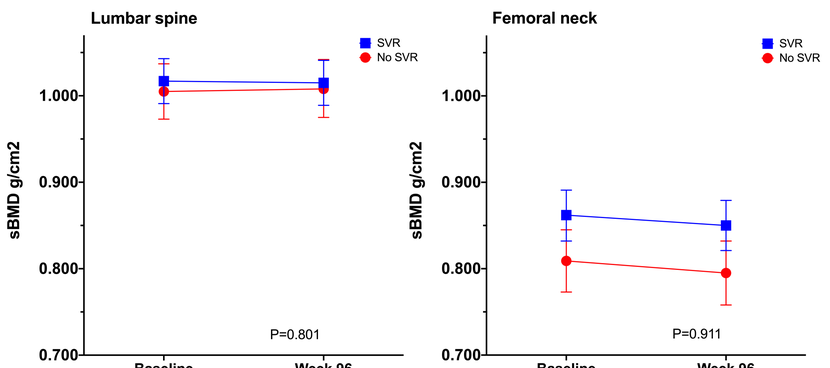
Variable	OR	95%CI	*P*
Age	1.041	0.934-1.162	.468
Male sex	1.228	0.467-3.234	.677
BMI	0.877	0.764-1.008	.065
CD4+/CD8+	1.165	0.955-1.421	.133
Methadone	2.225	0.797-6.214	.127
Tenofovir	0.621	0.282-1.366	.236

Femoral Neck

Variable	OR	95%CI	*P*
Age	1.140	1.015-1.281	.027
Male sex	0.429	0.085-2.177	.307
BMI	0.872	0.695-1.093	.234
IDU	2.459	0.371-16.285	.351
Methadone	2.447	0.300-19.955	.403
Tenofovir	0.978	0.268-3.568	.973

***Variables analyzed:** Age, sex, BMI, smoking, alcohol intake, methadone use, HIV transmission category, CDC clinical category, cART, tenofovir use, HIV-RNA, CD4+ cell count, nadir CD4+ cell count, CD4+/CD8+ ratio, HCV genotype, HCV-RNA, prior anti-HCV therapy, liver stiffness, cirrhosis, hemoglobin, albumin, creatinine, calcium, phosphate, vitamin D, T4, TSH, PTH

Changes in sBMD from baseline to 96 wk in responders and non-responders



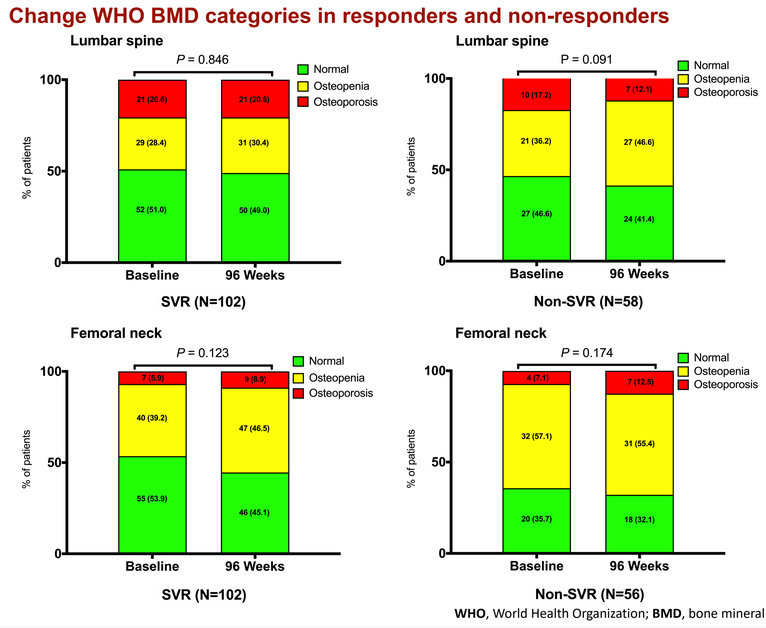
	No SVR			SVR		
	Mean	Upper Limit	Lower Limit	Mean	Upper Limit	Lower Limit
Baseline	1.005	1.037	0.973	1.017	1.043	0.991
Week 96	1.008	1.042	0.975	1.015	1.041	0.989

	No SVR			SVR		
	Mean	Upper Limit	Lower Limit	Mean	Upper Limit	Lower Limit
Baseline	0.809	0.845	0.773	0.862	0.891	0.832
Week 96	0.795	0.832	0.758	0.850	0.879	0.821

Linear mixed-models for longitudinal data were used in analyses to account for repeated measures with SVR and time as fixed effects, and the patient as a random effect. P value refers to the significance of the interaction (i.e., the impact of SVR on the time-course of the variable).

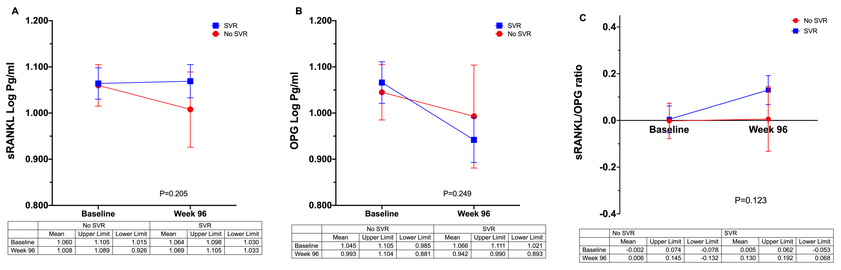
sBMD, standardized bone mineral density

Change WHO BMD categories in responders and non-responders



WHO, World Health Organization; **BMD**, bone mineral density

Changes in biomarkers from baseline to 96 wk in responders and non-responders



	No SVR			SVR		
	Mean	Upper Limit	Lower Limit	Mean	Upper Limit	Lower Limit
Baseline	1.060	1.105	1.015	1.064	1.098	1.030
Week 96	1.008	1.089	0.926	1.069	1.105	1.033

	No SVR			SVR		
	Mean	Upper Limit	Lower Limit	Mean	Upper Limit	Lower Limit
Baseline	1.045	1.105	0.985	1.066	1.111	1.021
Week 96	0.993	1.104	0.881	0.942	0.990	0.893

	No SVR			SVR		
	Mean	Upper Limit	Lower Limit	Mean	Upper Limit	Lower Limit
Baseline	-0.002	0.074	-0.078	0.005	0.062	-0.053
Week 96	0.006	0.145	-0.132	0.130	0.192	0.068

Estimated means (95% CI) of plasma biomarkers concentrations at baseline and 96 weeks in responders and non-responders: sRANKL (A), OPG (B), and sRANKL/OPG ratio (C).

Linear mixed-models for longitudinal data were used in analyses to account for repeated measures with SVR and time as fixed effects, and the patient as a random effect. P value refers to the significance of the interaction (i.e., the impact of SVR on the time-course of the variable).

Conclusions

1. In this cohort of HIV/HCV-coinfected patients with compensated liver disease, the prevalence of osteoporosis at lumbar spine and femoral neck was 17.6% and 7.2%, respectively.
2. No significant correlation was found between liver-stiffness and BMD.
3. After 96 weeks, eradication of HCV following anti-HCV therapy was not associated with significant changes in BMD.
4. In this population group, lifestyle and other factors may have a greater impact on BMD than HCV or the severity of liver fibrosis.
5. These findings do not support a causal association between HCV infection and reduced BMD in HIV/HCV-coinfected persons.

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