

SEVERE ALTERATIONS IN CORTICAL AND TRABECULAR BONE MICROARCHITECTURE IN LUNG TRANSPLANT RECIPIENTS



Valentinitsch, A.* (1), Fischer, L.* (1), DiFranco, M.(1), Schueller-Weidekamm, C. (2), Kainberger, F. (1,2), Langs, G. (1), Patsch, J. (1,2) (I) CIR Lab, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna (2) Department of Biomedical Imaging and Image-guided Therapy, .Medical University of Vienna

Purpose

Organ transplant recipients often suffer from impaired bone strength arising from a combination of pre-existing secondary osteoporosis and disease aggravation in the post-transplant phase caused by various factors such as immunosuppressive therapy.

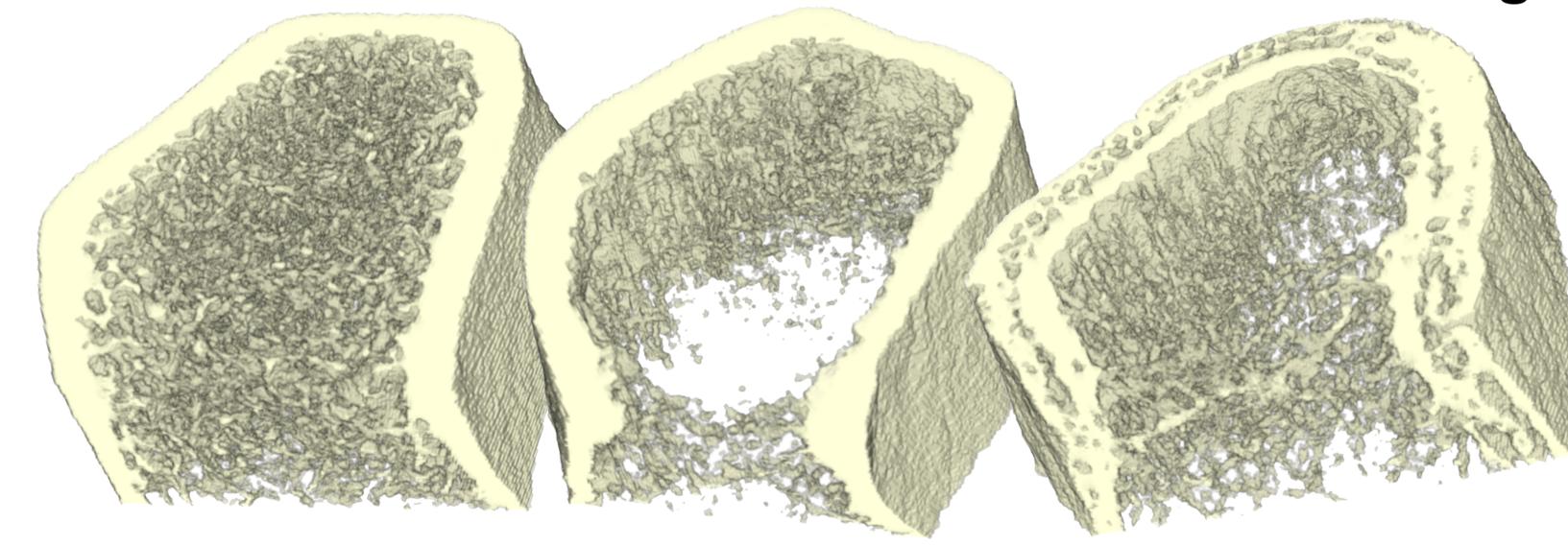
In lung transplant (LUTX) recipients, the post-transplant drug regimen is particularly intense and fracture rates are high. Although, low bone mineral density [I] and altered states of bone turnover [2] have been described after LUTX, bone microarchitecture status has not been investigated in depth.

Patients and Methods

	Female (n=72)		Male (n=49)	
	CoF (n=41)	LuTXF (n=31)	CoM (n=19)	LuTXM (n=30)
Demographics				
Age (years)	40.6±2.2	47.6±2.3	38.5±3.5	44.2±3.1
Race	Caucasians (100%)	Caucasians (100%)	Caucasians (100%)	Caucasians (100%)
BMI (kg/m²)	22.64±0.48	19.73±0.60a	25.59±0.78 ^c	20.82±0.66b
LuTX indication (n)				
COPD	n.a.	15/31 (49%)	n.a.	11/30 (37%)
Parenchymal	n.a.	6/31 (19%)	n.a.	7/30 (23%)
Vascular diseases	n.a.	6/31 (19%)	n.a.	5/30 (17%)
CF	n.a.	4/31 (13%)	n.a.	7/30 (23%)

- All parameters are given as mean \pm SEM. Significances (by ANCOVA)
- are marked in bold. All p-values were adjusted for age as a covariate.
- p < 0.05, Co female vs. LuTX female p < 0.05, Co male vs. LuTX male
- p < 0.05, Co female vs. Co male

Defect Cluster Periostal Change Control



After recovery from surgery, 61 patients (female: n = 31, male: n = 30; age = 45.9 ± 14.9yrs), and 60 healthy, age, and gender-matched controls (Co) underwent high resolution peripheral quantitative computed tomography (HR-pQCT) of the ultradistal radius. Scans were analysed with the standard and cortical analysis software of the manufacturer, and a 3D texture-based clustering method for trabecular bone (TMAC)[3]. Based on 3D morphology, TMAC defined three types of trabecular bone: TMACI contained thick trabeculae with low intertrabecular spacing, TMAC2 was characterized by trabeculae of intermediate morphometric quality, and TMAC3 was defined as regions with thinner, inhomogeneous trabeculae. Paired t-tests were used to compare mean differences between LuTX and Co.

Table 1: Geometry, bone mineral density, trabecular and cortical bone microarchitecture and mechanical competence of the ultradistal radius in healthy men and women, men and women with recent lung transplantation.

	Female (n=72)		Male (n=49)	
	CoF (n=41)	LuTXF (n=31)	CoM (n=19)	LuTXM (n=30)
HR-pQCT evaluation	(11—41)	(11–31)	(11-13)	(11–30)
Geometry				
Ct.Pm (mm)	66.60±0.90	66.50±0.78	77.54±1.46 ^c	78.81±1.90 ^d
Ct.Ar (mm ²)	47.42±1.51	42.68±1.85	70.48±2.66 ^c	55.46±3.15 ^{b,d}
Tb.Ar (mm ²)	197.16±6.57	203.45±6.69	255.31±11.92°	278.13±13.77°
Bone Mineral Density	107.10±0.07	200.4010.00	200.01211.02	270.10210.77
BMD (mg Ha/cm ³)	308 57+10 52	277.10±10.63	364.26±10.93°	293.32±14.24 ^b
Ct.BMD (mg Ha/cm ³)	1005.66±6.11	998.22±9.49	959.77±9.75°	936.62±17.21°
Tb.BMD (mg Ha/cm³)	148.55±5.13	130.87±7.79	207.41±6.32 ^c	161.40±10.37 ^b ,
pTb.BMD (mg Ha/cm³)	205.14±5.44	190.32±7.45	264.68±6.31 ^c	217.21±9.72 ^{b,c}
mTb.BMD (mg Ha/cm³)	109.26±5.13	89.72±8.27 ^a	167.86±6.59 ^c	122.93±11.26 ^b ,
Trabecular Bone	109.2013.13	09.7 Z±0.Z1	107.00±0.39	122.33±11.20
Microarchitecture				
BV/TV (%)	12.44±0.43	11.05±0.70	17.27±0.53 ^c	13.30±0.83 ^b
Tb.N (1/mm)	1.85±0.03	1.69±0.08	2.15±0.05 ^c	1.87±0.07 ^b
Tb.Th (mm)	0.07±0.00	0.06±0.00	0.08±0.00 ^c	0.07±0.00 ^b
Tb.Sp (mm)	0.48±0.01	0.61±0.06	0.39±0.01 ^c	0.49±0.03 ^b
Tb.1/N.SD (mm)	0.20±0.01	0.36±0.08a	0.16±0.01 ^c	0.24±0.03 ^b
TMAC 1 (%)	40.53±1.07	38.56±1.34	42.87±1.50	43.04±2.35
TMAC 2 (%)	42.50±1.28	36.02±2.20a	47.78±1.10 ^c	34.83±1.89 ^b
TMAC 3 (%)	16.97±1.56	25.42±2.87a	9.34±1.20 ^c	22.13±3.13 ^b
Cortical Bone				
Microarchitecture				
Ct.Th (mm)	0.82±0.03	0.78±0.03	1.02±0.04 ^c	0.90±0.04d
Ct.Po.V (mm ³)	5.30±0.56	7.43±0.87	14.53±1.38 ^c	25.75±8.08d
Ct.Po (%)	1.27±0.14	2.57±0.50	2.32±0.24 ^c	4.27±0.93d
Ct.Po.Dm (µm)	0.15±0.00	0.17±0.00a	0.17±0.00 ^c	0.18±0.01
Ct.Po.Dm.SD (µm)	0.06±0.00	0.07±0.00a	0.07±0.00 ^c	0.07±0.00
Mechanical Competence				
Stiffness, k (kN/mm)	67.80±1.90	62.05±2.31	110.81±4.04 ^c	87.54±4.52b,d
F _{max} (kN)	3.19±0.09	2.92±0.11	5.13±0.18 ^c	4.04±0.20 ^{b,d}
σ_{max} (Mpa)	13.19±0.48	11.88±0.47	15.73±0.58 ^c	12.04±0.61b

All parameters are given as mean ± SEM. Significances (by ANCOVA) are marked in bold. All p-values were

- adjusted for age as a covariate.
- a p < 0.05, Co female vs. LuTX female ^b p < 0.05, Co male vs. LuTX male
- ^c p < 0.05, Co female vs. Co male

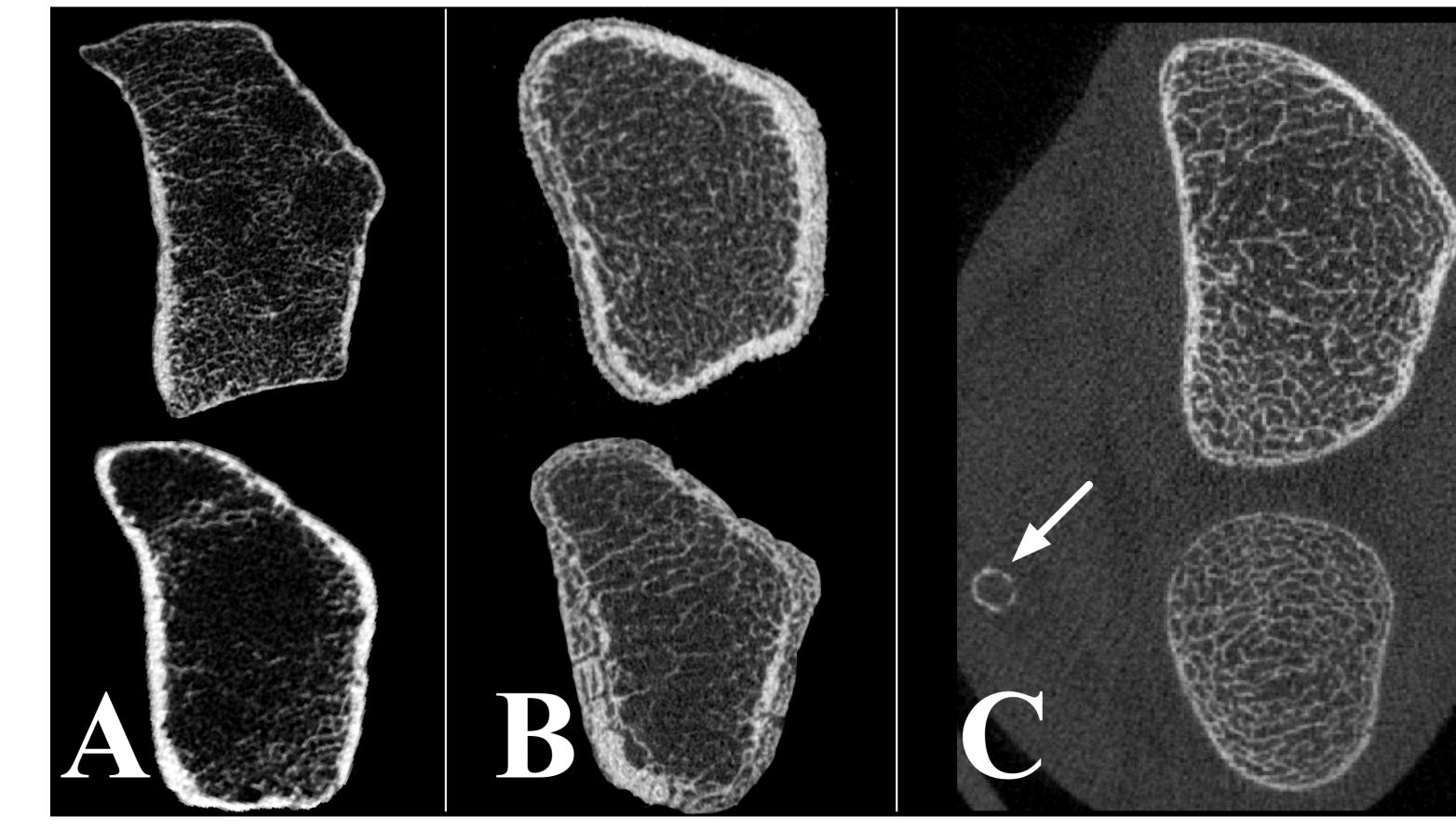


Fig. 2: Trabecular defect clusters (A), periostal changes (Pierre-Marie-Bamberger; B), calcifications of the radial artery and/or the ulnar artery.

Results

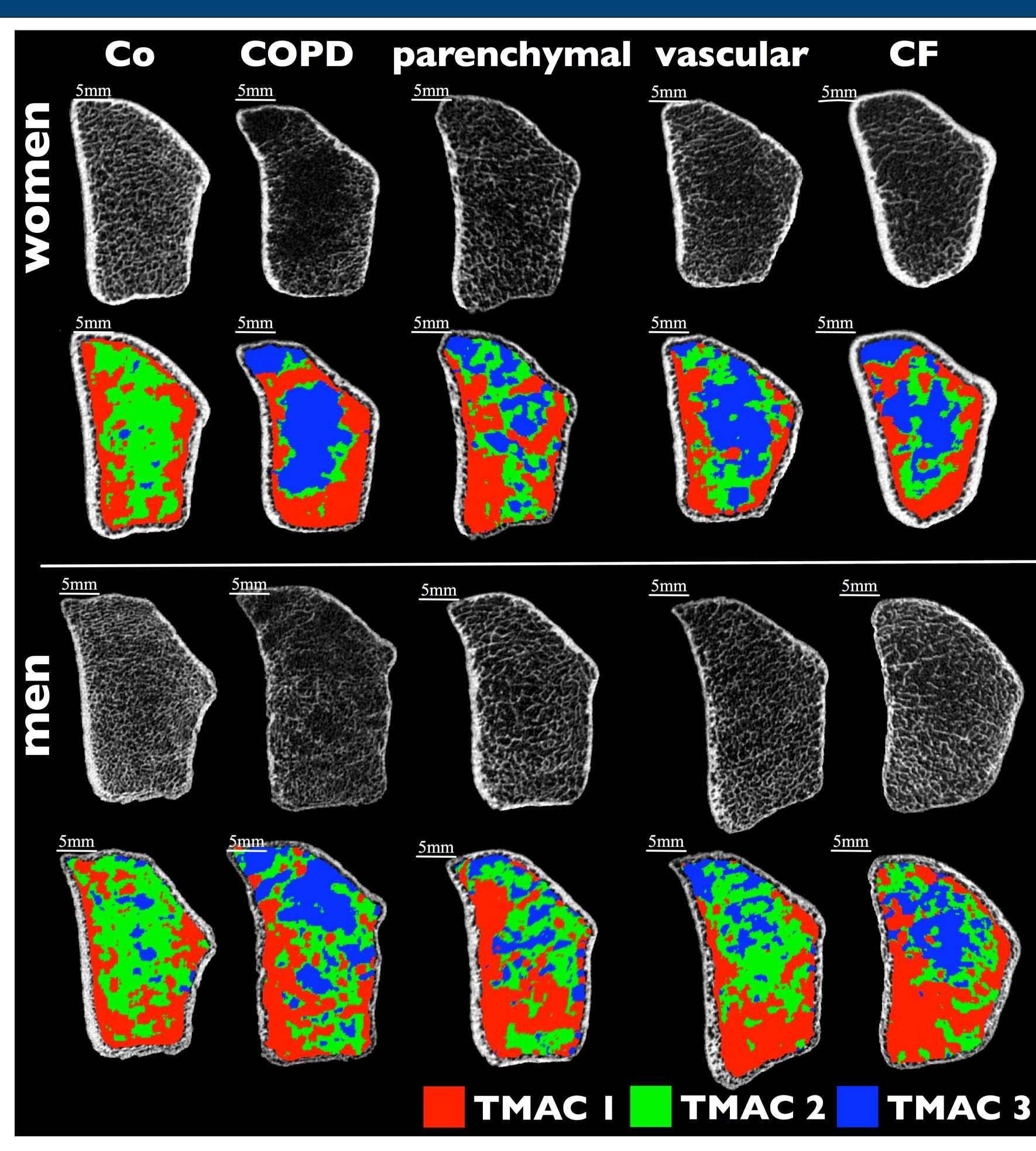


Fig. I: Representative HR-pQCT grey scale images (top row) and TMAC overlays (bottom row) for female and male controls and women/men with recent LuTX (per indication; columns).

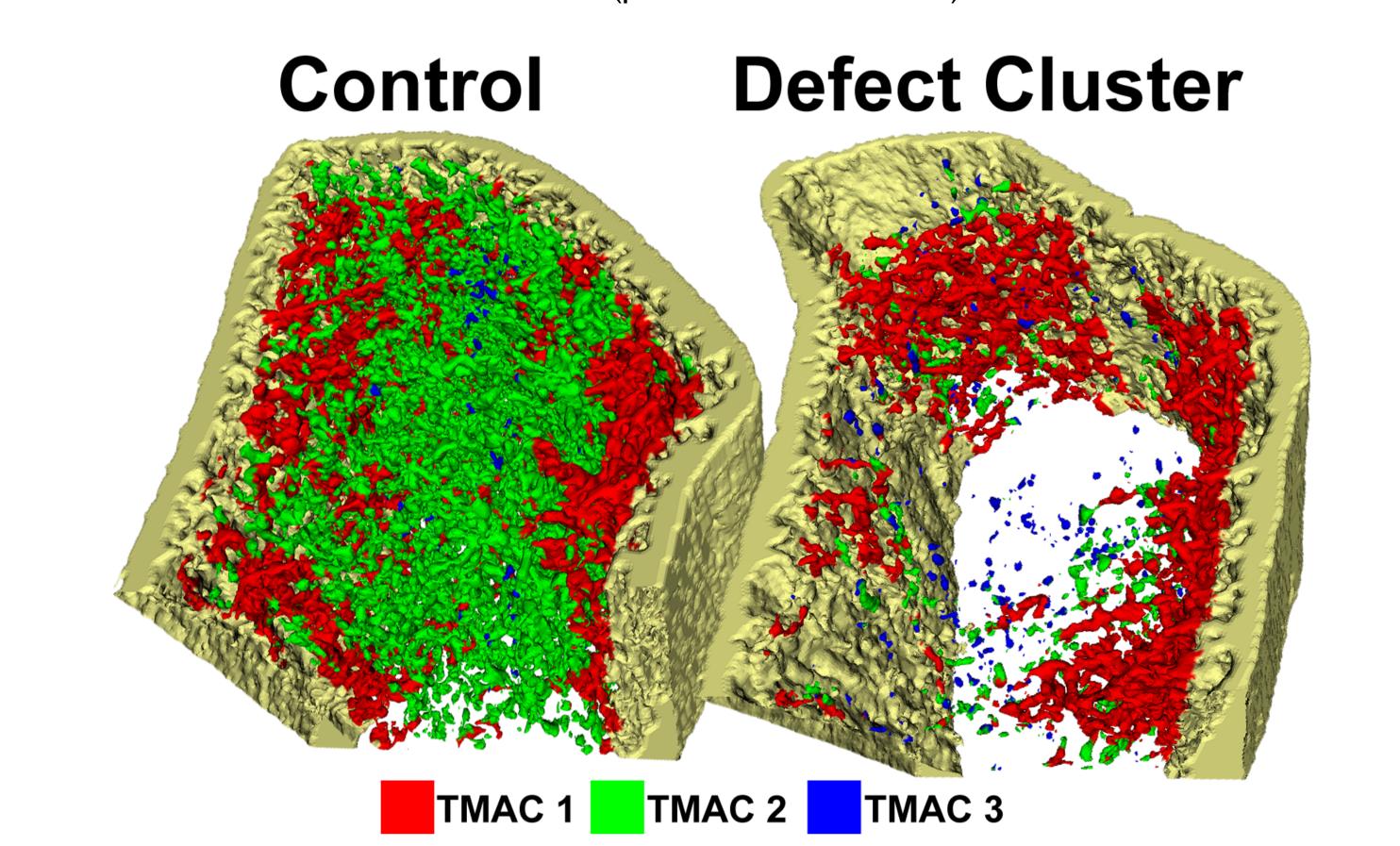


Fig. 3: Representatives of 3D reconstruction of TMACs. TMACI: regions of dense, thick, and homogeneous trabeculae. TMAC2: regions of intermediate trabecular density and thickness but relatively high number and homogeneity of trabeculae. TMAC3: regions with low trabecular density, number and thickness as well as high trabecular heterogeneity.

Female transplant recipients exhibited larger and more heterogeneous cortical pores (+13.3%, p=0.009; +16.7%, p=0.029), a trend towards higher cortical porosity (+102.4%, p=0.063), greater trabecular heterogeneity (+80%, p=0.044) and lower mid-trabecular BMD (-17.9%, p=0.049) than healthy women.

Male transplantation recipients had lower cortical area (-21.3%, p=0.001), global BMD (-19.5%, p=0.002), trabecular BMD (-22.2%, p=0.003), BV/TV (-23%, p=0.002), trabecular number (-13%, p=0.006), trabecular thickness (-12.5%, p=0.023), stiffness (-21%, p=0.001), failure force (-21%, p<0.001), overall bone strength (-24%, p<0.001) and larger trabecular separation and network heterogeneity (+25.6%, p=0.015; +50%, p=0.036) than healthy men.

There were trends for higher cortical porosity (+84.1, p=0.074) and lower cortical thickness (-11.8%, p=0.068) in male transplant recipients versus healthy men. Male transplant recipients also had lower stiffness (-21%, p=0.001), failure force (-21%, p<0.001) and bone strength (-24%, p<0.001) than healthy men.

Abbreviations:

CoF = healthy women **CoM** = healthy men **CF** = cystic fibrosis

LuTXF = women with lung transplantation **LuTXM** = men with lung transplantation **COPD** = chronic obstructive pulmonary disease

Conclusion

Our results indicate that cortical integrity and trabecular bone microarchitecture are both severely impaired in lung transplant recipients.

Although, the morphologic pattern seems to vary with gender, men and women are affected by significant deficits in peripheral bone microarchitecture. Thinning and porosity of cortical bone might thus be crucial factors leading to disproportionally high risk of fragility fractures in lung transplant recipients.

References

[1] A. Trombetti, M.W. Gerbase, A. Spiliopoulos, D.O. Slosman, L.P. Nicod, R. Rizzoli, Bone mineral density in lung-transplant recipients before and after graft: prevention of lumbar spine post-transplantationaccelerated bone loss by pamidronate, J Heart Lung Transplant. 19 (2000) 736–743.

[2] M. Aringer, H.P. Kiener, M.D. Koeller, O. Artemiou, A. Zuckermann, G. Wieselthaler, et al., High turnover bone disease following lung transplantation, Bone. 23 (1998) 485–488.

[3] A. Valentinitsch, J.M. Patsch, A.J. Burghardt, T.M. Link, S. Majumdar, L. Fischer, et al., Computational identification and quantification of trabecular microarchitecture classes by 3-D texture analysis-based clustering, Bone. 54 (2013) 133–140.

Funding

This research was supported by the Austrian National Bank Anniversary Fund (Project Nr. 13468); EU (FP7-ICT-2009-5/257528, KHRESMOI), OPTIMA; Austrian Science Fund (P 22578-B19, ProjectULMARCH), and a Marie Cure Intra European Fellowship with the 7th European Community Framework Programme (FP7-PEOPLE-2010-IEF).

