

Clinical implications of systematic vertebral fracture assessment on chest CT scans in smokers with or without COPD

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Social and scientific impact

In this thesis, we studied the associations between clinical determinants such as age, sex, smoking status, smoking history, bone attenuation (BA) measured on computed tomography images (CT) and thoracic kyphosis with prevalent and incident vertebral fractures (VFs) in smokers with and without chronic obstructive pulmonary disease (COPD). Additionally, we aimed to study the associations between BA and VF location and the association between VFs and coronary artery calcification (CAC) in this specific population. We used data from the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, which is a non-interventional, observational, multicentre study that was initiated to search underlying mechanisms of disease progression in subjects with COPD and to identify biomarkers that may serve as surrogate endpoints and therefore could measure disease progression. In the ECLIPSE study, CT scans of the chest were performed at baseline, one year follow-up, and three year follow-up and the CT images formed the basis for this thesis.

In **chapter 2**, we first studied the reproducibility of three imaging modalities (lateral chest X-ray, chest computed tomography (CCT) and lateral dual-energy X-ray absorptiometry (DXA) images) that are often used in clinical practice to study the level of agreement of these imaging modalities for diagnosis of vertebral deformities from the fourth thoracic to the first lumbar vertebra (T₄ to L₁). We found excellent reproducibility of height measurements of vertebrae with all three imaging modalities and concluded that these imaging techniques could be used for opportunistic screening of vertebral deformities in COPD patients. This finding is of great importance for clinical practice given the importance of diagnosing VFs in subjects of 50 years and older, since the presence of VFs is associated with the risk of vertebral and non-vertebral fractures and higher mortality risk.

In **chapter 3**, we found that one out of four subjects in the ECLIPSE cohort (mean age 61 years, 61% males, 81% with COPD) had a prevalent VF. Additionally we found that a prevalent VF at baseline was a major risk factor for a subsequent VF in the following three years, since 59% of the subjects with a prevalent VF had an incident VF. Based on these findings we propose to systematically evaluate the presence of VFs in patients with COPD who have chest X-rays or chest CTs made for pulmonary evaluation. Improvement in patient care can be achieved by increasing awareness among pulmonologists and radiologists about the clinical importance for recognizing VFs.

In the **chapters 4 to 7**, we found that low bone density (measured by BA) and increased thoracic kyphosis angles were associated with incident VF risk, while for example age and sex were not. We also found an association between CAC and prevalent VFs. Both CAC and VFs can be asymptomatic, but can have more serious medical consequences when left untreated. Additionally, load/strength ratio seems to play a role in VF location within the spine, meaning that certain areas within the thoracic spine are more likely to fracture due to loading patterns in daily life, while fractures in other areas are more likely to be the result of low bone density. The findings in **chapters 4 to 7** attribute to the concept of COPD as a complex multicomponent disease with pulmonary but also extrapulmonary events and comorbidities and that imaging techniques primarily used for pulmonary evaluation could also be used for detection of extrapulmonary disorders like osteoporosis, CAC and VFs.

Based on the findings in this thesis, we strongly believe that opportunistic evaluation of CT images should focus on further automation of detection of low BA, VFs and CAC in patients with COPD. Automated assessment will not only result in more objective assessment, but will also decrease the workload on medical practitioners, and allow for assessment of all pulmonary CT scans at computational costs only, making this extremely suitable for opportunistic screening programs.

The research presented in this thesis is therefore not only relevant to clinicians such as pulmonologists and radiologists, but also for technicians and software developers given the relevance of adequate automated image analysis.

The findings in this thesis have been widely distributed to and recognised by the scientific society. The work of all chapters was presented at international and national conferences and published in peer reviewed international journals including the highest ranked journal in the field of bone research: Journal of Bone and Mineral Research (**chapters 3 and 5**). **Chapter 2** was published in the journal Osteoporosis International in 2018 and was the most frequently downloaded paper from the orthopaedic springer journals in 2018, with 43.000 downloads. The work presented in **chapter 3** was awarded with a young investigator award by the American Society of Bone and Mineral Research in 2017.