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

Summary

This thesis focusses on the clinical implications of systematic vertebral fracture assessment on chest computed tomography (CT) scans in smokers with or without chronic obstructive pulmonary disease (COPD). The data presented in this thesis are primarily obtained from the ECLIPSE study. The ECLIPSE (Evaluation of COPD longitudinally to identify predictive surrogate endpoints) study is a non-interventional multicentre international study following patients with COPD over three years, 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 (Clinicaltrials.gov identifier NCT00292552; GlaxoSmithKline study SCO104960). A unique feature in the ECLIPSE study is that chest CT scans were obtained at baseline, after one year and after three year with CT scanners that were used in clinical practice. For this thesis we systematically evaluated bone attenuation (BA) and vertebral fractures (VFs) on chest CT scans at baseline, one- and three-year follow-up among the participants with and without COPD of the ECLIPSE study. We specifically aimed to study the associations between clinical determinants such as age, sex, smoking status, smoking history, CT-measured BA and thoracic kyphosis with prevalent and incident VFs. 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.

Although the gold standard for VF diagnosis is a lateral X-ray image, VFs can also be diagnosed on chest CT or lateral dual-energy X-ray absorptiometry (DXA) images. In clinical practice, these three imaging techniques are often applied, but radiological reports on diagnosed deformities may not always be congruent. In **chapter 2**, we studied the level of agreement for diagnosis of vertebral deformities from T_4 to L_1 on chest CT scans, lateral dual-energy X-ray absorptiometry (DXA) images of the spine and lateral X-ray images of the thoracic spine (the current gold standard for assessment of vertebral deformities according to the Dutch guideline). This study was performed in a population of 87 subjects (57% males, 66% with COPD) that participated in a clinical trial related to osteoporosis in COPD patients (NCT01067248) at the Catharina Hospital (Eindhoven, the Netherlands) using SpineAnalyzer^{TM} morphometry software (Optasia Medical, Cheadle, UK).

After excluding vertebrae that were not evaluable because of anomalies or other deformities, we applied the criteria of Genant et al. to quantify the deformities based on the measured height loss as no deformity (height loss <20%: grade 0), mild deformity (20% ≤ height loss < 25%: grade 1), moderate deformity (25% ≤ height loss < 40%: grade 2) or severe deformity (height loss ≥40%: grade 3).

We found that intraclass correlation coefficient (ICCs) for vertebral height measurements were excellent (>0.94) ant that Kappa's were good to excellent (0.64–0.77). For vertebral deformities fractures, sensitivity (51%–73%) and positive predictive values (57%–70%) were fair to good for

all three modalities and specificity and negative predictive value were excellent (≥96%). We concluded that the performance of chest CT and to a lesser extent of lateral DXA images indicated that these imaging techniques could be used for assessment of vertebral deformities in COPD patients.

Subsequently, in **chapter 3** we evaluated the prevalence and the one- and three-year incidence of VFs on chest CT scans in 1239 subjects of the ECLIPSE population (61% male, 81% with COPD). In this population, 253 subjects (20.5%) had ≥1 prevalent VF, and the cumulative incidence of VFs was 10.1% within one and 24.0% within three years. After adjustment for age, sex, body mass index (BMI), pack-years, and smoking status, prevalence and incidence were similar between smokers and COPD GOLD stages. Importantly, after one year, 29.2% of the subjects with a prevalent VF had an incident VF, compared with 5.1% in absence of a prevalent VF. The risk of incident VFs within one year and three years (hazard ratio (HR): 5.1, 95% confidence interval (CI) [3.6-7.4]) and 3.6, 95% CI [2.9-4.6] respectively) was therefore strongly associated with the presence of prevalent VFs. In addition, VF risk was higher with number and severity of prevalent VFs, and subjects with an incident VF within the first year had a high risk of a subsequent incident VF within the two following years.

In this study, more than half of the smokers and subjects with COPD with a prevalent VF or an incident VF within the first year sustained a subsequent VF within three years, indicating that (former) smokers with or without COPD with a prevalent VF or recent incident VF have a high imminent VF risk.

In **chapter 4**, we further studied the association between BA and prevalent VFs on chest CT scans and the risk of incident VFs among the (former) smokers with and without COPD from the ECLIPSE study. BA was measured semi-automatically in regions of interest (ROIs) of approximately 275 mm^3 in vertebrae T_4 to T_{12} (fractured vertebrae were excluded from measurements) using a self-written algorithm in Matlab and expressed in Hounsfield Units (HU).

We observed that subjects with a prevalent VF had a significantly lower BA compared to subjects without prevalent VFs (155.6±47.5 HU vs. 162.6±46.2 HU). BA and prevalent VFs were significantly associated with one- and three-year VF incidence, while age, sex, BMI, smoking status, smoking history, and presence of COPD were not. These results, based on systematic evaluation of chest CT scans suggest that the combination of BA and prevalent VFs was strongly associated with the short-term risk of incident VFs in smokers with or without COPD.

It is known that the presence of VFs in the thoracic spine often leads to increased thoracic kyphosis and in computational models it had been shown that greater kyphosis angles lead to increased loading on vertebral bodies. However, the association between severity of kyphosis and VF incidence in patients was largely unknown. In **chapter 5**, we therefore studied the association between prevalent VFs and severity of kyphosis, and the association between severity of kyphosis and incident VF risk using chest CT scans form 1239 ECLPISE study participants. We measured kyphosis angles between vertebrae T_4 and T_9, and between T_4 and T_{12}. Although kyphosis was measured in supine position on the chest CT images, this study showed that the presence, number and severity of VFs were associated with greater kyphosis angles. The mean increase in kyphosis angle within three years was small, but significantly greater in subjects with incident VFs compared to those without. After adjustment for BA and prevalent VFs, a greater baseline kyphosis angle was independently associated with incident VFs within one and three years (HR 1.34, 95% CI [1.12-1.61] and 1.29, 95% CI [1.15-1.45], respectively). These findings support the theory that greater kyphosis angle contributes to higher biomechanical loads in the spine.

In addition to kyphosis angles, also daily activities influence loading on the vertebral bodies. It has been suggested that loading during daily activities is highest in the vertebra T_7-T_8 and T_{11}-T_{12}, suggesting these vertebrae could be at higher fracture risk. Indeed, most VFs are observed in the mid-thoracic and thoracolumbar areas of the spine. In **chapter 6**, we hypothesised that VFs in the areas that bear the highest loadings during daily activities, the most common VFs (T_7-T_8 and T_{11}-T_{12}), occur at higher BA than VFs in less common locations (T_4-T_6 and T_9-T_{10}). Baseline chest CT images of T_4-T_{12} in smokers with and without COPD from the ECLIPSE study were analysed for the presence of VFs according to the method described by Genant. BA, expressed in Hounsfield units (HU), was measured in all non-fractured vertebrae.

Compared to subjects without prevalent VFs, there was a gradually lower BA for subjects with VFs only at the common locations (cVFs; -15%), VFs only at the less common locations (lcVFs; -25%, $p<0.05$ vs. cVFs) and VFs at both common and less common locations (-32%, $p<0.0001$ vs. cVFs) (all $p<0.0001$ compared to subjects without VF, $p<0.0001$ for trend). At each vertebral level from T_4 to T_{12}, a lower BA was associated with cVFs (OR between 1.5-1.9 for each 50 HU lower BA), lcVFs (OR between 2.2-3.4) and both lcVFs and cVFs (OR between 3.8-4.6). These findings suggest the contribution of BA to the load/strength ratio of vertebrae differs between vertebral locations and that other factors besides BA, such as vertebral load during daily activities or caused by a fall, may determine the location of a VF.

In **chapter 7**, we evaluated the association between VFs and CAC, given the high prevalence and incidence of VFs we found in chapter 3 and the fact that smoking is also strongly associated with cardiovascular events. Of 586 participants in the ECLIPSE study, (62% male, 70% with

COPD) we systematically evaluated the presence of VFs and CAC. VFs were categorised according to the method described by Genant and CAC was expressed in Agatston score and categorised as zero, medium (1-400) and high (>400). Of all subjects, 21% had a prevalent VF and 23% had an incident VF within three year, and 196 subjects (33%) had low, 266 subjects (45%) had medium (1-400), and 124 subjects (21%) had high (>400) Agatston scores.

Prevalent VFs were associated with medium and high Agatston score (OR = 1.83, 95% CI [1.01-3.30] and 3.06, 95% CI [1.45-6.47], respectively). After adjustment for BA, prevalent VFs were still associated with high (OR = 2.47 [1.13–5.40]), but not with medium Agatston score. Agatston score at baseline was not associated with short-term VF incidence. These findings indicate that in clinical practice, (former) smokers with or without COPD, who are assessed for and diagnosed with either VF or CAC, should be screened for the other.

Given the high prevalence and incidence of VFs in COPD subjects, we propose to systematically evaluate the presence of VFs at chest X-ray or chest CT scans 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. Patients with VFs should be further evaluated and treated according to local osteoporosis and fracture prevention guidelines.