On structural spinal damage in patients with radiographic axial spondyloarthritis

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CHAPTER 7

Summary and general discussion

In this thesis we focused on the detection, prevalence, progression and predictive factors of lesions in the whole spine in patients with radiographic axial spondyloarthritis (r-axSpA). We aimed to gain insight into the development of syndesmophytes and facet joint ankylosis to better understand the disease etiology. We formulated three research aims. Our first aim was to assess the validity of the Computed Tomography Syndesmophyte Score (CTSS), which is a scoring method designed to assess low dose Computed Tomography (ldCT) images for the presence and growth of syndesmophytes in the whole spine. Using this technique, we looked at structural spinal damage and its risk factors. Our second aim was to understand known drivers for syndesmophyte formation, vertebral corner inflammation and vertebral corner fat deposition, and the interplay between these drivers. Our third aim was to study two bony lesions in the spine: syndesmophytes and facet joint ankylosis. We first mapped facet joint ankylosis and its progression in the whole spine, and next studied its association with syndesmophyte development.

In this chapter I will summarize our findings, discuss their implications for practice and research and discuss future perspectives.

Aim 1: Detection of syndesmophytes on low dose CT

LdCT is a promising imaging method, combining the best of CT scans (better visibility) with the best of conventional radiography (lower levels of radiation than conventional CT scanning protocols). Syndesmophytes detected on CT can be scored using the CTSS.[1] Validation of the CTSS was started by comparing the assessment of syndesmophyte formation and progression with CTSS to assessment with the mSASSS, which is the current golden standard for detection of spinal structural damage.[2] This showed that the CTSS is more sensitive in detection of syndesmophytes and in detection of progression of syndesmophytes than the mSASSS. This left certain aspects of the validation of the CTSS to still be studied. In **chapter 2** we assessed the construct validity of the CTSS. This was performed in accordance with the Outcome Measures in Rheumatology (OMERACT) handbook on how to assess the truth aspect of a measure.[3] We assessed the construct validity in two parts: 1) by assessing whether detection of syndesmophytes on CTSS was concurrent with syndesmophyte detection on mSASSS on the corner level and 2) by correlating both the CTSS and mSASSS with measures of spinal mobility and making a comparison of the results. We performed these analyses in the Sensitive Imaging in Ankylosing Spondylitis cohort (SIAS).[1] This cohort included patients with a diagnosis of r-axSpA and at least one syndesmophyte. We found that indeed the majority of syndesmophytes on ldCT were also visible on the same corners on conventional radiography at the same time or two years later. We also observed an increase in this agreement over time, thus

a part of the syndesmophytes on ldCT was not visible yet at the same time on radiography but became visible two years later. This corroborated our previous finding that ldCT is a more sensitive measure and can thus detect syndesmophytes earlier than radiography. When we calculated the agreement the other way around, thus the proportion of syndesmophytes on radiography that were also visible on ldCT at the same time, we observed much higher proportions. Thus, syndesmophytes seen on radiography are nearly always also seen on ldCT at the same time, while syndesmophytes seen on ldCT are often but not always also visible on radiographs at the same time or two years later. For our second hypothesis we found that the CTSS had moderate to substantial correlations with spinal mobility measures and the composite measure BASMI. Furthermore, the CTSS did not correlate with the hip mobility measure inter malleolar distance, which was in agreement with our hypothesis. The mSASSS showed fair to substantial correlations with the spinal mobility measures and BASMI and showed fair correlations with inter malleolar distance. Numerically, all correlation coefficients of CTSS were higher compared to the ones from mSASSS, which shows that the CTSS correlates at least as well, if not better, as the mSASSS with the domain of spinal mobility.

Implications and future perspectives

Both our hypotheses were confirmed, thus we can conclude that the CTSS has good construct validity. As mentioned, earlier studies from our research group assessed other aspects of the CTSS on which we expanded.[1,2] We know that the CTSS can assess syndesmophyte detection and progression, that it is a more sensitive measure than the mSASSS and that it correlates well with a construct it is expected to correlate with. With these results combined, a strong evidence base is laid for the use of the CTSS in studies. We used the OMERACT handbook to guide the process of validation and use it now to assess whether the validation is completed.

The OMERACT handbook distinguishes three pillars which describe the evidence that is needed for an instrument to be approved by the OMERACT filter: truth, feasibility and discrimination.[3] The truth pillar assesses whether the measure is a match with the target domain and whether the numeric scores make sense. The feasibility pillar assesses whether the measure is feasible/practical to use, and the discrimination pillar assesses whether the measure can discriminate between groups in the setting of interest. We assessed construct validity which is part of the truth pillar. We saw that the construct validity is good and the CTSS does reflect the target domain of structural spinal damage. Other parts of the truth pillar are content validity, face validity and inter-method reliability. Content and face validity were thoroughly considered when developing the CTSS, by taking into account the aspects that needed to be included in the measure and how the measure matches the concept of structural spinal damage. The last aspect of the truth pillar, inter-method

reliability, was assessed in a previous study which assessed the inter-rater reliability.[1] Thus, with the addition of our study, the truth pillar of the OMERACT filter is complete.

The feasibility pillar was not formally assessed but information on several important aspects of feasibility is readily available. Feasibility includes the burden on the patient and researcher, the cost of the measure, the time and effort it takes, and translations that might be required. The cost of a CT scan, while difficult to estimate precisely due to differences across institutions and countries, is generally higher than that of conventional radiographs of the spine. The availability of a CT scanner is comparable to that of conventional radiography in hospitals. The ldCT protocol can be used on normal CT scanners and does not require a separate machine. The burden on the patient for a CT scan can be expressed in the experience of undergoing a ldCT, the time and effort it takes, and the radiation dose endured. A CT scan with the ldCT protocol takes about 10 minutes to perform, which is a relatively minor time investment. The patient lies still during this time commonly with the arms above their head. While a CT scan has a short tube which does not completely cover the patient, patients can still experience signs of claustrophobia during the scan. The radiation dose the patient is exposed to for ldCT images of the whole spine is more than for conventional radiography images of the cervical and lumbar spine, but much less compared to a conventional CT scanning protocol of the spine. The increased radiation dose compared to radiography is part of the trade-off that is made of to achieve better visibility. Lastly, while the ldCT protocols can be executed by any radiology technician that handles CT scanners, the CTSS is a measure that requires training before it can used. This is however standard for imaging measures, and no different than for the mSASSS. In conclusion, the CTSS is a measure that can have a slightly higher patient burden and larger cost per patient compared to the mSASSS. This, however, is a trade-off for the benefits of the CTSS over the mSASSS. For the individual patient the benefits are that more information is available regarding their state and progression of disease. For the use in a trial or study, the benefit is that the CTSS is a highly sensitive measure. Thus, while it can be more expensive per patient than the mSASSS, its use instead of mSASSS could result in requiring a smaller patient population or a shorter follow-up, both of which provide a great reduction in costs, time and effort.

The discrimination pillar of the OMERACT filter includes test-retest reliability, responsiveness, discrimination in clinical trials and the degree to which the meaning of the scores can be easily understood. Responsiveness has been studied before and shown to be good with a whole spine smallest detectable change (SDC) of 14.4, which is small compared to its range of 0-552. Additionally, of the patients with progression a large proportion (37%-

43%) showed progression above the SDC.[1] While inter-reader reliability has been reported, the test-retest reliability has not yet been assessed. The CTSS has also not been used in a clinical trial before, therefore its discrimination between groups has not been assessed. Currently there are no medications available that have proven to be able to reduce structural damage during the period of a trial, which makes it at the moment impossible to test this aspect of validity. However, group discrimination has been assessed and proven for spinal mobility measures. Of all spinal mobility measures, the lateral spinal flexion and Bath Ankylosing Spondylitis Metrology Index (BASMI) were most impaired in patients and best discriminated between patients with different disease severities.[4] We have shown in our study that the CTSS correlates well with spinal mobility measures, and it correlates best with lateral spinal flexion and BASMI. Thus, while we have not assessed the discriminative abilities of the CTSS ourselves, we do have evidence that the CTSS correlates well with measures that have been proven to discriminate well. Lastly, the discrimination pillar asks for thresholds with which an easily understood meaning is given to the measure. The CTSS is a semi-continuous measure with a range of 0-552 and no cutoffs are defined within this range. This is not uncommon, e.g. the mSASSS is also a semi-continuous measure without thresholds. The CTSS is designed to be interpreted along the range of 552 points, in which higher points indicate more structural spinal damage. Furthermore, because we have shown that the CTSS correlates with spinal mobility, we do know that larger CTSS scores reflect a higher degree of spinal impairment.

In conclusion, all pillars from the OMERACT filter have been addressed almost completely and the CTSS is deemed a valid and reliable measure. On the test-retest reliability no data is available for the CTSS. However, test-retest reliability is always stronger than reliability across raters, and this latter aspect has been shown to be very good for the CTSS. Therefore the absence of the test-retest reliability assessment should not preclude use of the CTSS in further studies and clinical trials. The only other aspect of validity that remains missing is the discrimination between groups. This aspect, however, is also absent for the mSASSS due to the lack of drugs that have a proven efficacy on structural spinal damage between groups. As discussed, there are clear benefits of using the CTSS instead of another measure like the mSASSS in clinical trials. This will enable us to learn more about the whole spine instead of only the anterior cervical and lumbar corners, and it can even be more feasible because probably fewer patients and possibly a shorter follow-up are required.

Aim 2: predictive MRI imaging factors for syndesmophyte development

Syndesmophytes are a hallmark of r-axSpA and can lead to severe spinal deformities and limitation of movement and function.[5-7] Prevention of syndesmophyte development is therefore an important goal, and understanding the factors that contribute to syndesmophyte development is crucial. In **chapter 3** we studied the association of vertebral corner inflammation and vertebral corner fatty lesions on the development and progression of syndesmophytes. We performed these analyses in the SIAS cohort. We used 18 definitions of patterns of inflammation and fatty lesions. All analyses were on the vertebral corner level. Two types of outcomes were used: 1) the development of a new syndesmophyte, and 2) either the development of a new syndesmophyte or the growth of an existing syndesmophyte. Both inflammatory and fatty lesions were associated with both outcomes with odds ratios of around two. The lesions were associated both when occurring in absence of the other lesion and when the other lesions was left out of consideration. When inflammatory lesions preceded or coincided with fatty lesions, the association was statistically significant for outcome 2 (the development of new syndesmophytes or the growth of existing syndesmophytes). The absence of inflammatory and fatty lesions on all three timepoints was protective for both outcomes. These findings add to the existing literature by showing that inflammatory and fatty lesions are associated with both the development and the growth of syndesmophytes in the whole spine. In our findings we also observed patterns in which inflammatory lesions are followed by fatty lesions, and as mentioned this was associated with new development of syndesmophytes or growth of existing syndesmophytes. This finding is in line with the literature, where fatty lesions are reported to follow inflammatory lesions.[8-10] This specific sequence of lesions is thought to be of importance for how syndesmophytes develop. However, this has been studied in terms of associations but not with causal methods. Therefore, in **chapter 4** we aimed to understand whether inflammatory lesions more often cause syndesmophyte development with or without intermediate fatty lesions in this same dataset (SIAS). However, we found it essential to validate in an independent cohort. As this second, independent, cohort, we used data from the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) clinical trial.[11] We used a causal mediation model to separate the effect of inflammatory lesions on syndesmophyte formation into the effect that travels through the intermediate occurrence of a fatty lesions (the indirect effect) and the effect that is not explained by an intermediate fatty lesions (the direct effect).[12,13] From our study in **chapter 3** we knew there was an association between inflammatory lesions and syndesmophytes in the SIAS dataset.[14] Similarly, a previous study on the ASSERT data had shown an association between inflammatory lesions and syndesmophytes.[9] Hence, we knew before

the start of the analyses that in both datasets the association of inflammatory lesions with syndesmophytes would be found, but we did not know the causal paths with fatty lesions within this association. In both datasets we observed that corners more often developed fatty lesions if an inflammatory lesion was present at baseline versus when there was no inflammatory lesion at baseline. However, when testing the causal model, the indirect effect was very small compared to the total effect in both datasets (2% in SIAS and 10% in ASSERT). Thus, the effect of inflammation, for the largest part, did not require a fatty lesion as a mediator before a syndesmophyte occurred.

Implications and future perspectives

Our study in **chapter 3** confirmed the effects of inflammatory and fatty lesions in the whole spine. As the same effects were shown earlier in studies assessing only the anterior cervical and lumbar corners, the addition of our study completes this research question.[8-10,15-17] With this accumulation of studies, little doubt is left whether inflammatory and fatty lesions are risk factors for syndesmophyte development. At the same time, it is clear that these effects do not explain the whole process of syndesmophyte development, because we confirmed in our study that many syndesmophytes occur without the preceding inflammatory or fatty lesions. In principle this could be a detection error. As post-inflammatory lesions, fatty lesions should, in principle, not resolve and once developed usually remain visible on MRI. In this case the time interval between the last MRI and the syndesmophyte detection could play a role, in which a shorter time interval might detect fatty lesions that appear shortly before syndesmophyte development. Inflammatory lesions, however, can resolve. If a study was performed where MRI scans are performed frequently, e.g. every month, and over a longer period, e.g. 5 or 10 years, it could be that the effect of inflammatory lesions on syndesmophyte development is bigger than what is reported in the current available studies. It seems unlikely, however, that such a study will result in the finding that inflammatory lesions are fully responsible for the development of syndesmophytes, nor is such a study feasible to perform. In **chapter 4** we aimed to better understand the role of fatty lesions in the association between inflammatory lesions and syndesmophytes and found that fatty lesions only mediate the effect in a very small portion of cases. Thus, mostly when an inflammatory lesion is followed by a syndesmophyte, no fatty lesion occurred in between. This finding can influence how we view the order of events leading up to syndesmophyte formation. The hypothesis in literature was that, since inflammatory lesions and fatty lesions are both associated with syndesmophyte formation and since fatty lesions often occur after inflammatory lesions, this must be the natural sequence resulting in syndesmophyte formation. We do want to stress that we did find fatty lesions to be associated with syndesmophyte development in **chapter 3** and we did observe that fatty lesions occurred more often if an inflammatory lesion had

occurred previously, only we did not observe a strong mediating effect of fatty lesions in **chapter 4**. Because this was the first study assessing this model, we performed the analyses simultaneously in two independent datasets. The conclusion from the two datasets was the same, which corroborated our final conclusion. Nonetheless, our analyses had a relatively short follow-up of two years, and had one timepoint for each of the lesions to develop. Therefore it could be valuable if studies with a longer follow-up and more MRI scans would be performed on the same research question, to consolidate or refute our findings.

Concluding, we now know that both inflammatory and fatty lesions are associated with syndesmophyte development and growth in the whole spine. We furthermore learned that fatty lesions only barely mediate the effect of inflammatory lesions on the development of syndesmophytes.

Aim 3: understanding facet joint ankylosis and its association with syndesmophyte development

Next to syndesmophyte development, patients with r-axSpA can develop facet joint ankylosis. In **chapter 5** we assessed facet joint ankylosis in the whole spine using low dose CT. To our knowledge this was the first study assessing facet joint ankylosis in the whole spine in r-axSpA patients. The analysis was performed on vertebral units (VUs). Four VUs, C5-C6 until T1-T2, were left out of consideration. These are VUs where the readers had difficulties assessing the joints due to poor image quality. This is a well-known problem when making CT scans; the cervico-thoracic segment is difficult to visualize due to presence of the shoulders. On a group level, we found that facet joint ankylosis occurred in every VU level, thus when looking at all patients there was no VU that was not ankylosed in any of the patients. Most ankylosis occurred in the thoracic segment. Over a period of two years, the mean progression of ankylosed facet joints per patient in the whole spine was 1.0 joint (SD 2.8) for CT reader 1 and 1.1 joints (SD 2.6) for CT reader 2. Forty-eight percent of the patients had at least one new ankylosed facet joint over a period of two years, taking the whole spine into account. The other patients showed no change or, for a few patients, negative change (i.e. fewer ankylosed facet joints, attributable to scoring error). Almost all progression occurred in the thoracic spine. Because facet joint ankylosis is a type of bony lesion in the spine that may lead to fusion of a joint, it is thought to be associated with bone formation and therefore syndesmophyte development.[18-21] Consequently, we next evaluated whether patients that had progression (i.e. in increase in number) of facet joint ankylosis also had progression of syndesmophytes measured with the CTSS. We observed that higher progression scores of facet joint ankylosis were generally found in patients with higher syndesmophyte progression scores. We

also saw that some patients showed progression of one lesion but not of the other. To determine whether progression was present, the SDC was taken as a cutoff which was 1.98 for facet joint ankylosis and 14.4 for the CTSS. Of the 44 patients in the analysis, four patients (9%) had progression of both facet joint ankylosis and syndesmophytes, eight patients (18%) had progression of facet joint ankylosis only, nine patients (20%) had progression of syndesmophytes only and 23 patients (52%) had no progression of either lesion. These results combined inform us that syndesmophytes and facet joint ankylosis both occur and progress in patients with r-axSpA and that a relation can be seen between the two.

Therefore, in **chapter 6**, we looked more closely at this association and modelled them at the VU level. We studied 1) whether the presence of facet joint ankylosis is associated with new syndesmophytes on the same VU and 2) whether the presence of bridged syndesmophyte(s) is associated with new facet joint ankylosis on the same VU. We specifically used bridged syndesmophytes as a predictor because our underlying assumption is that the rigidity in the spine caused by the ankylosis of the facet joints or the vertebrae is what causes further bone growth in the same or adjacent VU. We know from our previous chapters that inflammation is a risk factor for syndesmophyte development, thus we adjusted all analyses for inflammation on the vertebral bodies and, to be sure, for inflammation in the posterior elements, which include the facet joints. We explored the associations further with two types of secondary analyses. First, we assessed these models not with associations on the same VU, but with the outcome on one or two VUs above or below the predictor. This is to see whether a bridged syndesmophyte or ankylosed facet joint can also influence facet joint ankylosis or syndesmophyte formation in adjacent VUs. Secondly, we assessed whether the magnitude of the predictor influenced the strength of the association on the same VU. Thus, we categorized the predictors with facet joint ankylosis in zero, one or two joints and bridged syndesmophytes in zero, one, two, three or four quadrants. We found consistent statistically significant results in all types of analyses for the hypothesis that bridged syndesmophytes are associated with the development of facet joint ankylosis. For the hypothesis in the other direction, where facet joint ankylosis is associated with subsequent syndesmophyte development, results were also found in favor of the hypothesis, yet fewer models yielded statistically significant results and with slightly lower odds ratios than for the association between bridged syndesmophytes and facet joint ankylosis. We also found that for the association of bridged syndesmophytes with the development of facet joint ankylosis, odds ratios increased the more bridged syndesmophytes were present at baseline. The same was observed for the association of facet joint ankylosis with the development of syndesmophytes, but with smaller odds ratios. Taking the results of all these analyses together, we see there is indeed evidence that facet joint ankylosis and syndesmophytes are

associated with each other's development, in which the association between bridged syndesmophytes and subsequent facet joint ankylosis seems to be stronger than the association between facet joint ankylosis and subsequent syndesmophyte development. This is on the same VU, but also on adjacent VUs. And we observe a dose-effect response, in which a greater presence of the predictor results in a higher odds ratio for the development of the outcome. It is important to note that these results can only be interpreted for the population we selected. Part of the inclusion criteria for the SIAS study were that patients had at least one syndesmophyte. Thus, on a patient level, patients in this study could not show facet joint ankylosis without having at least one pre-existing syndesmophyte anywhere in the spine. One previous study which did not use the presence of syndesmophytes as an inclusion criterion, found that while most patients with facet joint ankylosis also had bridging syndesmophytes, a small portion of patients (between 5% and 8%) had facet joint ankylosis but no syndesmophytes anywhere in the cervical spine.[19] Important to note however is that in that study only the cervical spine was assessed.

Implications and future perspectives

This is, to our knowledge, the first and only study assessing the interplay between facet joint ankylosis and syndesmophyte development using inferential methods. Previous studies described the occurrence of facet joint ankylosis and syndesmophytes and found that assessing facet joint ankylosis in addition to syndesmophyte development led to capturing more patients with progression of spinal structural damage.[18,19] Our study in **chapter 5** confirmed these findings, by showing that there is a proportion of patients who have detectable progression of facet joint ankylosis in the absence of detectable syndesmophyte progression when these lesions are studied in the whole spine. We observed that most occurrence and progression of facet joint ankylosis occurred in the thoracic spine, further emphasizing the benefit that using ldCT can have in understanding and monitoring spinal lesions in r-axSpA patients. In our studies with facet joint ankylosis we did not make comparisons with patients without axSpA, non-radiographic axSpA (nr-axSpA) patients or r-axSpA patients without syndesmophytes. Therefore, we cannot extrapolate our findings outside of r-axSpA patients with syndesmophyte presence. Thus we cannot say, based on our findings, if facet joint ankylosis occurs more often in patients with r-axSpA than in patients with other forms of axSpA or people without axSpA, although we do know from previous studies that facet joint ankylosis is not involved in the inflammatory process in rheumatoid arthritis.[22] A recent abstract compared facet joint involvement in r-axSpA, nr-axSpA and non-axSpA patients and reported facet joint ankylosis to occur most in r-axSpA patients, but other forms of facet joint involvement, including joint space narrowing, to occur also in nr-axSpA patients.[23] Nonetheless, because we observe the association between bridged syndesmophytes and

facet joint ankylosis in **chapter 6**, it seems obvious that facet joint ankylosis plays an important role in r-axSpA, regardless of whether it occurs in people without the disease. Therefore while, to our knowledge, no studies have been performed on facet joint ankylosis in the whole spine in the general population, such studies do not seem to be required since it will not diminish the fact that facet joint ankylosis is an important feature in r-axSpA patients. Because facet joint ankylosis is proven to be so widely present in r-axSpA patients and to be associated with syndesmophyte development, our most important implication for future research is that we suggest that facet joint ankylosis is to be taken into account in future studies assessing structural spinal damage. When the vertebral bodies are assessed for syndesmophyte presence, the facet joint can easily be assessed as well on the same images. This is possible on conventional radiographs and, as we showed, on whole spine ldCT.[18] As for future research projects, it would be interesting to assess facet joint ankylosis in the whole spine in an (r-)axSpA population without the prerequisite of having syndesmophyte presence. This can inform us which is the starting lesion in the whole spine: facet joint ankylosis or syndesmophyte presence. Syndesmophyte presence is always seen as the hallmark feature of r-axSpA. Performing such a study can answer whether syndesmophytes indeed develop first, or whether perhaps their start can be initiated by facet joint ankylosis which, as we showed in **chapter 6**, can be a risk factor for syndesmophyte development. Additionally, studies assessing the effect of medication on structural spinal damage, although these are rare, could take both syndesmophyte progression and facet joint ankylosis progression as the outcome. It would be most interesting to see whether facet joint ankylosis responds to drug treatment. Another interesting study on facet joint ankylosis, is to better understand if, and how, inflammatory lesions influence the development of facet joint ankylosis. We have seen in **chapter 6** that in half of the models in which the development of facet joint ankylosis was adjusted for the presence of posterior element inflammation, this association with inflammation was statistically significant. Thus, this leads us to hypothesize that inflammation is not only a risk factor for syndesmophytes, but also for facet joint ankylosis. This needs to be assessed in a study specifically aimed at this research question.

In conclusion, we learned that facet joint ankylosis is an important factor in r-axSpA and may be worthwhile to be included in studies assessing structural spinal damage in patients with r-axSpA.

Concluding remarks

In this thesis we focused on structural spinal damage in r-axSpA patients. We found the CTSS to be a valid tool that can be used in research settings for the detection of syndesmophytes in the whole spine. The use of the CTSS over an instrument such as the mSASSS can lead to a more sensitive detection of syndesmophytes and the benefit of visualizing the whole spine, rather than only the anterior cervical and lumbar vertebral corners. We found that both inflammatory and fatty corner lesions are associated with syndesmophyte development and growth in the whole spine. With this finding, we believe the accumulation of evidence is complete on this topic and no more studies are needed to establish whether these associations exist. We concluded that corners with inflammatory lesions do not require fatty lesions to develop a syndesmophyte. Lastly, we found facet joint ankylosis to occur in the whole spine but mostly in the thoracic spine and we found this to be associated with syndesmophyte development. Therefore, we recommend studies that assess structural spinal damage to also assess facet joint ankylosis and to do so in the whole spine, e.g. with ldCT. With these findings we hope to have made valuable contributions to the body of knowledge on structural spinal damage in patients with r-axSpA.

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