Author's response to reviews

Title: Baseline new bone formation does not predict bone loss in ankylosing spondylitis - 10-year follow-up.

Authors:

Mariusz Korkosz (mariuszk@mp.pl)
Jerzy Gąsowski (jerzy.gasowski@wp.pl)
Piotr Grzanka (plpg@poczta.onet.pl)
Janusz Gorczowski (gorczowski@mp.pl)
Wojciech Pluskiewicz (osteolesna@poczta.onet.pl)
Sławomir Jeka (s.jeka@wp.pl)
Tomasz Grodzicki (tomekg@su.krakow.pl)

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Author's response to reviews:

Dr Melissa Norton
Editor-in-Chief
BMC Musculoskeletal Disorders,

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Dear Dr Norton,

Attached, please find our itemized answers to queries of the Reviewers regarding our manuscript titled “Baseline new bone formation does not predict bone loss in ankylosing spondylitis - 10-year follow-up”

Author’s response

Reviewer 1 – dr Thomas Lang

1. The main conclusion of our study was that irrespectively of baseline radiologic stage the trabecular bone density decreased over 10-year follow-up, when assessed with QCT. We do agree with Reviewer that this might reflect an effect of aging. We have had however control group of age-matched healthy males retrieved retrospectively from our DXA database. At baseline and follow-up we have had no statistically significant difference between groups with regard to DXA spine results (data not showed). Taking into account baseline disease duration averaged 16.5 (±8.6) years we can assume that in this relatively early AS, trabecular bone loss discovered in QCT (confirmed by other authors as well) could be already balanced by outer layer bone gain – thus DXA summarizing inner and outer bone density in AS was not different (ie. lower) from controls, as expected. At follow-up spine trabecular bone density in AS was significantly decreased as proved in QCT – but spine DXA still remained not different from controls, what we cannot explain and what might be due to low sample size or
spine osteoarthritis (osteophytes and hypertrophic posterior elements) in controls. We also have done baseline QCT in 12 controls with spine osteoarthritis and showed that their BMC was higher than patients (141.71 mg/cm\(^3\)±34.26 SD versus 77.49 mg/cm\(^3\)±43.46 SD, respectively, p=0.001) (Korkosz M, Głuszko P, Marcinek P. Comment on bone mineral density and bone turnover markers in a group of male ankylosing spondylitis patients. J Clin Rheumatol. 2002 Dec;8(6):359-60). Unfortunately, only three controls were suitable for follow-up QCT so we failed to collect control QCT. Nevertheless we agree with Reviewer that it is impossible to separate the possibility of age-related phenomenon in our group and in order to clarify this we add a sentence in the Discussion section.

Standard calibration phantom (Picker) was supplied and recommended by manufacturer (Marconi) – we add a sentence in the Methods section. However, we used the same phantom at baseline and follow-up, so the relative BMC values (g/cm\(^3\)) we presented in the article gave a true trend towards lower values; but we agree that T-scores calculated were not based on Polish population reference data and these were not used for the statistical analysis.

2. The few sentences were added in Discussion section explaining how radiographic score corresponds with new bone formation. We agree with Reviewer that taken from population point of view our group is of modest size, what we stressed in Discussion section. However, to our best knowledge this is still largest group of AS patients followed for a substantial number of years using advanced CT/X-Ray phenotyping. We did not detect significant QCT vs. DXA correlation level even this modest number of patients was enough to pick-up other relations.

3. We add few sentences to Discussion section about fractures risk in natural history of AS and association of QCT values and vertebral fracture status in case-control studies.

4. After reviewing this patient’s data we have no clear explanation why his neck and Ward’s BMD rose in such extent. We thank the Reviewer for the very important suggestion to perform a sensitivity analysis after exclusion of an outlying observation in neck and Ward’s triangle data. After exclusion of this individual the p value for change in DXA neck measurement did not change. However we observed a small yet statistically significant decrease in DXA measurement of Ward’s triangle which represents trabecular bone and is compatible with our QCT findings. This observation strengthens the possible impact of our message that the measurement of trabecular bone (either QCT or DXA Ward’s triangle) should replace integral measurement of cortical and trabecular bone (DXA neck or spine) in assessment of AS patients.

We added a sentence to the discussion section regarding the results of this sensitivity analysis.

5. We assumed that radiologic changes to be followed in our study were new bone formation – namely syndesmophytes. That is why we have chosen the Devogelaer staging which focus on syndesmophytes and give clear cut “border” between early new bone formation (stage 0—I) and advanced (stage II-IV). This unable us to divide our patients into early (7 pts) and advanced (8 pts) groups at
baseline. On follow-up it turned out that 6 out of 7 subjects from early group “progressed” into advanced. In both baseline groups QCT values decreased significantly but baseline radiologic severity, i.e. syndesmophytes did not predict progression of bone loss. It was inserted in sub-chapter “Relationship between QCT and new bone formation”. If this is truth that the inflammation is a trigger mechanism for both BMD loss (inflammatory osteoporosis) and bone growth (syndesmophytes etc.) in seronegative spondyloarthropaties and these processes run in parallel and are coupled therefore is there any prognostic parameter (in our case – syndesmophytes) which could predict bone loss and in a wider perspective fractures. The answer was “no” according to our study – but contrary to Karberg et al because they suggested that it seems likely that in ankylosing spondylitis bone loss parallel new bone formation. Obvious question – which is currently being addressed in research agenda – when we stop the inflammation should we expect BMD gain (already proven with TNF-inhibitors) and new bone formation stopped (questionable). That is why the link between osteoporosis and syndesmophytosis in AS is being currently an important research target.

6. The section Statistical analysis was expanded according to Reviewer’s suggestion.

7. The brief description of QCT acquisition and processing was added in the Materials and methods section.

8. The Figure 3 was added comprising lumbar spine X-ray and QCT scans of one of the patients at baseline.

Reviewer 2 – dr Jesus Garrido

1. We thank the Reviewer 2 for the important remark. Based on relationship between mean values and their respective standard deviations (tab. 1) we indeed assumed that there is no significant departure from the assumption of normality of our data. However, in our moderately sized group, for the sake of clarity when presenting data on absolute scale, we added median as well as the 25th and 75th percentile values.

2. A – It is beyond any doubt that the time-wise analysis is of interest, however in all our patients the follow-up time was exactly 10 years. Thus we assume that time as a constant, has had similar effect in all of them.

B – We do agree with the Reviewer’s remark, however we fear that further subdivision of our data might yield spurious results when it comes to formal statistical significance, as in some of the strata the count is less than 5.

3. Again we agree with the remark. Yet again we stress that in our data the follow-up time was a constant and thus cannot influence the interaction term.

4. The section Statistical analysis was expanded according to Reviewer’s suggestion.

Other amendments

We added 5 references.
We updated tab. 1 – according to Reviewer 2’s remarks – it is currently in horizontal orientation and we decided to upload it as separate file. We added fig. 3 – according to Reviewer 1’s suggestion. We tried to do our best to improve the linguistic quality of our manuscript.

Our second co-author’s (dr G#sowski) family name contains a special character (# – a with an appendage), we would be grateful if this could be included.

We are grateful for the opportunity to amend our manuscript and sincerely hope that after revision it can be considered further.

We look forward to hearing from you before long, Sincerely

Mariusz Korkosz, MD, PhD