Author's response to reviews

Title: The implications of 18F-FDG PET for the diagnosis of endoprosthetic loosening and infection in hip and knee arthroplasty: Results from a prospective, blinded study

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Author's response to reviews: see over
The paper by Delank et al. analyzes the potential of positron emission tomography (PET) to diagnose and differentiate the two most common complications of joint replacement, loosening and infection. To this end, a total of 27 patients with 36 hip and knee prostheses were included in the study. In addition to the PET scans, a bone scintigraphy was acquired in 28 of the 36 prostheses (77.8%). Diagnostic reference of the study were the results of surgical intervention (27/36) or clinical examination (9/36). Five of the joint replacements turned out to be infected while 31 of the prosthetic components were loosened (proximal component: 16 cases, distal component: 15 cases). The PET scans were analyzed qualitatively and quantitatively. While the quantitative approach using standard uptake values was able to reliably identify pathological processes, it showed substantial limitations in differentiating loosening from septic or aseptic infection. Under utilization of qualitative criteria, loosening was correctly diagnosed in 76.4% by PET and in 75% by bone scan. In contrast, septic infection could be diagnosed correctly by PET in 100% whereas bone scintigraphy proved to be largely ineffective.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. While the criteria for the qualitative interpretation of the PET acquisitions are given in detail (Fig. 1), no such thing can be found for the bone scan. A corresponding amendment should be made. Furthermore, it should be mentioned on page 6 (Materials and Methods) that the bone scans were acquired in triple-phase technique.

   - On page 6 we completed the informations about the bone scans.

2. The qualitative criteria for the diagnosis of pathological processes of joint replacements described in the paper by Reinartz et al. were developed exclusively for hip arthroplasty. This limitation should be mentioned in the text. So far, our group has scanned about 60 painful knee prostheses. In contrast to hip arthroplasty, we were unable to find any consistent criteria for the loosening of knee prostheses. Only the criterion for an infection of the prosthesis could be verified. In this context, it should be mentioned how many hip prostheses and how many knee prostheses were included in the study. Furthermore, both subgroups should be tested separately. It would be of great interest whether the accuracy of PET imaging is comparable for hip as well as knee arthroplasty or whether results are discrepant.

   - It’s right that the qualitative patterns described by Reinartz are developed for hip arthroplasty. Because of missing a better system we used the same patterns also for knee-prosthesis. It is conscious to the authors, that characteristics of a knee joint are quite different compared with hip arthroplasties (side 11). Especially the large synovial surface of knee joint is the reason for different uptake patterns. The co-author of our paper (M. Schmidt) discussed this special problem not long time ago in a personal talk with the head
of Mr. Reinartz department, Professor Büll (DGN congress 2004, Rostock). The idea for testing both subgroups separately is good, but not efficient in view of just 5 knee prostheses.

3. The relatively low accuracy of PET in detecting prosthetic loosening is explained by the lack of cellular elements in the region between the cemented bed and the prosthesis. Were all joint replacements cemented? If so, it should be stated, if not, the exact number of cemented and cementless prostheses should be given. In this context, it would be of interest to test whether the type of implantation (cemented vs. cementless) has an impact on the imaging results.

- The exact number of cemented versus uncemented prosthesis is completed on page 4. The impact of the type of fixation on the imaging results is mentioned in tabel 2b

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. On page 2, the word "microbiologic" should be replaced by "microbiological".
   - Is corrected

2. The name of the author cited on page 3 is "Cremerius" instead of "Cremius".
   - Is corrected

3. The formula for the calculation of the SUV is incorrect. The denominator should read (decay corrected injected dose [Bq] x body weight [kg]) instead of (decay corrected injected dose [Bq] / body weight [g]).
   - We discussed this point with our expert for medical physics and still think that our formula is correct. The standard uptake is a value without a dimension. Therefore the units of numerator and denominator must be the same and for that reason both must be a fraction. Besides this you can find this formula in the paper:
     
     P.J. Ell, S.S. Gambhir
     
     Nuclear Medicine in Clinical Diagnosis and Treatment
     
     3rd Edition, Volume 2
     
     Page 1839 - 1840
     
     Churchill Livingstone, Edinburgh London New York... 2004:

4. On page 5, second paragraph, and on page 8, last paragraph, the word prosthesis is used in singular instead of plural (prostheses).
   - In the hole paper this orthographic mistake is corrected

5. In Table 1, the first column of the last row reads "Not loosened component" instead of "No loosened component".
6. Some of the references are not cited according to the journal's style. This should be corrected.
   • Is corrected

7. The citation of the paper by Reinartz et al. is incorrect. The authors should be named in the following order: Reinartz P, Mumme T, Hermanns B, Cremerius U, Wirtz DC, Schaefer WM, Niethard F-U, Buell U. The citation given in the manuscript is based on the erroneous data set entry of the Medline, which hopefully will be corrected soon.
   • Is corrected

Discretionary Revisions (which the author can choose to ignore)
Accept after minor What next?: essential revisions
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No
Declaration of competing interests:
I declare that I have no competing interests.
Reviewer's report
The implications of 18F-FDG PET for the diagnosis of endoprosthetic loosening Title: and infection
in hip and knee arthroplasty: Results from a prospective, blinded study
Version: 1 Date: 27 September 2005
Reviewer: Ide Christiaan Heyligers

Reviewer's report:
In this study the authors compare the results of 18F-FDG-PET, (Technetium ?) bone scans and radiographs with intraoperative findings, histopathology and microbiology of hip and knee endoprosthesis planned for revision due to loosening.
Is the question posed by the authors new and well defined?
The aim of the study is to evaluate the clinical value of PET for the diagnosis of inflammation or loosening. So far not much results from PET studies concerning this topic are available. In this way the question is new and well defined.

1. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
The group of 27 patients scheduled for revision needs to be described more in detail:
- how many knees, and how many hips were operated?
- were the implants fixed with or without cement?
- what was the postoperative time of each implant revised?
I suggest to present this information in a table.
- The demand for more details of the 27 patients is correct and we give these additional information’s on page 4.

2. The authors don’t give any details of the radiological (radiolucent lines?, which zone’s?, subsidence?) and bone scan findings (3 phase technetium?, where activity?).
How exactly the extent of abrasion, “using radiologic and intraoperative findings” was classified is unclear.
Because of bilateral prosthesis in the revised patients an extra 9 joints were examined with PET.
These joints were not operated, so there were no intraoperative findings. Why and how the authors classify them as “no or little abrasion” stays unclear. The bone scan-based evaluations were compared with intraoperative findings. Of this group however the implants were not revised. So the “gold standard” used to compare the results of the PET scans (Intraoprative findings, histology) was not available in 9 “extra” joints.
- The additional information’s about radiological and bone scan findings and extend of abrasion are given at page 5/6. The 9 additional, not operated, joints were based on this definition of abrasion classified as “no or little abrasion”. It’s right that 9 “extra” joints could not compared with an intraoperative and histological result. But by clinical examination, radiological findings and the blood test we got no advice for a loosening or infection of the prosthesis.
3. It is unclear why the authors don’t use an indium leucoscan as gold standard for infection.
   - It is right, that from a nuclear medicine point of view, gold standard to demonstrate an infection is an indium leucoscan. But out of the 9 not revised patient’s we could use the method with a bigger argumentative force. This was the microbiological examination of intraoperative collected tissue. Beside this, the indium leucoscan is a method with a very high demand for man-power, with an inferior resolution and a high radiation exposure. Therefore today we can not use this method for a routine examination in Germany.

4. Are the data sound and well controlled?
   The authors don’t mention the statistical methods they used. The groups are rather small. Hip - and knee implants are not described separately, but in one group.
   - Data were analysed using descriptive statistics expressing values as mean ± standard deviation. Groups were compared by use of Mann Whitney test and results were considered significant in case of a p-Value < 0.05.

5. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes
   - No comment

6. Are the discussion and conclusions well balanced and adequately supported by the data?
   In the study loosening is classified based on the anchoring release during surgery. Because no details are presented about the different implants, this is unclear.
   - The exact number of cemented versus uncemented prosthesis is completed on page 4. The impact of the type of fixation on the imaging results is mentioned in tabel 2b

7. The loosening process is different between cemented- and cementless implants and also the reaction on “a few hammer blows”. A good cemented implant without loosening can for example sometimes easily be taken out of the cement mantle without much force (the Exeter stem for instance). At page 10 mechanical loosening between the cement bed and the prosthesis is described. It depends however very much on the prosthesis used if this can be classified as loosening.
   - The argument is right, that the loosening process is different between cemented and cementless implants. But in our study we want to verify the implication of 18F-FDG PET for the diagnosis of endoprosthetic loosening and infection. Although it is a very important argument we think for the mean question of our study, the loosening process has a subordinated importance.
8. Two groups are described; implants with and without revision (indication). These are different groups with different indications for extra investigation with radiography, bone- and PET scans. Therefore these groups may not be mentioned as one group in “a prospective blinded study”; the 9 non-revised implants for example can not be mentioned in Table 1.
   • Answered with question 2.

9. The criteria for abrasion-mediated inflammatory reaction are subjective and unclear.
   • The radiological measure of PE-abrasion is decentralization of the head within the cup. Details of measurement are described at page 6. Qualitative visual analysis of tracer distribution according to the classification system for hip arthroplasty of Reinartz et al. was done and correlated with the PE –abrasion.

10. The PET results concerning infection were not related to indium scans. This is of interest because this investigation is often used to diagnose infection in the clinical situation. The used criteria (results after revision) can not be used in the clinical situation to plan surgery.
   • Answered with question 3.

11. The investigated groups are small and the sensitivity and specificity of the criteria of Reinartz for infection are unclear (how significant is only pattern 5 rated as infection ? Is this a well accepted classification system, or still experimental ?). In Table 1 only 2 out of 5 septic implants were classified as infection due to Reinartz. Therefore the conclusion that “the presumption of septic prosthetic loosening can be ruled out with a negative PET result” is not proven enough.
   • Due to our results we believe to be able to say that with a negative PET result a septic loosening can be excluded. In contrast to this we cannot differentiate between septic inflammation and an inflammation as a result of wear especially with a pattern 4 or 5.

12. Do the title and abstract accurately convey what has been found ?
   In the abstract the extra group of 9 implants which were not revised is not mentioned. These were however used to draw conclusions. See also earlier remarks.
   • The fact of 9 additional examined joints which were not revised, is now mentioned in the abstract.

13. Is the writing acceptable ?.
   I am not a native speaker in English and therefore I consider myself not the right person to answer this question.
   • No comment

14. In my opinion the remarks are reason for a major compulsory revision.
I declare that I have no competing interests.
   • No comment