Title: Histometric data obtained by in vivo confocal laser scanning microscopy in patients with systemic sclerosis

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Version: 1 Date: 13 Mar 2002

Reviewer: Prof Henrica de Vet

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

This paper describes a phase 1 diagnostic study in which the properties of a potential diagnostic test are compared in a population with the disease versus a healthy population. A second control group is composed of patients receiving the same therapy for another disease. Although the authors do not clearly state the purpose of the second control group, I guess that the reason is to be sure that the differences between the diseased and the healthy population are not caused by the therapy.

Background.

The reasons to perform this study are not clear. Throughout the text I have looking for it. The authors state that in the 'Background' section: 'Diagnosis is SSc is based mainly on clinical features and the pattern of antibodies and is difficult in early stages. Therefore it would be a benefit, if time-saving, non-invasive methods could give hints for diagnosing SSc.' In this sentence it does not appear that the current diagnosis is invasive (clinical features). Moreover this study is not focused on early stages of the disease.

By the last sentence in the discussion section, the authors suggest that histometric data of the skin can help in the diagnosis of SSc in other organs: 'As patients with severe involvement of the pulmonary function and the esophagus all got the feature of a relatively high PC, this parameter could possibly serve as a non-invasive method in staging of the fibrosis and controlling disease advance and effectiveness of therapy, too.'

Last sentence of the background: 'changes in vivo' should be changed in 'differences in vivo'.

Methods.
- This design is not a non-randomised controlled trial as the authors state in the abstract. It is a diagnostic study with case-control design, performed retrospectively as the test is performed after the disease is diagnosed.
- Some measurements are performed four or ten times or even more than ten times. It is not stated whether the location of the measurement on the arm changed and how was decided where to measure.

- Why were measurements repeated so many times. Was that because of large variation in the measurements. It is informative to present data about the variation in the single measurements of the individual patients.
- In the analysis of a diagnostic study the multiple measurements of the characteristic can be taken into account.

Data presentation.
- Five small figures like the current figure 2 are far more informative than the mean and standard deviations. For diagnostic purposes it is the amount of overlap in values between the diseased and the healthy population that is most informative.

Discussion.
- The second control group has a mean age of 36 years, the other groups are around 50 years of age. Does this difference in age affect the characteristics under study?
- As the patients (number 13, 14 and 15)... Table 1 shows that patient 15 has only a mild pulmonary involvement. Patient 5 also has severe esophagus involvement and mild pulmonary involvement and is not mentioned here.

Conclusion
- The conclusion that 'CLSM is .......a promising technique for dermatological research and diagnosing' is too strong in my opinion, considering the study design. I think it is only allowed to state that the diagnostic evaluation of the histometric data should proceed with the next step: testing in a population where the test is later to be used, for the purpose it is later to be used, and defining cut off points, and number of repetitions (if necessary) for an accurate outcome .
- Line 3: 'changes' should be changed in 'differences', because of the cross-sectional design.

Summarising (compulsory revisions):
- With regard to the conclusions: The authors should weaken their conclusion, and state that this is the first step in the long process of diagnostic evaluation.
- With regard to the detail of information: The authors should state more clearly what the current diagnostic tools are diagnosing SSc. Furthermore they should clearly describe the diagnostic purpose of the histometric data in the future: diagnosing (early?) stages of (only dermatological?) SSc, staging of SSc with dermatological involvement, controlling disease advance or effectiveness of therapy. Moreover the authors should give more information about the reasons and locations of the large numbers of measurements per patient.
- With regards to data presentation. Figures which show the amount of overlap between the three groups are far more informative than means and standard deviations
- The writing is acceptable.

Misspellings:
Page 4, line 8, 'fulfilled' instead of 'fullfilled'
Page 9, second line: As the patients (number 13, 14 and 15)
Page 9, last line: controlling' instead of 'controling'
Competing interests:

None declared.