Author’s response to reviews

Title: Systematic review with meta-analysis: Cytokines in fibromyalgia syndrome

Authors:

Nurcan Üçeyler (ueceyler_n@klinik.uni-wuerzburg.de)
Winfried Häuser (whaeuser@klinikum-saarbruecken.de)
Claudia Sommer (sommer@uni-wuerzburg.de)

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Author’s response to reviews: see over
Dear Dr. Patel,

thank you very much for giving us the opportunity to revise our manuscript “Systematic review with meta-analysis: Cytokines in fibromyalgia syndrome” by Nurcan Üçeyler, Winfried Häuser, and Claudia Sommer. We also thank the reviewers for their very constructive criticism and suggestions. We have carefully considered all aspects and have also made the changes in manuscript format according to the instructions of BMC Muskuloskeletal Disorders. Please find below our point-to-point answers to the reviewers’ comments and questions.

Sincerely,
Nurcan Üçeyler, MD

Department of Neurology, University of Würzburg
Josef-Schneider-Str. 11, 97080 Würzburg, Germany
phone (+49)-0931-201-24617
fax (+49)-0931-201-23489
mail ueceyler_n@klinik.uni-wuerzburg.de
Answers to reviewers:

Reviewer 1:

The paper is worthy of publication.
1) Some parts of the results simply recite the tables and the prose is a bit turgid. The text should be more interpretive

We agree that the results section does not read very fluently giving all these data. We now thoroughly condensed the text, which meant that the supplementary tables had to be moved to the main manuscript. To make it easier to understand the main results we have now added a short passage where applicable at the end of each subsection stating clearly what was found.

2) Rather than being a review of existing publications, it should also guide an investigator so that future studies will not make some of the errors or repeat the deficiencies that the authors note. Hence, a paragraph should be added relating some of the following points: 1) For serum or plasma, at least two samples should be drawn on separate days 2) the time of day draw should be similar due to circadian changes, 3) patients should be off medication that can influence results, 4) the duration of symptoms of FM should be listed, 5) the setting and environment of study patients should reflect community rheumatologic fibromyalgia ideally, 6) power calculations should be performed in advance 7) serum cytokine levels probably are a poor reflection of cytokine activity, production, and its not certain how much is in cells vs in tissue. Therefore, stimulated production of cytokines or tissue staining for cytokines is superior. The best methodology for doing this should be briefly mentioned.

We thank the reviewer for this suggestion. Several of the above mentioned points were already mentioned in the initial version of the manuscript (s. page 17); we have now implemented another passage adding some further aspects (s. page 18-19).

Reviewer 2:

The methodology of this interesting study appears sound. I have only few suggestions:
a) the listing of study results and quality etc. should be exclusively in the table. Summary data could go into the main text. The way it is written now, the result section is difficult to read. I would prefer the tables in portrait format - much easier to read electronically.

We now thoroughly condensed the text, which meant that the supplementary tables had to be moved to the main manuscript. We have also included some summarizing sentences at the end of the results paragraphs to make the take home messages clearer. As to the tables: we have changed the format accordingly.

b) please explain in the methods section why plasma and serum results need to be listed separately.

We assessed the results of plasma and serum separately to reflect the situation in the studies and to point to the diversity of material used. Furthermore, serum
samples were almost exclusively investigated with ELISA kits, while plasma was mostly investigated with different types of immunoassays. In addition, we also analysed the combined results when regarding plasma and serum as “blood” in the systematic review and the meta-analysis (see bottom of supplementary tables 1 and 2 and page 15).

c) where you discuss plasma IL-8, you seem to compare positive plasma results with negative serum results (page 12, line 3); if this is not a mistake, then again its not clear why you report these separately at all.

We thank the reviewer for this remark and apologize for the typo. We have corrected the sentence to “In four studies no intergroup difference could be found for plasma IL-8 levels”.

d) one worry with negative study results is that the test kits used may not be able to pick up raised cytokine levels at the low concentration seen in FMS. There has been a development of test kits over time, which you should discuss. Can you either reassure readers, that this was not a problems, or alternatively list those studies using kits which would not have been expected to detect those levels seen in the positive studies.

We thank the reviewer for raising this very important issue! The problem is that the majority of studies do not give details on the kit used let alone its sensitivity. This is one item which we therefore listed in W-MeQS as a quality indicator (see items 1 and 3). To list those papers that used kits with inadequate detection limits would indeed be very helpful, but we are not able to create such a list due to lack of information in the publications. We have now included a passage on the importance of considering method sensitivity in cytokine measurements in the revised manuscript (see page 18).