Author’s response to reviews

Title: Statin using periodontitis patients have markedly fewer periodontal lesions - a cross-sectional study

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Version: 3 Date: 5 December 2007

Author’s response to reviews: see over
Author's response to reviews
Title: Statin use is associated with fewer periodontal lesions, a cross-sectional study

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Version: 4 Date: 05 December 2007
Author's response to reviewer Francesco D’Aiuto:

COMMENT number 1.
The reviewer correctly interprets that our study describes cumulative measures of clinical signs of periodontitis in relation to prior use of statin medication. However, he finds the manuscript lacking a logical sequence in the study design and therefore argues that its interpretation is not straightforward. Below, we give point-to-point answers to the reviewer’s detailed comments. This is the point-to-point answer to reviewer D’Aiuto’s comment number 1.

COMMENT number 2.
The aim of this study was to investigate the impact of statin medication on standard clinical measures of periodontal inflammatory tissue destruction. We compare subjects with periodontitis, either using or not using statins. The target population of our study was formed by periodontitis patients referred for treatment of advanced chronic periodontitis to the University Dental Clinic of the Health Centre of Helsinki. The information obtainable with this approach can not be acquired when comparing study subjects with healthy controls. Statistical analysis provides sufficient tools for controlling possible confounding factors with this study design.

The present study is not a validation study, as the reviewer correctly points out.

As suggested by the reviewer, the aim of the study is now clearly stated at the end if the Background section of the revised manuscript page 3/21, lines 18-19:
“In this retrospective study, our aim was to examine the effect of statins on clinical indices of chronic periodontitis.”

COMMENT number 3.
The title of the manuscript describes the results of the study. As a response to the reviewer’s comment Nr 2, we conclude that the title of the manuscript appropriately includes the aim and describes the content of the paper correctly.

**COMMENT number 4.**
The measure obtained from clinical periodontal examination (PPD and CAL) describe established periodontal tissue destruction. It is obvious that deep periodontal pockets liberate more inflammatory mediators and cytokines than shallow pockets, thus contributing more to the inflammatory burden. In the present study we used periodontal probing pocket depth (PPD) values to describe periodontal inflammatory injury. The number of tooth surfaces with increased PPD values reflects the total inflammatory burden caused by the local periodontal inflammation and experienced by the individual. PIBI takes into account the larger inflamed subgingival surface area in the deeper periodontal pockets. We hypothesise that this better reflects the potential impact of deep periodontal pockets on inflammatory burden.

**COMMENT number 5.**
The clinical tool used in this study is widely used and has been described in detail earlier. A reference for the clinical tool has been given, see references 19-22:

**COMMENT number 6.**
Each patient was assessed by two examiners. As a standard procedure in a dental school, a clinical teacher, the periodontist, validates the measurements of a dental student.

The effect of intra- and inter-examiner variation is reflected in the degree of deviation of the results and not in the observed differences of the means between the groups.
COMMENT number 7.

In comment #7, the reviewer takes up three possible confounding factors: Presence of dental plaque, obesity and socio-economic status. We argue that PPD and PIBI reflect results of inflammatory tissue destruction, and do not reflect current dental plaque. The PPD and PIBI values also reflect the potential inflamed connective tissue area adjacent to the teeth. Unlike the marginal gingiva, the subgingival area is not accessible to the patient for cleaning. Thus, indices based on the presence of dental plaque and reflecting the subjects’ self care of oral health do not necessarily reflect the potential inflammation burden caused to the body by subgingival microbiota. The plaque index is not provided, because in this context we consider the probing depth values clinically more important. In the manuscript, we emphasize that all patients were having periodontitis and referred by a local dentist to the university dental clinic for treatment of chronic periodontitis, and did have poor oral hygiene.

“All subjects had poor oral hygiene, evident as visible dental plaque and gingival bleeding on probing.”

Correctly, the reviewer refers to body weight and poor socio-economic status as possible confounding factors. Both of these factors have been reported to associate with chronic periodontitis. Unfortunately, recordings of body weight and socio-economic status are not included in the protocol used in the dental school where the patient data originates from. Thus, we are not in the position to provide this type of socio-economic data. We have added this limitation to the discussion section, page 9, lines 15-18: “Low socio-economic status has been reported as a predisposing factor for chronic periodontitis [28]. CVD is associated with low socio-economic status [29]. Statin users are CVD risk patients. Thus, it is unlikely that statin medication selects patients with high socio-economic status and that this could affect the results.”

A reference to an article on socio economic factors has been added.

COMMENT number 8.

The reviewer states the need of referencing other published work on statins and on going trials on the subject. Only a limited number of studies have addressed statin medication and periodontitis.
One of these is an animal model and the two others focus on tooth loss as a result of periodontal inflammation, which is not the focus of our study.


According to the U.S. national institute of health service at ClinicalTrials.gov [checked Oct 26 2007] there are no ongoing trials with statins and chronic periodontitis.

**COMMENT number 9.**
The reviewer suggests that the discussion section should include either validation of PIBI or a reference to a separate validation study.

First, the PPD measurement is a common clinical method with standardized probes and a defined probing force.

Second, PIBI is a weighted index derived from PPD measurements and, actually, a linear transformation of the PPD score where the deep pockets are multiplied by integer 2. Therefore, the statistical variation in PIBI score is caused by variation in PPD measurements.

Multiplication of the number of deep pockets by an integer does not make it less valid than the original score. However, by weighting the deep (<6mm) pathological pockets we get an index with a wider range that helps assess the amount of tissue destruction already evident.
As PIBI is not a composite index and no claims are made about its correlation with levels of inflammatory markers, we state that a validation study seeking for a linear relationship with existing systemic markers such as CRP or TNF-alpha would be interesting but not a prerequisite for the presentation of the results of the current study.

**COMMENT number 10.**
The reviewer suggests that the conclusions should be more conservative and without speculation. We revised the conclusions of the manuscript according to the reviewer’s suggestions, see page 11, lines 10-12:

“Our results indicate that patients on statin medication exhibit fewer clinical signs of periodontal inflammatory injury than subjects without the statin regimen. This may lead to development of novel therapeutic approaches.”

**COMMENT number 11.**
Add a clear aim and rationale consistent with the manuscript text, into the abstract background section. Revised according to the suggestion, see page 2, lines 5-6 “The aim of this study was to examine the effect of statins on clinical markers of chronic periodontitis.”

**COMMENT number 12.**
Background section, last paragraph, please add "localized" to inflammatory diseases. Revised according to the suggestion, see page 3 lines 14-15 “Gingivitis is one of the most prevalent localized inflammatory diseases in the adult population”

**COMMENT number 13.**
Please in this [background] section also write on the consistent association of periodontitis with systemic inflammation.———Revised according to the suggestion, see page 3, lines 17-19:
“This medium-grade inflammation may place a considerable burden on the cardiovascular system and contribute to CVD [15-18], and has been shown to be associated with systemic inflammation [22].”

COMMENT_number 14.

In the methods section paragraph on the collection of clinical periodontal parameters, rather than collection which implies active recording this was a retrospective analysis this is a gathering of information. Please rephrase.

Revised according to the suggestion, see page 4, lines 12-13.

“For all teeth, we extracted recordings of six periodontal Probing Pocket Depth (PPD) values…”

COMMENT_number 15.

In the methods section a clearer definition of smokers (current, former..) should be given as it seems to play a significant effect on the outcomes of the statistical analyses.

Revised according to the suggestion, see page 4 lines 7-8:

“We extracted the following data from the patient records: age, gender, reported current smoking, and use of statin medication.”

COMMENT_number 16.

Results section, periodontal inflammatory injury paragraph, initial letter T might refer to "total"? Revised according to the suggestion, letter deleted.

COMMENT_number 17.

Please use a consistent and easier terminology to describe the cumulative clinical periodontal parameters.
We prefer to use exact terminology to avoid misinterpretations.

COMMENT_number 18.

Table 1, please define smokers (current..) and present measures of variability for age.

Revised to include SD and range, see Table 1:

Smokers are defined as current smokers.

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<td>Revised according to the suggestion, see Table 2.</td>
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| Mean age (SD) | 57.4 (8.7) | 44-69 | 52.3 (8.5) | 42-69 |
Author's response to reviewer Pauline J Ford
Title: Statin using periodontitis patients have markedly fewer periodontal lesions - a cross-sectional study

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Version: 4 Date: 05 December 2007
Author's response to reviews:
Reviewer's report:

Title: Statin using periodontitis patients have markedly fewer periodontal lesions - a cross-sectional study
Version: 1 Date: 28 August 2007
Reviewer: Pauline J Ford
Reviewer's report:

General
The authors examine periodontal probing pocket depths in patients using statins and compare this to patients who are not using statins. A novel index to simplify the large amount of data collected for each patient was used to show that patients on statins exhibited a lower periodontal inflammatory burden than those patients not on statin medication. The authors postulate that this is due to the anti-inflammatory effects of these drugs, and that this may lead to new therapeutics for treatment of periodontitis.

The results of this study are very interesting and the novel index has been used to very good effect in simplifying the data to enable meaningful conclusions.

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

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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)

COMMENT number 1.

Data was collected from dental records. Did the authors consider the effect of
different operators measuring pocket depths?

**ANSWER TO COMMENT number 1**

Please see above in the answers to reviewer Francesco.

**COMMENT number 2.**

There is an intrinsic difference between the groups that the authors have failed to discuss. This is that the statin users will either have CVD or have been diagnosed as being at high risk of CVD. This introduces possible confounders which have not been taken into account.

**ANSWER TO COMMENT number 2**

*We withdraw conclusions on cardiovascular disease. Still, it remains unsolved whether CVD could cause deepened periodontal pockets as the reviewer suggests.*
COMMENT number 3.
Abstract line 11: The authors state that the PIBI was used to ‘estimate systemic effects of periodontitis’. While I support the use of this index, I would argue that the systemic effects of periodontitis were not examined in the present study. Similarly in Table 2, the use of the title ‘Systemic inflammatory burden’ is not justified.

ANSWER TO COMMENT number 3
We removed the word “systemic” from We leave references to systematic effects from the manuscript. The subtitle of Table 2 as suggested. see Table 2 of revised manuscript.

COMMENT number 4.
Page 3 line 23: While there is much evidence to support the concept of an inflammatory burden which may contribute to CVD, the authors’ statement that ‘inflammation may place a considerable burden on the cardiovascular system’ is an oversimplification and requires a more precise explanation.

ANSWER TO COMMENT number 4
In this study we bring up this item and offer a possible explanation for our observations. We do not state that this is a complete proof of a single pathologic mechanism in formation of any disease.

COMMENT number 5.
Page 6 line 10: Why was the presence of rheumatic disease examined? This is not explained.

ANSWER TO COMMENT number 5
There were two reasons: first, the dental school protocol includes asking for existing disease and medications to avoid prescription drug interactions. Second, rheumatoid arthritis is a possible confounding factor as it is associated with increased incidence of CVD.
COMMENT number 6.
Figure 2 – According to the legend, the y axis measures PIBI. If this is correct, the units and values on the graph need to be amended.

ANSWER to COMMENT number 6.
We spell out that the mean of patients not on statin medication is set to 100 %.
Discretionary Revisions (which the author can choose to ignore)

**Which journal?:** Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

**What next?:** Accept for publication in BMC Medicine after minor essential revisions

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**
I declare that I have no competing interests
Author's response to reviewer Björn Klinge

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Version: 4 Date: 05 December 2007
Author's response to reviews:

Discretionary Revisions (which the author can choose to ignore)

COMMENT number 1

"In methods section it can be questioned whether probing pocket depth per se is a valid indicator of periodontal pathology/inflammation. Normally bleeding on probing is considered better to reflect inflammation than PPD. Authors may want to consider this. Thus the so called "novel index" is not necessarily reflecting inflammation, but rather pocket depth."

ANSWER TO COMMENT number 1

We share the opinion of the reviewer. Both PPD and PIBI reflect pocket depth that is a current indicator of periodontal pathology. We are aware of the literature covering bleeding on probing as an indicator of current histological inflammation. The aim of the study is to measure inflammatory tissue destruction that is independent of current inflammation, that is, pocket depth.

COMMENT number 2

"In results section it is reported about visible dental plaque gingival bleeding on probing, it is however not clear how these registrations were made."

ANSWER TO COMMENT number 2

The presence of plaque was recorded according to the standard procedure, by recording it for index teeth only. We cannot see how this is related to the results, but have provided the method in the revised manuscript. We sincerely thank for this valuable comment that increases the value of the paper.

COMMENT number 3

"Discussion p9 the reference 27 is not correctly quoted. Socio-economic status is not a pre-disposing factor when adjusted for smoking."

see p. 4 lines 10-12

"Individual scores for visible plaque were extracted from the records. This corresponds to criteria for scores 2 and 3 of the Plaque Index System [20]. The percentage of inspected surfaces with visible plaque was calculated."
**ANSWER TO COMMENT number 3**

We do not comment on this, please do see reviewer Fransisco D’Aiuto’s extensive comments on socio-economic status. In other respects, we agree with reviewer Klinge.

**COMMENT number 4**

"Relates to my concern about PPD as a marker for inflammation. p10 is discussed the use of PPD to describe inflammation. I question the validity and suggest at least a comment on the relevance of PPD to assess inflammation.”

**ANSWER TO COMMENT number 4**

According to the suggestion that is in line with other reviewer’s suggestions, we have revised the manuscript to address sequelae of inflammation in the periodontium.

see page 10 lines 11-12:

“"We used periodontal probing pocket depth (PPD) values to describe periodontal inflammatory injury.”

**Which journal??**: Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

**What next??**: Accept for publication in BMC Medicine after minor essential revisions