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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 80834

Title: Periodontal treatment and microbiome-targeted therapy in management of periodontitis-related nonalcoholic fatty liver disease with oral and gut dysbiosis

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06282354
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Saudi Arabia

Author's Country/Territory: Japan

Manuscript submission date: 2022-10-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-17 06:48

Reviewer performed review: 2022-10-17 08:37

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This paper has the potential to be accepted, but some important points must be clarified before we can proceed. The points are summarized as follows The title is well written, precise, and meet the objectives of the study. There are some shortcomings in the abstract, last lines in the abstract need to improve with the special concern how this review is beneficial for human beings.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06272086
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: France

Author's Country/Territory: Japan

Manuscript submission date: 2022-10-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-17 12:07

Reviewer performed review: 2022-10-26 07:30

Review time: 8 Days and 19 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
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SPECIFIC COMMENTS TO AUTHORS

Please find my comments in the attached file.

Comments to the authors: Periodontal treatment and microbiome-targeted novel therapy in the management of periodontitis-related nonalcoholic fatty liver disease with oral and gut dysbiosis

I thank the authors for writing this review on the association between periodontitis and NAFLD involving the oral and intestinal microbiome. This review is particularly important in a context of increasing prevalence of metabolic diseases and new results with innovative microbiota sequencing. It therefore seems essential to work jointly on the study of the oral and fecal microbiota.

Title: The title focuses on treatments while the epidemiology and pathophysiology of periodontitis and NAFLD are also partly described.

Method: No details were provided on the methodology used to write this review. It is necessary to describe the methodology justifying the exhaustiveness of the work. Was the PRISMA methodology used? Is there a Flowchart?

2. Periodontal disease as a risk factor for systemic diseases

2-1. Diabetes

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It would be interesting to know the prevalence of periodontitis in diabetic patients and vice versa; is the prevalence higher compared to the general population? Are there data in the literature

P5: "modulating bacterial-mucosal immunity-inflammation may alleviate type 2 diabetes" è Please, specify by what mechanisms and the impact on periodontitis

P6: "In addition, although the diversity of the subgingival and supragingival microbiome decreases when subjects with type 2 diabetes are compared to normoglycemic individuals, the bacterial shift in individuals with periodontitis is less prominent in type 2 diabetes subjects than in normoglycemic individuals" è One hypothesis mentioned in the review, justifying these results, is the modification of the oral microbiota by tobacco. What other factors are known to alter the oral microbiota? tooth brushing?

- ⇨ Immune modifications and the associated inflammation are an integral part of the association of these 2 pathologies. Thus it would be interesting to present the **inflammatory status** associated with diabetes but also with the metabolic syndrome and to discuss similarities with the inflammatory status of periodontitis.
- ⇨ Furthermore, it would also be interesting to briefly discuss the specificity of periodontitis in the onset of metabolic diseases. Indeed, can other inflammatory diseases, infections also be associated with the onset of metabolic diseases?
- ⇨ It would also be interesting to describe the **modifications in the gut microbiota observed during diabetes but also metabolic syndrome or obesity.**

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2-2. Metabolic syndrome

P8:

"Metabolic diseases alter the gut microbiome" è Could modifications of the gut microbiota also be at the origin of metabolic diseases?

"obesity can alter the oral microbiome of individuals with type 2 diabetes" è idem, could modifications of the oral microbiome also be at the origin of the onset of obesity?

"Additionally, alterations in the gut microbiome have been linked to obesity and metabolic syndrome" è Please specify what these alterations are?

3. Relationship between periodontal disease and NAFLD

P9:

"The relationship between periodontitis and NAFLD is supported by a number of epidemiological studies" è Please add references

"Cross-sectional studies have … for estimating the degree of fatty liver and liver fibrosis" è Please add references

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"Akinkugbe et al. followed 2,623 non-NAFLD … was diagnosed by abdominal ultrasonography and serum ALT levels" è Please add reference. Can you complete with statistical indicators?

"In a 13-year cohort study of 6,165 subjects participating in a Finnish population-based health study, Helenius-Hietala et al. found a positive correlation between the proportion of sites with deep periodontal pockets and the hazard ratio for the development of severe liver disease è Please add reference

4. Mechanisms by which periodontal disease exacerbates NAFLD based on the Oral-Gut-Liver axis

P11:

" Kawamoto et al. [16] found that fecal samples from patients with severe periodontitis were enriched in Acidaminococcus, Clostridium, Lactobacillus, Bifidobacterium, Megasphaera, and Romboutsia compared to those from healthy subject" è It would be particularly interesting to comment on the modifications of the fecal microbiota observed during periodontitis with those during NAFLD, obesity, diabetes...

P13:

What about the red and orange complex observed in periodontitis in metabolic pathologies (diabetes, metabolic syndrome)?

P14: T forsythia è *T. forsythia*

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- ⇨ It would be interesting to develop this part by describing in particular the similarities observed in the dysbiosis of the oral and gut microbiota. It would thus perhaps be more judicious to integrate this part after the description of the oral / gut dysbiosis during periodontitis and NALFD
- ⇨ What about *P. gingivalis* in NAFLD patient without periodontitis?

7. Relationship between gut dysbiosis and NAFLD

* Are there data on oral dysbiosis of NAFLD patients: specify

8. Periodontal approaches in the prevention and treatment of NAFLD

8-1. Management of oral microbiota with conventional periodontal treatment

P18:

"Yoneda et al 37 reported that in a single-arm intervention study,…..led to a significant improvement in AST and ALT at 3 months after treatment." è Did this study also investigate markers of glucose metabolism?

"prebiotics are defined as fermented foods containing dietary fiber that activate intestinal bacteria and probiotics" è Activation but also modifications in the composition of intestinal bacteria

- ⇨ What are the consequences of the proposed treatments on systemic inflammation?

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9. Conclusion

"… induces gut dysbiosis and is involved in the pathogenesis of NAFLD" è also oral dysbiosis