SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Systemic factor effects on orthodontically induced inflammatory root resorption: A systematic literature review [provisional title].	
2.	Authors (names, affiliations, contributions)	Linn Haugland, DMD. Department of Orthodontics, University of Bergen and Specialist Oral Health Center for Western Norway Department: Rogaland. Norway haug.linn@gmail.com Marit Midtbøe, Cert. Orthodontist, PhD., Associate Professor Department of Orthodontics, University of Bergen. Norway. Marit.Midtbo@uib.no Kasper Dahl Kristensen, Cert. Orthodontist, PhD. Specialist Oral Health Center for Western Norway Department: Rogaland. Norway KDKI@odontologi.au.dk Vaska Vandevska-Radunovic, Cert. Orthodontist, PhD., Professor Department of Orthodontics, University of Oslo. Norway vaska.vandevska-radunovich@odont.uio.no	
3.	Other contributors (names, affiliations, contributions)		
4.	Contact person + e-mail address	Linn Haugland, DMD Department of Orthodontics, University of Bergen, Årstadveien 19, 5009 Bergen Telephone: +47 55 58 66 00 haug.linn@gmail.com	
5.	Funding sources/sponsors	Remaining authors had no financial support for the submitted work	
6.	Conflicts of interest	Authors affirm that we have no financial affiliation or involvement with any commercial organization that has a direct financial interest in any matter included in this research.	
7.	Date and location of protocol registration	December, 2015	

8.	Registration number (if applicable)		
9.	Stage of review at time of registration	We have run a preliminary search and done a test for data extraction	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Systemic factors are shown to affect the degree of orthodontically induced inflammatory root resorption (OIIRR). However, a systematic overall assessment of their impact on OIIRR has not yet been reported. We aimed to systematically assess the risk of any intervention(s) that could induce systemic effect on OIIRR in human or animal subjects.	
	Research question		
11.	Specify the disease/health problem of interest	Orthodontically induced inflammatory root resorption (OIIRR)	
12.	Specify the population/species studied	Patients and animals with fixed orthodontic appliances	
13.	Specify the intervention/exposure	Systemic factor intervention defined as: systemic or hormonal disorders, specific diet regimen, LLLT, ultrasound therapy and any systemic or local administration of substances that might interfere directly or indirectly with bone physiology.	
14.	Specify the control population	A matched control group with fixed appliance and without intervention (placebo, sham treatment)	
15.	Specify the outcome measures	OIIRR quantitatively measured on histological sections, by radiographs or tomographic imaging	
16.	State your research question (based on items 11-15)	How do systemic factors affect the degree of OIIRR in animal and human subjects?	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	☑MEDLINE via PubMed ☑Web of Science ☐SCOPUS ☑EMBASE Others, namely: Cochrane Central Register of Controlled Trials, EBM Reviews (Cochrane database of systematic reviews), LILACS (Latin American and Caribbean Center on Health Sciences), Grey literature (Google Scholar) Unpublished literature (ClinicalTrials.gov) ☐Specific journal(s), namely:	
18.	Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21])	The search terms were developed for MEDLINE and modified to operate in all of the selected databases. Search terms included root resorption, orthodontics and tooth movement.	

		MEDLINE search: (("root resorption"[All Fields] OR "root resorption"[MeSH Terms]) (("orthodontics"[MeSH Terms] OR "tooth movement"[All Fields]) OR ("orthodontics"[MeSH Terms] OR "orthodontics"[All Fields])) NOT ("endodontics"[MeSH Terms] OR ("endodontics"[MeSH Terms] OR "endodontics"[All Fields]))	
19.	Identify other sources for study identification	☑Reference lists of included studies ☐Books ☑Reference lists of relevant reviews ☐Conference proceedings, namely: ☑Contacting authors/ organisations, namely: Corresponding author will be contacted whenever there is a need for additional or clarifying information. ☐Other, namely:	
20.	Define search strategy for these other sources	Google Scholar, Google.	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	1. Title/abstract screening. 2. Full text screening	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	a. Per phase, two of the reviewers (VVR) and (LH) will independently screen for relevant studies. b. Discrepancies will be resolved either by discussion or by a third reviewer (when no agreement is met by the two reviewers).	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: Randomized and controlled clinical trials, cohort studies, case control studies and animal experiments, with split-mouth design included. Exclusion criteria: Studies with fewer than five animals/subjects in each group	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: Patients and animals with fixed orthodontic appliance Exclusion criteria: Patient and animals without fixed appliance	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: Systemic factor intervention defined as: systemic or hormonal disorders, specific diet regimen, LLLT, ultrasound therapy and any systemic or local administration of substances that might interfere directly or indirectly with bone physiology.	

		Exclusion criteria: N/A	
26.	Outcome measures	Inclusion criteria: OIIRR quantitatively measured on histological sections, by radiographs or tomographic imaging Exclusion criteria: Studies that do not measure OIIRR quantitatively	
27.	Language restrictions	Inclusion criteria: No restrictions Exclusion criteria: N/A	
28.	Publication date restrictions	Inclusion criteria: Studies published up to search date Exclusion criteria: No past date restriction	
29.	Other	Inclusion criteria: N/A Exclusion criteria: Double publications (e.g. reviews, thesis).	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: Title and abstract screening. 1. Type of study. 2. Type of intervention. Selection phase: Full text screening. 1. Type of study. 2. Type of subjects 3. Type of intervention. 4. Outcome measures.	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	Authors, title, year, language, contact author e-mail	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Experimental groups, number of subjects per group.	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Animal species, strain, age, weight, gender	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	Type of systemic factor, route of administration, dose, frequency, duration of systemic factor, timing relative to fixed appliance, duration of fixed appliance, timing of fixed appliance, type of experimental group, type of control group	
35.	Outcome measures	Measurement of orthodontically induced inflammatory root resorption (OIIRR) by histological sections, radiographs or tomographic	
36.	Other (*e.g.* drop-outs)	Number of teeth OIIRR assessment method	
	Assessment risk of bias (internal validity) or study quality		
37.	Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved	a. Two reviewers will independently assess risk of bias of included studies. b. Discrepancies will be resolved either by discussion or by a third reviewer (when no agreement is met by the two reviewers).	

38.	Define criteria to assess (a) the internal validity of included studies (*e.g.* selection, performance, detection and attrition bias) and/or (b) other study quality measures (*e.g.* reporting quality, power)	☑By use of SYRCLE's Risk of Bias tool[4] ☐By use of SYRCLE's Risk of Bias tool, adapted as follows: ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows: ☑Other criteria, namely: the Cochrane Collaboration risk of bias tool for human studies	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	For all outcome measures (mentioned at 35) we are only interested in continuous data for OIIRR.	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	Data will be extracted preferably from published data (explicit numeral). If data is not available in the text we will extract data from graphs (if available) by using special designed software (http://avpsoft.com/products/udruler/). Whenever necessary, an electronic mail will be send to the correspondent author for further information. If no answer is obtained within a week or there is no contact information, other authors will be randomly contacted. After five weeks, if no answer is received, the study will be excluded from analysis.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	a. Two reviewers will independently extract data from included studies. b. Discrepancies will be resolved either by discussion or by a third reviewer (when no agreement is met by the two reviewers).	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	To all systemic factors meta-analysis is intended.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	A minimum of 2 articles per outcome measure is required No restrictions in terms of heterogeneity will be applied, instead, sources of heterogeneity will be investigated through sensitivity and subgroup analysis.	
	If a meta-analysis seems feasible/sensible, specify (for each outcome measure):		
44.	The effect measure to be used (*e.g.* mean difference, standardized mean difference, risk ratio, odds ratio)	To all systemic factors: - Standardized Mean Difference and 95% confidence intervals will be calculated for all the variables.	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	To all systemic factors: - Random effects model	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	I-square	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	Animal species. Gender Administration method. Dose, duration and timing of systemic factor Duration and timing with fixed appliance Outcome assessment method	

		Outcome measure Studies with high risk of bias	
48.	Any sensitivity analyses you propose to perform	Effect of possible interactions by species, gender, administration method, dose, duration, and timing of drug	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	Correction for multiple time points Correction for multiple use of control group	
50.	The method for assessment of publication bias	Funnel plot, if applicable	
Final approval by (names, affiliations):			Date: