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	**Diabetes mellitus and bone regeneration: a systematic review and meta-analysis of animal studies**	
2.	Authors (names, affiliations, contributions)	Camargo WA Hoekstra JW Bronkhorst EM Jansen JA van den Beucken JJ de Vries, R Van Luijk, J	
3.	Other contributors (names, affiliations, contributions)		
4.	Contact person + e-mail address	Winston Camargo – winston.camargo@radboudumc.nl	
5.	Funding sources/sponsors	No	
6.	Conflicts of interest	No	
7.	Date and location of protocol registration	28/01/2015 (first version)	
8.	Registration number (if applicable)		
9.	Stage of review at time of registration		
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	The complications associated with diabetes and osteoporosis not only affect the quality of life of the patients but are also a major strain on both health and social services.(1, 2) Both diseases interferes drastically on bone regeneration, increasing the bone loss through alterations during bone healing process.(3, 4) Diabetes Mellitus has been known to have an effect on the skeletal system.(5) Changes related to osteoblasts, chondrocytes, mesenchymal stem cells, and osteoclasts have been observed, reducing the bone formation and elevating the bone resorption, resulting in bone loss.(3, 4) Osteoporosis is characterized by reduced bone mass and disruption of bone architecture, resulting in an increased risk of fractures which represent the main clinical consequence for the disease.(1, 6, 7) In order to address the bone loss, a large variety of bone substitutes has been tested to help and induce bone regeneration.(8) The aim of this systematic review is to provide the basis for a better understanding how these compromised conditions affect the bone defect healing, either or not in combination with bone substitute materials.	
	Research question		

11.	Specify the disease/health problem of interest	bone regeneration	
12.	Specify the population/species studied	All animal species	
13.	Specify the intervention/exposure	Diabetes Mellitus induced chemically, surgically or spontaneously/genetically	
14.	Specify the control population	Healthy animals	
15.	Specify the outcome measures	percentage of bone formation	
16.	State your research question (based on items 11-15)	What is the effect of diabetes mellitus on bone regeneration through bone substitutes in animal models for bone defects?	
	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 ☐Other, namely: ☐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])	Search strategy applied to Pubmed and adapted to the other databases: **Component 1:** **Bone Substitute** Bone Substitutes [Mesh] OR Bone Cements[Mesh] OR Calcium Phosphates[Mesh] OR Bone Transplantation [Mesh] OR Bone Density Conservation Agents [Pharmacological Action] OR Beta-tricalcium Phosphate[Supplementary Concept] OR alpha-tricalcium Phosphate[Supplementary Concept] OR Tricalcium Phosphate[Supplementary Concept] OR ((Bone [tiab] OR Bones [tiab]) AND (Substitute [tiab] OR Substitutes [tiab])) OR ((Artificial [tiab] OR Artificials [tiab]) AND (Bone [tiab] OR Bones [tiab])) OR ((Bone [tiab] OR bones [tiab]) AND (Replacement [tiab] OR Replacements [tiab])) OR ((Calcium[tiab]) AND (Phosphate[tiab])) OR Hydroxyapatite[tiab] OR Beta-tricalcium Phosphate[tiab] OR Tricalcium Phosphate[tiab] OR Tricalcium Orthophosphate [tiab] OR Tricalcium Diphosphate [tiab] OR Tricalcium Phosphate Ceramic [tiab] OR beta-TCP [tiab] OR Dicalcium Phosphate [tiab] OR Calcium Superphosphate [tiab] OR Bone Graft[tiab] OR Osseous Graft[tiab] OR Synthetic Bone[tiab] OR Bioactive Glass[tiab] OR ((Bone [tiab] OR Bones [tiab]) AND (Cement [tiab] OR Cements [tiab])) OR ((Xenografts[tiab] OR Alloplastics[tiab] OR Allografts[tiab] OR autogenous[tiab] or Autologous Graft[tiab]) AND (Bone[tiab]) Or (Bones[tiab])) **Component 2:** **Diabetes** Diabetes Mellitus[Mesh] OR Diabetes Mellitus, Experimental[Mesh] OR Glucose Metabolism	

		Disorders[Mesh] OR Diabetes [tiab] OR Diabetic [tiab] or Diabetics[tiab] OR Hyperglycemia [tiab] OR Hyperglycaemia [tiab] OR High Blood Sugar [tiab] OR Streptozocin [tiab] OR STZ[tiab] OR Alloxan[tiab] **Component 3:** **Animal** Search filter for animal studies [9]	
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: ☐Other, namely:	
20.	Define search strategy for these other sources	N/A	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	1 - Initial pre-screening based on title/abstract 2 - Full text screening	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	a. Two reviewers 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:* Study with intervention and control group *Exclusion criteria:* Not an animal experiment Not original paper No bone substitute	
24.	Type of animals/population (*e.g.* age, gender, disease model)	*Inclusion criteria:* "Diabetic" animals induced chemically, surgically or spontaneously/genetically and "Healthy" Laboratory animals under the same bone substitute material *Exclusion criteria:* No healthy control group	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	*Inclusion criteria:* Any kind of bone substitute included in a bone defect *Exclusion criteria:* N/A	
26.	Outcome measures	Inclusion criteria: Bone formation (%) Exclusion criteria: Not histomorphometrical data	
27.	Language restrictions	Inclusion criteria: No language restriction Exclusion criteria: N/A	
28.	Publication date restrictions	Inclusion criteria: No date restriction Exclusion criteria: N/A	
29.	Other	Inclusion criteria: N/A Exclusion criteria: N/A	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: 1 - Initial pre-screening based on title/abstract:	

		No bone substitute Not diabetes Not an animal experiment 2 - Full text screening No bone substitute Not diabetes Not an animal experiment Not an original paper Not bone formation data No control group	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	Authors, title, year of publication	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Experimental groups Number of animals per group	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	All diabetic animal models	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	Size of bone defect, type of bone substitute material, implantation period, location of surgery	
35.	Outcome measures	Bone formation/mass (%)	
36.	Other (*e.g.* drop-outs)	N/A	
	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:	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	Histomorphometrical bone formation in percentage	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	1)Extract data from text or tables 2)Extract data from figures 3)Contact authors for data not presented in paper If no answer is obtained within a week or there is no contact information, other authors will be randomly contacted. After three 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 the data. 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)	Meta-analysis	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	A meta-analysis will be performed if more than 3 studies report on a specific outcome measure.	
	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)	Mean differences or 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)	Random effect model	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	I^2	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	Animal species Gender Type of bone substitute Type of bone defect Period under diabetic condition	
48.	Any sensitivity analyses you propose to perform		
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	N/A	
50.	The method for assessment of publication bias	Funnel plot, if applicable (i.e. 10+ studies included in meta-analysis).	
Final approval by (names, affiliations):		Date:	

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8. Jones JR. Review of bioactive glass: from Hench to hybrids. Acta biomaterialia. 2013;9(1):4457-86. Epub 2012/08/28.
9 Hooijmans CR, Tillema A, Leenaars M, Ritskes-Hoitinga M. Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed. Lab Anim. 2010;44(3):170-5.
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