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Systematic Review

Clinical research activity in periodontal medicine: a systematic mapping of trial registers

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Abstract

Aim: The primary aim of the study was to systematically map registration records on periodontal medicine in clinical trial registers. The secondary aim was to assess the evolution of periodontal medicine in clinical periodontal research as a whole.

Material and Methods: We searched all registration records related to periodontology in the World Health Organization International Clinical Trials Registry Platform. For registration records classified in the field of periodontal medicine, we assigned the 2015 MeSH® term for the most precisely corresponding systemic condition.

Results: Fifty-seven systemic conditions have been hypothesized to be linked with periodontal diseases, covering nearly 2% of the diseases indexed in MeSH. In addition to diabetes, cardiovascular disease or preterm birth, other systemic conditions have been the subject of registration records, such as anaemia, liver diseases, dyspepsia or ankylosing spondylitis. A trend towards increasing diversification of systemic conditions has appeared over time. About a third of registration records in clinical periodontal research deals with periodontal medicine.

Conclusions: Periodontal medicine now constitutes an important part of clinical periodontal research. Research activity in periodontal medicine has grown continuously since the early 2000s, and exploration of registers gives a useful up-to-date snapshot of this constantly evolving field of research.

Key words: clinical trials; periodontal diseases; periodontal medicine; periodontitis; systematic review

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Since the 1990s, the periodontal community has increasingly pointed towards links between periodontal health and systemic conditions, leading to the practical "periodontal medicine" concept. Periodontal medicine establishes a two-way relationship between periodontal diseases and overall health (Williams & Offenbacher 2000, Garcia et al. 2001). The idea that periodontal diagnosis and treatment could not only preserve the function and aesthetics of the natural dentition but also prevent untoward effects on a patient's overall health (Matthews 2000), has rapidly spread in the professional (Paquette et al. 2015) and academic (Wilder et al. 2009) communities. Several pathophysiological mechanisms have been put forward, such as bacteraemia, endotoxaemia, and release of inflammatory mediators from periodontal tissues or from an induced acute-phase response (Schenkein & Loos 2013, Van Dyke

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& van Winkelhoff 2013, Hajishengallis 2015).

The European Federation of Periodontology and the American Academy of Periodontology organized a "workshop on periodontitis and systemic diseases", and reviewed many systemic conditions in association with periodontal diseases. Peer-reviewed reports from this workshop were published in the 2013 supplements of the Journal of Clinical Periodontology (volume 40 Suppl. 14) and the Journal of Periodontology (volume 84 Suppl. 4). These supplements highlighted three major topics that have been extensively investigated in the literature since the 1990s: the links of periodontal diseases with 1) cardiovascular diseases (D'Aiuto et al. 2013, Dietrich et al. 2013, Tonetti & Van Dyke 2013), 2) diabetes (Borgnakke et al. 2013, Chapple & Genco 2013, Engebretson & Kocher 2013), and 3) adverse pregnancy outcomes (Ide & Papapanou 2013, Michalowicz et al. 2013, Sanz & Kornman 2013). A fourth topic (Linden et al. 2013, Linden & Herzberg 2013) concerned associations reported between periodontitis and cancer, chronic kidney diseases, chronic obstructive pulmonary disease, mild cognitive impairment, metabolic syndrome, obesity, or rheumatoid arthritis. Other narrative reviews such as that by (Gulati et al. 2013), have also reported, but with relatively scant evidence, possible links between periodontal diseases and erectile dysfunction, gastrointestinal disease, osteoporosis, pneumonia or prostatitis. Virtually all original studies describing these associations have concluded on the probable existence of confounding factors (not always modifiable), that could explain the co-occurrence of adverse conditions between oral and overall health (Dietrich & Garcia 2005, Kolk et al. 2012). Thus, well-designed observational studies are necessary to better understand these associations (Dietrich & Garcia 2005, Linden et al. 2013). Working group 4 of the workshop on periodontitis and systemic diseases concluded that the field of periodontal medicine was still wide open, with gaps that must be addressed. Globally, the periodontal community agrees that the causation/severity effect of periodontal diseases on cardiovascular diseases, diabetes and adverse pregnancy outcomes needs to be further investigated (Linden & Herzberg 2013), as shown by recent non-significant results of large, multicentre, randomized controlled trials (RCTs) or meta-analyses (Offenbacher et al. 2009, Engebretson et al. 2013, Li et al. 2015). RCTs are also desirable to develop more precise clinical guidelines for the periodontal management of patients with systemic conditions (Borgnakke et al. 2013).

During the 1990s, clinical trial registers began to be strongly promoted in biomedical research, with the aim of increasing transparency in clinical research (Moher 1995). In 2005, the International Committee of Medical Journal Editors (ICMJE) recommended that authors of RCT publications register their studies in a publicly accessible trial register (De Angelis et al. 2005). As the start of clinical trial registers coincided with the development of periodontal medicine at the end of the 1990s, the registers provide a good opportunity to map research activity in periodontal medicine. As far as we know, there has not yet been any attempt to systematically map and tabulate the systemic conditions thought to be potentially associated with periodontal diseases. Moreover, optimizing future research resources requires an objective identification of gaps and emerging trends. In particular, systemic conditions related to periodontal diseases could be catalogued to describe patterns of actual research activity, potentially revealing common pathophysiological hypotheses (Linden & Herzberg 2013).

The primary aim of this study was to describe the systemic conditions that have been hypothesized to be related to periodontal diseases, by systematically mapping clinical trial registers. The secondary aim was to assess the evolution of periodontal medicine in clinical periodontal research as a whole.

Material and methods

We followed the PRISMA statement (Moher et al. 2009) for conduct and reporting of systematic reviews.

Search strategy and exclusion criteria

We searched in the World Health Organization International Clinical Trials Registry Platform (ICTRP, www.who.int/trialsearch/). This platform is an umbrella group of 16 registries worldwide, including ClinicalTrials.gov. The latter is under the responsibility of the U.S. government and, at the time of writing, contains more than 200,000 studies from 190 countries, of which 40% originated from the USA. All of these registries must "be accessible to the public at no charge, be open to all prospective registrants, be managed by a not-for-profit organization, have a mechanism to ensure the validity of the registration data, and be electronically searchable" (De Angelis et al. 2005).

We employed an iterative search strategy to adopt a systematic approach for knowledge discovery. This iterative process took shape as the process evolved (Finfgeld-Connett & Johnson 2013). The first iteration was "periodontal", and the final iteration (i.e. the final search strategy) was "periodont* OR gingiv* OR *implantitis". The search was performed in each register, without a time limit. The last search was conducted for all registers on 27 May 2015.

Registration records not dealing directly with clinical periodontal research (e.g. on orthodontic research, prosthodontic research, non-periodontal surgery research, and research on apical periodontitis) were excluded from the analysis.

Categorization of registration records

A trial was defined as "any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome" (De Angelis et al. 2005). Clinical and/or biological outcomes were considered. On the basis of record contents, we classified as "observational studies" any registration records of cross-sectional, case–control, cohort or diagnostic studies (since most trial registers are open to registration of observational studies (Loder et al. 2010)).

Among the registration records included, we defined four categories of studies:

i. *Category A: Periodontal medicine – Periodontal intervention to improve (or prevent) a systemic condition.* The intervention could be any type of periodontal treatment. The systemic condition could be any type of adverse condition (or a special physiological process), excluding any type of stomatognathic disease.
ii. *Category B: Periodontal medicine – Intervention for a better understanding of the links between oral and overall health (B1) OR Observational study of a possible link between periodontal disease and a systemic condition (B2).*

Category B1 included any trial adding to knowledge in periodontal medicine without fulfilling the requirements for Category A.

Category B2 included any observational study focusing on both periodontal health and any type of systemic condition (excluding any type of stomatognathic disease).

iii. *Category C: Periodontal intervention to improve oral health.* The outcome was related to periodontal health, or could also be related – but limited – to any type of other stomatognathic diseases.
iv. *Category D: observational studies in periodontal research, without systemic assessment.*

Thus, we defined records in the field of periodontal medicine as those registered in categories A+B1+B2. In contrast, we defined as "periodontal dentistry" the area of research dealing with periodontal health at mouth level only (categories C+D). Observational studies were B2+D. No cross-category classification was allowed for a single registration. In case of multiple categorization, the record was placed in the highest-order category (i.e. A>B1>B2>C>D).

Description of systemic conditions

We used the 2015 Medical Subject Headings (MeSH®), from the U.S. National Library of Medicine, as already done in other mapping research (Shen et al. 2011, Komenda et al. 2015). MeSH® is a controlled vocabulary thesaurus used for indexing articles for PubMed (http://www.ncbi.nlm.nih.gov/mesh). It has 16 main branches [A to N + V + Z] and its hierarchical classification leads to narrower terms (taxa). For example within the [Diseases – C] branch, there are 26 main sub-branches representing narrower categories of disease (e.g. [C02] Virus diseases, [C07] Stomatognathic Diseases, or [C14] Cardiovascular Diseases). We considered as a potential systemic condition any MeSH term (taxon) that was not referenced in [C07]. Although the main term "Stomatognathic disease [C07]" is not commonly used in scientific and professional literature, sub-branches contain all common oral diseases, such as Periodontitis [C07.465.714.533] or Gingivitis [C07.465.714.258.480].

As the same MeSH terms are often found in several sub-branches, we drew up a simplified, tailored thesaurus to avoid redundancy in the mapping process (the one exception being for kidney diseases, where no distinction could be made between male and female disorders). We also considered the [Phenomena and Processes – G] branch, because it contained some possible relevant health conditions, such as pregnancy or menopause. The simplified thesaurus is provided in File S1.

Data processing, extraction and analyses

All registration records were exported from ICTRP into XML format, then parsed into a local database. A script was developed to minimize errors during the screening process and to computerize data for further analyses. The script was based on a Perl Web Dancer 1.3 framework (http://perldancer.org/).

Evaluators (PM, JNV) classified each registration record in Category A, B1, B2, C or D. Any discrepancies were resolved through discussion and consensus. The two evaluators (PM, JNV) also extracted the following items: year of study start, sample size, country of the main centre and register. Multiple records about the same study were identified, and only the main registration (put forward by the ICTRP) was taken into account to avoid duplicate information.

For registration records in the field of periodontal medicine (Categories A, B1 and B2), the two evaluators (PM, JNV) assigned the most precise term (taxon) of the MeSH classification, corresponding to the systemic condition described in the study. In cases with several distinct systemic conditions within a registration record, multiple assignments were allowed. The resulting tree was built up with all assigned MeSH terms, along with their proximal ramifications, since the MeSH classification is hierarchical.

Median and interquartile ranges were provided for continuous characteristics of studies, whereas frequencies and percentages were provided for categorical characteristics, as described (Califf et al. 2012).

Data visualization

Chord diagrams or connectograms (Krzywinski et al. 2009) were used to link the proportion of registrations by [Diseases-C] sub-branches, to 1) their categories (classified as described above as A, B1, B2, C or D) and 2) the start years (or anticipated start years) of the studies.

They were composed of two rings. The inner ring included categorical segments, the size of which was proportional to the corresponding number of registration records. The outer ring represented the corresponding relative percentage of each subpart of the segments. Coloured ribbons made connections between subparts of different categorical segments (Krzywinski et al. 2009). An annotated figure is provided in File S2 to help the reader's interpretation.

From the resulting MeSH terms tree, the visual mapping of systemic conditions potentially related to periodontal diseases was represented using a circular phylogenetic-like tree. After adequate formatting (nexus format), the phylogenetic-like tree was obtained with the tool available at http://itol.embl.de/ (Letunic & Bork 2007). Lines from the centre to the periphery of the circle represent the hierarchical tree structure of the MeSH®. At the end of each taxon, we added a two-coloured rectangular bar, of length proportional to the relative number of registration records in categories A (red) and B1+B2 (grey).

Results

A total of 966 registration records were retrieved from ICTRP, of which 144 were excluded because they did not deal directly with periodontal research (full list available in File S3).

Descriptive analysis of registration records

Among the 822 selected records, there were 129 trials classified in Category A, 36 trials in Category B1 and 77 in Category B2. Thus, there were 242 registration records (29.5%) dealing with periodontal medicine.

Complementarily, there were 524 trials classified in Category C and 56 studies in Category D, for a majority of 580 (70.5%) records dealing with periodontal dentistry. The term "*implantitis" was found in 21 titles of registration records, and none of these records were classified in the periodontal medicine field of research. There were 133 (16.2%) observational studies registered.

Some characteristics of registration records are presented in Table 1, and the list of all registration records by categories is available in File S3. More than half the records were registered in the American clinicaltrials.gov register. Registration records were mainly from Asia, Europe and North America: 51.4%, 23.9% and 14.8% for periodontal dentistry, 42.5%, 20.8% and 18.1% for periodontal medicine respectively.

Systemic conditions, once labelled as MeSH terms, were assigned into the narrowest taxon in the simplified tree (available in File S1).

Figure 1 represents the connections between Categories A, B1+B2, C, D and MeSH sub-branches from [C] and [G]. In this figure, registration records within the scope of periodontal dentistry are linked to the [C07] Stomatognathic Diseases branch.

Systemic conditions in periodontal medicine

Periodontal diseases were found to be linked to 17 of the 26 main sub-branches of the Diseases [C] branch, i.e. all [C] sub-branches except Parasitic Diseases [C03], Stomatognathic Disease [C07] (by voluntary design), Otorhinolaryngologic Diseases [C09], Congenital, Hereditary, and Neonatal Diseases and Abnormalities [C16], Disorders of Environmental Origin [C21], Animal Diseases [C22], Occupational Diseases [C24], Chemically Induced Disorders [C25] and Wounds and Injuries [C26]. Exploding the tree from each of the MeSH terms involved gave a total of 129 MeSH terms that have been potentially associated with periodontal diseases. This constitutes 1.95% of total [C] and [G] MeSH terms. Only two studies had multiple categories: JPRN-UMIN000008582 (Diabetes Mellitus and Arteriosclerosis) and JPRN-UMIN000013751 (Diabetes Mellitus and Rheumatoid Arthritis).

The super-tree in Figure 2 shows the 57 systemic conditions that have appeared in the tabulation to be related to periodontal diseases. We could distinguish between major topics (more than 30 records, i.e. diabetes, inflammation and cardiovascular diseases), intermediate topics (between 5 and 30 records, e.g. pregnancy complications, rheumatoid arthritis, respiratory tract diseases or kidney diseases) and minor topics (fewer than 5 records, e.g. neoplasms, gastroesophageal reflux, anaemia, liver diseases, dyspepsia, ankylosing spondylitis or male infertility). Minor topics were often designed as observational studies (Category B2). A complete list of these systemic conditions along with the corresponding numbers of registration records in Categories A, B1 and B2, is provided in File S4.

Evolution of registration records in periodontal research

Figure 3 shows that there is a clear trend towards growing registration of studies, according to their starting years from the late 1990s to 2014 and beyond. Relative to this growth, there is no major difference between periodontal medicine and periodontal dentistry: between 1998 and 2013, the average annual growth rate of records was 39% for periodontal medicine (A+B1+B2) and 35% for periodontal dentistry (C+D).

Table 1. Characteristics of registration records

	Periodontal dentistry (N = 580)	Periodontal medicine (N = 242)
Trial register	580	242
Australian New Zealand Clinical Trials Registry (ANZCTR)	8 (1.4%)	9 (3.7%)
Brazilian Clinical Trials Registry (ReBec)	0 (0%)	5 (2.1%)
Chinese Clinical Trial Register (ChiCTR)	13 (2.3%)	8 (3.3%)
Clinical Research Information Service (CRiS), Republic of Korea	3 (0.5%)	1 (0.4%)
ClinicalTrials.gov	299 (51.6%)	136 (56.2%)
Clinical Trials Registry – India (CTRI)	42 (7.3%)	16 (6.6%)
EU Clinical Trials Register (EU-CTR)	21 (3.6%)	2 (0.8%)
German Clinical Trials Register (DRKS)	10 (1.7%	5 (2.1%)
Iranian Registry of Clinical Trials (IRCT)	98 (16.9%)	21 (8.7%)
ISRCTN.org	24 (4.1%)	17 (7.0%)
Japan Primary Registries Network (JPRN)	39 (6.7%)	19 (7.9%)
Sri Lanka Clinical Trials Registry (SLCTR)	3 (0.5%)	0 (0%)
The Netherlands National Trial Register (NTR)	18 (3.1%)	2 (0.8%)
Thai Clinical Trials Registry (TCTR)	2 (0.3%)	1 (0.4%)
Cuban Public Registry of Clinical Trials	0 (0%)	0 (0%)
Pan African Clinical Trial Registry	0 (0%)	0 (0%)
Areas	535	221
North America	79 (14.8%)	40 (18.1%)
South America	39 (7.3%)	28 (12.7%)
Europe	128 (23.9%)	46 (20.8%)
Asia	275 (51.4%)	94 (42.5%)
Oceania	6 (1.1%)	12 (5.4%)
Africa	8 (1.5%)	1 (0.5%)
Study size		
Median (Q1–Q3)	48 (30–90)	76 (46–162)

The number of registered trials for periodontal dentistry and periodontal medicine is detailed by trial register and geographical area, and by median study size.

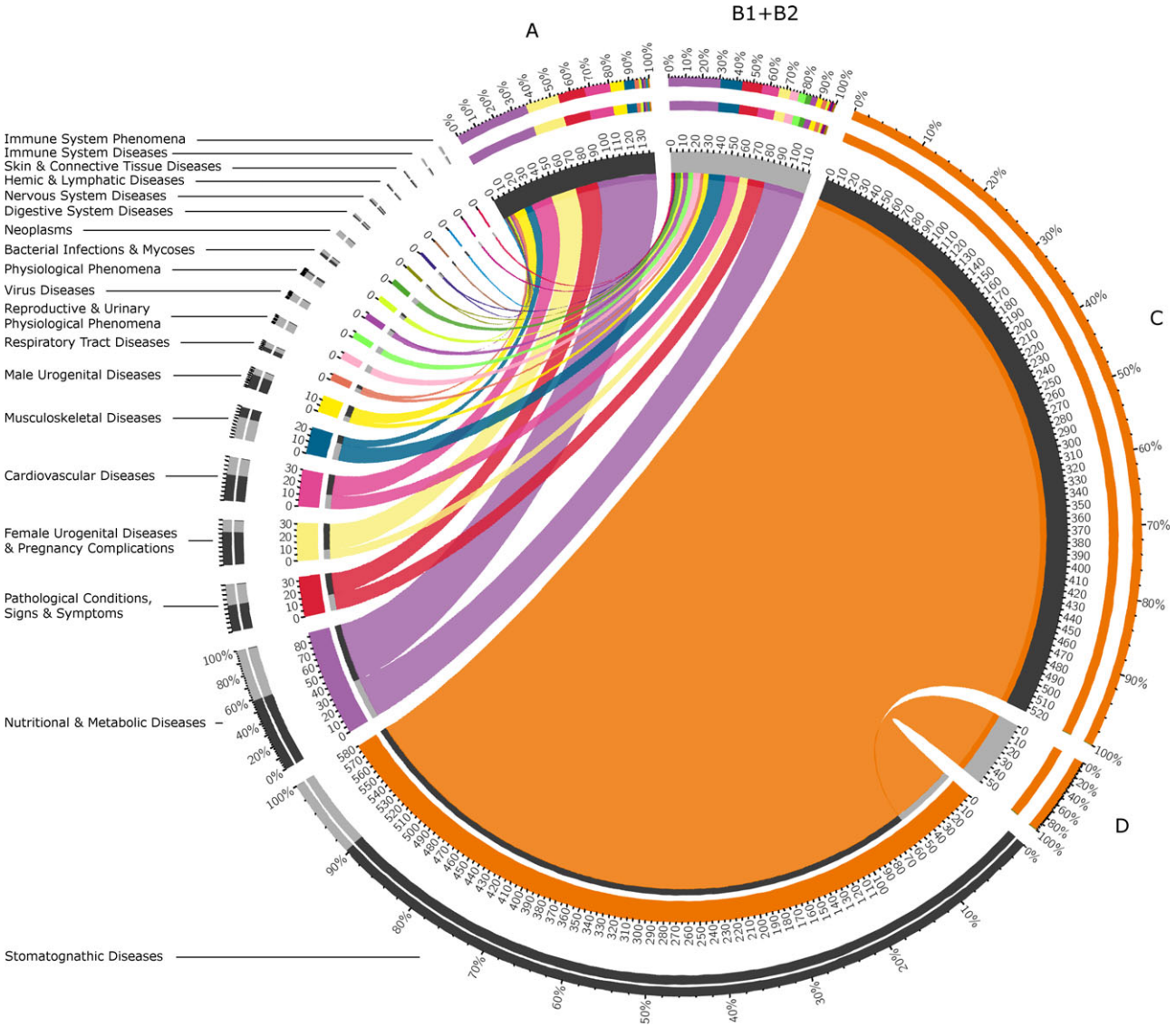

Fig. 1. Connections between study categories A, B (B1 and B2 combined), C, D, and terms in MeSH sub-branches from [C] and [G]. This chord diagram represents the proportion of studies dealing with each included sub-branch of the MeSH classification "Diseases" [C] and "Phenomena and Processes" [G], by category. Trials concerning periodontal intervention to improve (or prevent) a systemic condition are classified as A; trials concerning interventions for a better understanding of the links between oral and overall health or observational studies between periodontal disease and a systemic condition are classified as B1+B2. A and B1+B2 correspond to periodontal medicine. Periodontal dentistry (the area of research dealing with periodontal health at mouth level only) is interventional (C) or observational (D). Trial categories (on the right part of the figure) are shaded either dark (A or C) or light grey (B1+B2 or D). On the left part of the figure, each MeSH sub-branch with its colour code is listed in order of descending frequency. The outer ring of the figure indicates the proportion of studies, whereas the inner circle shows their absolute numbers. In each ring, the contribution of included sub-branches of MeSH [C] and [G] in each trial category is coded by coloured segments. These coloured segments are also sorted by frequency. An annotated figure is provided in File S2.

Figure 4 shows a temporal evolution of topics dealing with periodontal medicine, with the start dates of the studies. Diabetes, systemic inflammation, pregnancy complications and cardiovascular diseases have always been the main topics in periodontal medicine. A snowball effect can also be detected: minor topics in one period are likely to become intermediate topics later (e.g. musculoskeletal diseases, or male urogenital diseases). Finally, there appears to be a trend towards increasing diversification in the registration records.

Discussion

Periodontal medicine now constitutes an important part of clinical periodontal research, continuously growing since the early 2000s. Our analysis estimates that at least 1.95% of the MeSH terms (within the Disease and the Phenomena and Processes sub-branches) have now been hypothesized to be linked to periodontal diseases.

We showed that putative systemic conditions associated with periodontal diseases are diversifying over time. While research on cardiovascu-

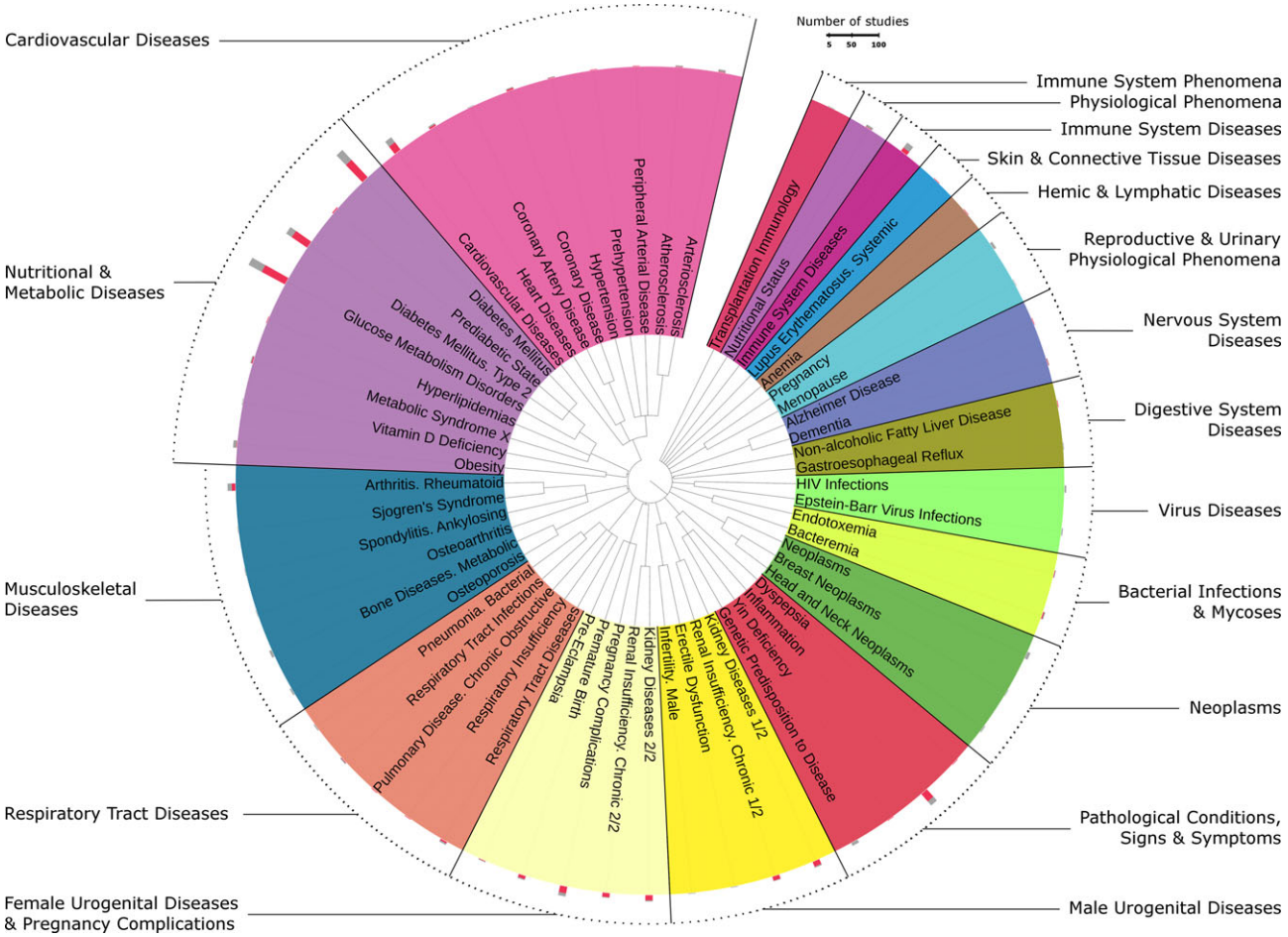

Fig. 2. Phylogenetic-like tree of systemic conditions that have been hypothesized in the registers to be related to periodontal diseases. Lines from the centre to the periphery of the circle represent the hierarchical tree structure of the MeSH classification. At the end of each taxon, a two-coloured rectangular bar has been added, with length proportional to the relative number of registration records in the A (red) and B1+B2 (grey) categories respectively. *Abbreviations:* trials concerning periodontal intervention to improve (or prevent) a systemic condition are classified as A; trials concerning intervention for a better understanding of the links between oral and overall health are classified B1 and observational studies of the link between periodontal disease and a systemic condition are classified B2.

lar diseases, diabetes or pregnancy complications is still very active, more and more systemic conditions are suspected to be linked with periodontal diseases and our systematic mapping found anaemia, liver diseases, dyspepsia or ankylosing spondylitis as examples of emerging topics in periodontal medicine.

Our results also indicate that periodontal medicine constitutes an important part of periodontal research. About a third of periodontal studies registered in trials registers deals with possible links between periodontal health and overall health. Although some researchers argue that periodontal medicine has been a "driving force for a considerable downscaling of research into periodontitis in its own right" (Baelum & Lopez 2013), that is not what we found in this analysis of clinical trial registers. Considering periodontal medicine as the new paradigm of periodontology, Baelum & Lopez (2013) underestimate the large amount of periodontal research still conducted with the aim of improving prophylactic, diagnostic, therapeutic or rehabilitative measures in periodontology. Though it is likely that periodontal medicine could have increased the funding opportunities for periodontal research (Baelum & Lopez 2013), there is no evidence whatsoever that it has a detrimental effect on what we call "periodontal dentistry".

This study has several limitations that should be considered. One major limitation is that all registration records were considered as having the same level of methodological quality. There is no consensus on how to assess the quality of registration records. A recent survey of records taken from ICTRP showed that there are still important problems with completeness of registration records (Viergever et al. 2014). This could have led to some inaccuracies in our systematic mapping process. For example only the main centre of the trials was extracted. ClinicalTrials.gov offers the possibility to also extract all the centres of a multi-centre study, and the mean number of centres per study may be an interesting parameter to investigate to explore worldwide scientific

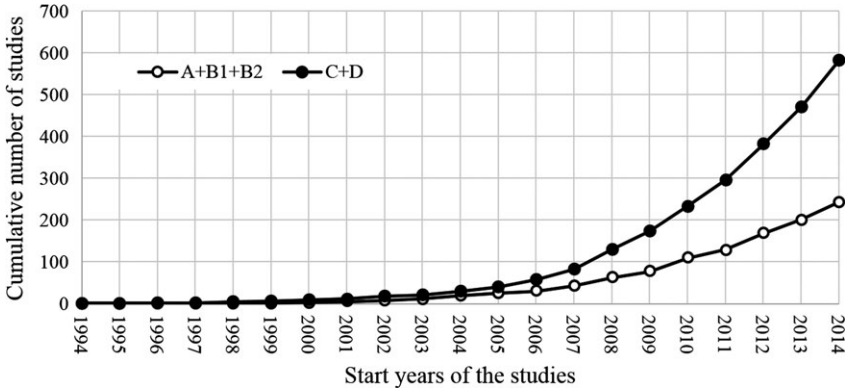

Fig. 3. Evolution of registration records in periodontal research according to their starting years from the mid-1990s to 2014 and beyond. On the *Y*-axis, the cumulative number of studies is represented for each start year noted on the *X*-axis. Periodontal medicine is represented in white circles (A+B1+B2) and periodontal dentistry in black circles (C+D). The mean annual growth rate of records between 1998 and 2013 was 39% for periodontal medicine and 35% for periodontal dentistry. Trials on periodontal intervention to improve (or prevent) a systemic condition are classified as A; trials on intervention for a better understanding of the links between oral and overall health are classified B1 and observational studies of links between periodontal disease and a systemic condition are classified B2. Periodontal intervention to improve oral health is classified as C; observational studies in periodontal research, without systemic assessment are classified as D.

interactions (Cheng et al. 2012). However, we have shown that the number of trial registrations is growing over time, which may reflect a wider variety of therapeutic interventions provided by professionals (Nishimura et al. 2002). This trend may be analysed as beneficial for patients but may also reflect a lack of consensus on efficacy and optimal periodontal care (Niederman et al. 2002). Another limitation is that only half of the existing biomedical journals have adhered to the ICMJE requirement in their instructions to authors (Hooft et al. 2014). In dentistry, instructions to authors of numerous journals require (e.g. J Dent Res, J Periodontol) or strongly encourage (e.g. J Clin Periodontol, Clin Oral Implan Res) authors who submit manuscripts reporting on a trial to register their trial. However, it has recently been shown that only one-quarter of RCTs published in oral health journals are publicly registered (Smail-Faugeron et al. 2015).

The number of systemic conditions that have been associated with periodontal diseases in the periodontal literature is likely to have been underestimated in our analysis. For example we did not find any registration records on the topic of prostatitis and periodontal disease, yet it has already been described in the literature (Joshi et al. 2010). One explanation is that our analysis was not designed to assess the overall literature but only trial registers. Periodontal research also requires preclinical models for preliminary safety and proof-of-concept before translation to humans (Sculean et al. 2015). There is currently no specific initiative for the registration of observational studies (Guyatt et al. 2011), laboratory research and/or animal research. We identified less than 20% of observational studies, and no *in vitro* or animal studies. A systematic mapping of the whole PubMed database would give a sharper picture of actual periodontal research and a representation of the interventional/observational ratio, allowing the discovery of pathophysiological links between periodontitis and systemic diseases through animal models (Hajishengallis et al. 2015). Comparison between animal and human studies should also be investigated (Perel et al. 2007).

Finally, our study could be criticized for taking only registration records into account, which have not been peer-reviewed. Analyses of published studies take advantage of the scientific peer-review process but publication is often delayed and negative trials are less likely to be published (Dickersin & Rennie 2012). Full-text final articles would give the opportunity to map the time needed between registration, start date and the end of the study. In spite of these limitations, exploration of registers gives a more up-to-date snapshot of the constantly evolving field of periodontal medicine.

It is also important to be cautious regarding inferences to be drawn and interpretations to be made from our analysis. First, we strongly emphasize that the fact of systemic conditions being associated with periodontal diseases in registration records does not mean that significant links were found between periodontal status and systemic conditions. This systematic mapping was simply aimed to tabulate topics of interest in periodontal medicine. Second, we emphasize the danger that the dental profession could press to justify the importance of dental treatment by highlighting its impact on various systemic conditions (Tenenbaum et al. 2007), such as the ones described in this study, although the causal relationships are still rarely proved. Such behaviour would undermine the credibility of scientific research and academic recommendations. Third, it is far from our intention to spread the idea that oral health and systemic health could be two different entities. As pointed out previously, talking about the "oral-systemic health connection" could unintentionally separate the mouth from the rest of the body (Nogueira-Filho & Tenenbaum 2011). In fact, we acknowledge that the overall health of patients is of tremendous importance for dentists seeking to achieve genuine whole-patient care.

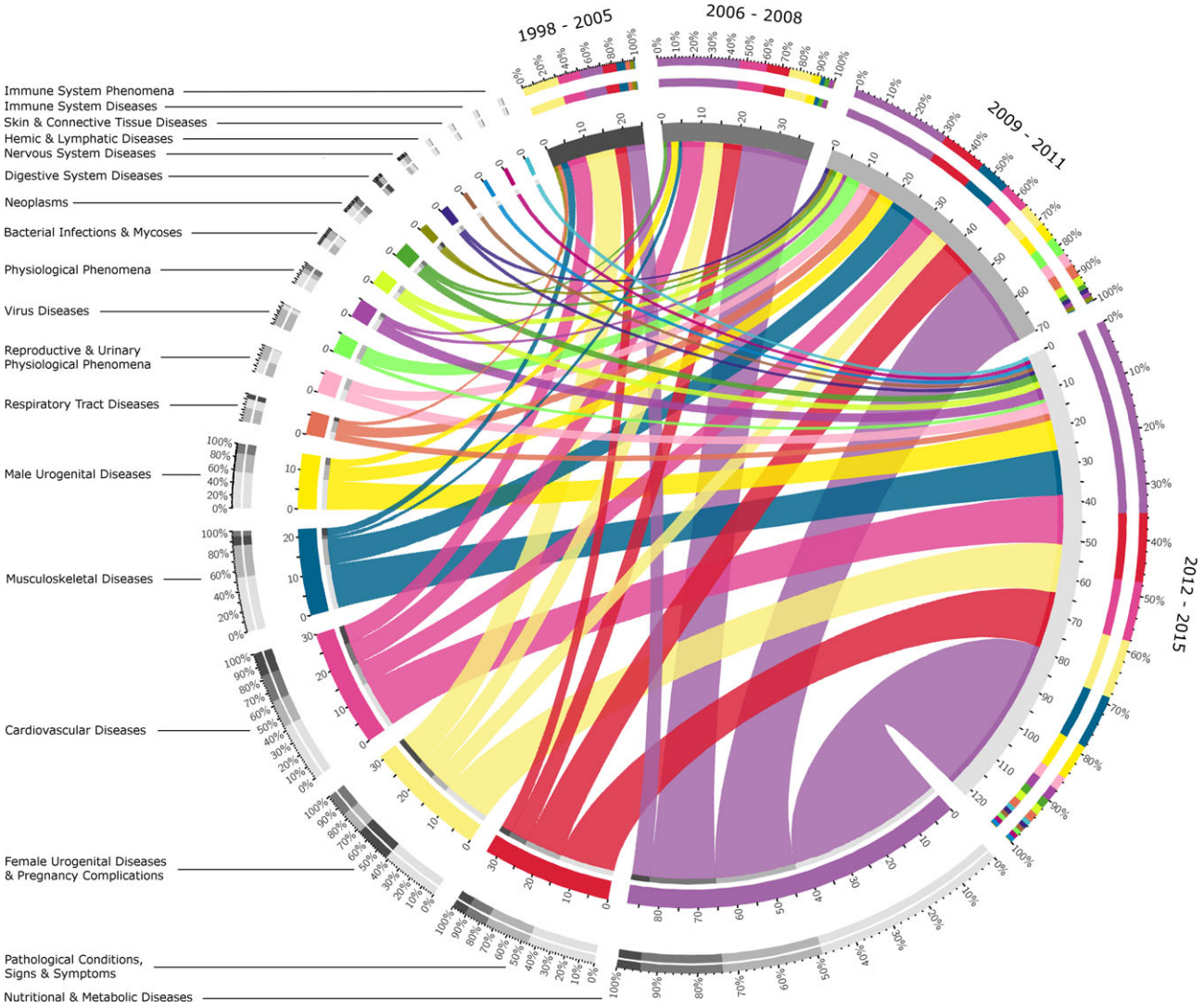

Fig. 4. Connectogram of the temporal evolution of topics dealing with periodontal medicine. This chord diagram represents the proportion of studies dealing with each included sub-branch of the MeSH classification "Diseases" [C] and "Phenomena and Processes" [G], linked to the respective start years of the studies (grouped in 4 periods: 1998–2005, 2006–2008, 2009–2011, 2012 and beyond).

From this study, several perspectives of research in periodontal medicine can be outlined.

More than ever, well-designed observational studies are needed to better understand associations between periodontal diseases and systemic diseases (Dietrich & Garcia 2005), since observational studies are often the only feasible method for studying most questions concerning risk. Although we analysed data from trial registers, we found a substantial proportion of the registered trials to be observational studies (16%). This was consistent with other fields of biomedical research, such as surgical oncology, where 15% of registration records in ClinicalTrials.gov were observational studies (Menezes et al. 2013).

Regarding the main topics (i.e. cardiovascular diseases, adverse pregnancy outcomes and diabetes), published RCTs have produced discordant results, but there is still a need to assess different modalities of periodontal treatment for individuals with systemic conditions (Vergnes 2014).

Although periodontal treatment modalities fell outside the scope of the present work, the screening of trial registers has revealed great diversity in this field (Drisko 2001, Bader 2010). We did not notice alternative methods of interventional research, such as n-of-1 trials (Lillie et al. 2011), a methodology that has never been investigated in periodontal research as far as we know. Finally, we also noted a lack of patient-centred outcomes in RCTs, while this concept is of fundamental importance considering that whole-person care is the cornerstone of periodontal medicine.

Perhaps the most exciting and challenging perspective in periodontal medicine would be the diversification of meta-research. The current prolific production of scientific information and the burst of metadata make systematic work very necessary to classify and strat-

ify all the accumulated data and knowledge (Altman et al. 2008). In addition to traditional systematic reviews (essentially based on deductive approaches), other validated approaches to systematic reviewing are hardly explored in periodontal medicine. For example realist syntheses (Rycroft-Malone et al. 2012), although time-consuming and human resource intensive, could give opportunities to develop more pragmatically insightful conclusions in periodontal medicine, while taking results from both fundamental sciences and clinical studies into account. Data mining and Knowledge Discovery in Databases (KDD) on periodontal research (Hettne et al. 2007), as initiated in the present analysis, would highlight the necessity for new research directions (Piatetsky-Shapiro & Frawley 1991, Fayyad et al. 1996), and would also identify gaps in research. The combination of bioinformatics tools and medical data would result in significant advances in the understanding of pathophysiology and individual susceptibility (Hettne et al. 2007). A first step in this direction could be the addition of "Periodontal Medicine" as a new taxon in the MeSH classification, for example as a sub-branch of Periodontics, under Health Occupations [H02], Dentistry [H02.163], Specialties, Dental [H02.163.876], Periodontics [H02.163.876.623].

In conclusion, analyses of trial registers showed that research in periodontal medicine is a very active field in periodontology. Fifty-seven systemic conditions have been hypothesized to be linked with periodontal diseases, which suggest the possibility of thinking in terms of common pathophysiological processes. Knowledge in periodontal medicine would guide practitioners towards both evidence-based and patient-centred approaches when treating patients with systemic conditions.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Simplified MeSH tree: systemic conditions that have been hypothesized to be linked with periodontal diseases, after labelling as MeSH terms. Bold: MeSH terms that were selected. Underlined: Proximal branches of selected MeSH terms. Branches that were removed for data visualization (phylogenetic-like tree and circos connectograms). *Refinement of the resulting MeSH tree before data visualization*. As the same MeSH terms are often found in several sub-branches, we drew up a simplified thesaurus to avoid redundancy in the mapping process. To gain in readability and to provide a visual map of systemic conditions in periodontal medicine, the resulting MeSH tree was refined in three steps. First, we removed six duplicate taxa. As all selected MeSH terms from Endocrine System Diseases [C19] were duplicated in Nutritional and Metabolic Diseases [C18], we kept only [C18] for data visualization. Similarly, as Sjogren's syndrome was already indexed in Skin and Connective Tissue Diseases [C17], we removed Eye Diseases [C11]. Population Characteristics [N01], Genetic Phenomena [G05], Mental Disorders [F03], and Diagnosis [E01] were also removed for duplication reasons. Second, the MeSH term "Kidney Diseases" was left in both Male Urogenital Diseases [C12] and Female Urogenital Diseases and Pregnancy Complications [C13]. Third, the Phenomena and Processes [G] branch was also selected to refer to 4 MeSH terms (i.e. [G07] Physiological Phenomena, leading to [G07.610.650]

Nutritional Status; [G08] Reproductive and Urinary Physiological Phenomena, leading to [G08.686.785.760.769] Pregnancy and [G08.686.157.500] Menopause; and [G12] Immune System Phenomena, leading to [G12.425.901] Transplantation Immunology). These procedures had no impact on the number of registration records described in the article.

File S2. Annotated figure (see Fig. 1) for connections between Categories A, B1+B2, C, D and MeSH sub-branches from [C] and [G]. This chord diagram represents the proportion of studies dealing with each included sub-branch of the MeSH classification "Diseases" [C] and "Phenomena and Processes" [G], linked to the respective category of studies. Trials concerning periodontal intervention to improve (or prevent) a systemic condition are classified as A; trials concerning intervention for a better understanding of the links between oral and overall health or observational studies of periodontal disease and a systemic condition are classified as B1+B2. A and B1+B2 correspond to periodontal medicine. Periodontal dentistry (the area of research dealing with periodontal health at mouth level only) is interventional (C) or observational (D).

File S3. Exhaustive list of the 966 registration records retrieved from ICTRP with the search strategy, by category (A, B1, B2, C, D, and excluded): registration numbers and titles. *Abbreviations:* A – Periodontal intervention to improve (or prevent) a systemic condition; B1 – Intervention for a better understanding of the links between oral and overall health; B2 – Observational study of possible link between periodontal disease and a systemic condition; C – Periodontal intervention to improve oral health; D – observational studies in periodontal research, without systemic assessment. Category A: 129 studies; Category B1: 36 studies; Category B2: 77 studies; Category C: 524 studies; Category D: 56 studies; Excluded: 144 studies.

File S4. Systemic conditions that have been hypothesized to be linked with periodontal diseases, after labelling as MeSH terms. A complete list is provided for the 57 systemic conditions that have been hypothesized to be related to periodontal diseases, along with the corresponding number of registration records in Categories A, B1 and B2. Colour code refers to the one chosen in Figures 1, 2 and 4. *Abbreviations:* A, Periodontal intervention to improve (or prevent) a systemic condition; B1, Intervention for a better understanding of the links between oral and overall health; B2, Observational study of periodontal disease and a systemic condition.

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Clinical Relevance

Scientific rationale for the study: "Periodontal medicine" establishes a two-way relationship between periodontal diseases and overall health. There has not yet been any attempt to systematically map and catalogue the systemic conditions potentially associated with periodontal diseases.

Principal findings: Fifty-seven systemic conditions have been hypothesized to be linked with periodontal diseases, which suggest the possibility of thinking in terms of common pathophysiological processes. Research in periodontal medicine is a very active field in current periodontal research.

Practical implications: Knowledge in periodontal medicine would guide practitioners towards both evidence-based and patient-centred approaches when treating patients with systemic conditions.