UMC St Radboud

College of Dental Sciences 2011 Research Report

Radboud University Nijmegen Medical Centre

Imagination is the beginning of creation.
You imagine what you desire,
you will what you imagine
and at last you create what you will.

George Bernard Shaw (1856-1950)

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Foreword

Imagination

"Imagination" is the theme of the 2011 Research report of the College of Dental Sciences of the Radboud University Nijmegen Medical Center. Imagination is the ability of the mind to form mental images of events that do not exist or have happened before. Imagination does not involve or is subject of external limitations, but can cross existing borders and allows to find unexpected combinations for the clarification of problems as occur in daily life. As a consequence, imagination is the key to development and is a great power in designing and inventing. Imagination is just not daydreaming, but strengthens creativity. Imagination is the key to new development and plays a pivotal role in scientific research. Progress in science is due largely to hypotheses which are developed by imagination, but are based on previously obtained data. Imagination is closely related to the phenomena of "Ideas" and "Creativity". Ideas can be considered as the constructive representation of imagination, while creativity involves the production of something novel. Creativity and knowledge creation by ideas and imagination play a crucial role in fostering innovation and are becoming increasingly important for our society. Therefore, imagination is an integral part of doing research. The creative process of a drafting a research hypothesis and study design is undoubtedly enhanced by imagination that accounts already in one's mind the imaginary outcome to a problem, which is also expressed in the quotes of George Bernard Shaw and William Blake at the beginning and end of this research report.

The current theme for the 2011 Research report intends to emphasize that the performance of dental research focusing on relevant dental problems is just an obligatory condition to provide an adequate academic environment for our dental students. In addition, research evidence is required for dental treatment approaches and the solution of clinical dental problems.

This research report is the visible reflection of what the imagination of researchers of the College of Dental Sciences has produced last year. On behalf of the Board of the College, I hope you will enjoy reading this report.

John Jansen, DSD, PhD
Head of the College of Dental Sciences
Radboud University Nijmegen Medical Centre

Radboud University Nijmegen

Radboud University Nijmegen (RUN) is one of the leading academic communities in the Netherlands. Renowned for its green campus, modern buildings, and state-of-the-art equipment, it has nine faculties and enrolls over 15.000 students. Radboud University Nijmegen is situated on a green campus in the oldest Dutch city. It's a welcoming, forward-looking, research-based centre of learning that covers the full range of academic disciplines. All the university buildings, lecture rooms, facilities and the University Hospital are situated together on the former Heyendael estate. The high quality of the university's postgraduate schools and research institutes has received national and international recognition.

"The Medical Centre (MC) is part of the RUN and is a leading knowledge centre for academic medicine and health care. The interconnection between research, education, and patient care, forms the core of the organization" . The Radboud University Nijmegen Medical Centre (RUNMC) includes about 8.000 employees and 2.500 students. The RUNMC is subdivided in the:

- Academic Hospital
- Medical Faculty
- Biomedical Sciences
- College of Dental Sciences

In the College of Dental Sciences, all dentistry related departments are grouped. Core tasks are education, research and patient care. Patient care is on behalf of the educational and research programs. The College of Dental Sciences aims to practice education, research and patient care at the highest levels in dentistry.

Research in the RUNMC is divided in six clinically relevant research areas:

- molecular life science
- cognitive neuroscience
- evidence-based practice
- oncology
- inflammatory and infectious diseases
- genetic and metabolic diseases

Each of these areas has a precise focus with ample critical mass which provides a unique position for excellence. Scientists of the College of Dental Sciences participate actively in the research areas molecular life sciences and evidence-based practice.

Introduction to the Dental Research Lines

The current research lines address the following important issues:

Etiology of dental & craniofacial phenotypes (Line 1)

The principal aim of this research line is to analyze the phenotypes and to unravel the etiology of specific dentofacial and craniofacial disorders. The ultimate goal is the prevention of these disorders, as well as to improve diagnosis, treatment and care of individual patients (personalized medicine). To this end, two main topics are pursued:

1. **Phenotypes of hypodontia, cleft lip and palate (CLP) and related craniofacial syndromes**
   This theme focuses on the macroscopic, microscopic and molecular characteristics of patient data from our orthodontic and CLP clinic (primary phenotype). These include two-and/or three-dimensional phenotypes - for which a productive partnership has been established with the Department of Maxillofacial Surgery in the 3D-Facial Imaging Research Group, 3D-FIRG- , as well as four-dimensional dentofacial imaging or cellular phenotypes. Links are made to variations in DNA, RNA and protein levels (see Topic 2). Associated complications are monitored in the clinics, including wound healing which leads to scar formation, growth deterioration and speech problems (secondary phenotype).
   Information on other potential contributing factors for common diseases/conditions (e.g. diabetes), drug use (e.g. phenytoin, cocaine), nutrition (e.g. vitamins) and environmental factors (e.g. smoking) of the parents and/or the patient will also be gathered from questionnaires.

2. **The etiology of hypodontia, CLP and related craniofacial phenotypes**
   This theme aims to elucidate the molecular mechanisms that cause the various patient (sub)phenotypes found in topic 1 by (epi)genomic analyses of DNA from patients with CLP, missing teeth, and unresolved craniofacial syndromes as well as of healthy controls. The significance of the found novel mutations will be verified at both the protein and functional level by probing in silico (bioinformatics), in vitro, and animal models. Other potential contributing factors are studied in animal models for pathological pregnancy, CLP, and wound healing. In this context, the effects of nutrition and other environmental factors during pregnancy are investigated. Research into putative protective pathways offers the possibility of developing novel therapeutic and preventive strategies in the field of CLP, hypodontia and scar formation.

Wound healing around implants (Line 2)

This research line involves a close cooperation between the Department of Biomaterials and Implantology-Periodontology. The challenge for biomaterials scientists is to understand the basic phenomena of wound healing and how to use this knowledge to develop new materials/approaches for replacing lost or damaged tissues. This area of research is called Regenerative Medicine (RM). The aim of RM is to seduce the body into self-healing, which can only be achieved by a sound fundamental understanding of structure-function relationships in normal and pathological tissues. RM builds on knowledge from engineering sciences, life sciences and clinical sciences and requires a multi-disciplinary approach. RM holds the promise of revolutionary advances in health care. The research covers three main topics:

1. **The development and characterization of novel implant surfaces**
   The use of surface covering layers (i.e. coatings) provides methods to control the biological response to materials and material devices including implants and prostheses. The aim of our research on biomaterial coatings is to optimize the biological response for specific applications of biomedical implants.
   Besides implant surface coatings, topographical texturing is widely recognized to be an predominant factor in the tissue integration of a biomaterial. The innovative aspects of this research are investigating increasingly smaller (5-100nm) structures, resembling the size range of naturally occurring extracellular matrix and making translational steps towards practical applications of micro and nanomodification of medical biomaterials/implants.

2. **The construction of synthetic bone substitutes**
   Healthy bone tissue is a dynamic tissue subject to constant remodelling by bone-forming and bone-resorbing cells. Still, large bone defects as caused by diseases, trauma or tumor resection cannot be healed by the regenerative capacity of bone tissue. With the aid of synthetic biodegradable materials, however, this self-healing capacity can be expanded to these so-called critical-sized defects. Therefore, the long-term goal is of this research is to develop an injectable, synthetic bone substitute that mimics the unique properties of native bone as close as possible.
   It is hypothesized that the optimal synthetic bone tissue-equivalent will be comprised of polymeric and inorganic composite components. Two separate approaches are being followed. First, injectable bone fillers with enhanced bone forming behavior have been developed based upon self-setting calcium phosphate cement matrices that are functionalized with degradable polymeric microspheres. The opposite approach is carried out by constructing biomimetic nanocomposites from injectable, flexible hydrogel matrices that are functionalized with mineral dispersions of CaP nanocrystals.

3. **The application of cells and growth factors in order to engineer the tissue response**
   The main emphasis of this theme lies on the development of tissue engineering strategies, using stem cells and growth factors. Two types of (adult) stem cells are extensively investigated, i.e. mesenchymal cells from bone marrow, and dental pulp stem cells. Current research interests include cell selection/ purification methodologies, multilineage differentiation of stem cells, effects of various (polymer, metallic, ceramic, and biological) scaffolding materials on cell differentiation, influence of biomechanical loading, transfection using viral and non-viral vectors, and growth factor optimalization of general culturing conditions.

Dental hard tissue disorders (Line 3)

The aim of the dental hard tissue disorders research line is to contribute to the evidence base for the treatment of disorders of dental hard tissues, in particular caries and wear. The research addresses the diagnosis, prevention and restorative treatment of these disorders. There are three key aspects within this line:

1. **Caries, with an emphasis on secondary caries**
   Treating dental caries is still an important task of the general dental practitioner (GDP). Caries occurs at all ages, and may be seen to increase in the older populations, as they retain their teeth for longer and oral care becomes difficult in frail and dependent elderly. Once fillings are made, the tooth is not “protected” from new caries development. On the contrary, dental fillings or restorations may be prone to secondary caries: lesions developing at the outline of restorations. A substantial effort is put into repairing and replacing such restorations. Our research is aimed at analysing the contributing factors from the restorations and their interaction with the tooth tissues, in the development of secondary caries.

2. **Tooth wear, with an emphasis on erosive wear and managing severe wear**
   Increasing attention has recently been given to the problem of tooth wear. Erosive tooth wear especially is seen as a growing problem in a younger population group. But also the restorative management of severe tooth wear is being recognised as a field requiring research effort to provide an evidence base for treatment decision. Our research is aimed at exploring the aetiological factors involved in (erosive) tooth wear and evaluating preventive strategies, for the management of early wear. Also, we evaluate different aspects of restorative treatment (including the postponement of restorative treatment) for the management of severe tooth wear.

3. **Practice-based research & quality of care**
   Increasingly we realise that the important and relevant questions regarding the outcome of dental treatment cannot be answered by in vitro, in situ or even most commonly used in vivo studies, including randomised controlled trials. Evaluating the outcome of treatments in "real life" requires a follow-up of many years, even decades. We turn to practice based research to provide us with the long follow-up time and the large numbers of patients and treatments needed for answering such questions. This also gives us the opportunity to study quality of dental care in a broader sense, including aspects of safety and practice organisation.

While the first two aspects cover specific disorders, the last deals with research methodology and more general quality-related issues. The research line is based on a collaborative effort between the Departments of Preventive and Curative Dentistry, Oral Function and Global Oral Health.

The department of Global Oral Health is an independently functioning unit within the research line, concentrating on collaboration with universities around the world in developing countries, in order to provide academic capacity building, as well as doing research which helps to advance knowledge in public oral health issues by developing and testing new approaches. Research efforts include affordable and efficient dentistry techniques, school health promotion programs, various aspects of the Atraumatic Restorative Treatment approach and implementation, advocacy processes for Affordable Fluoride Toothpaste and training on other methods.

Grants

Etiology of dental & craniofacial phenotypes

Title of Grant
EOS grant: Etiological genetic and environmental / occupational risk factors of cleft lip and palate and oligodontia
EOS grant: Isolation and differentiation of satellite cells from craniofacial and limb muscles
KNAW-China-Exchange: Biological Aspects of Orthodontics and Craniofacial Anomalies
Technology Foundation STW (2009-2012): The third dimension of facial surgery and orthodontics (imaging, planning and evaluation)
Dutch Burns Foundation (2010-2013): Wound healing project I - Induction of cell-protective proteins as novel strategy against oxidative stress and inflammation-induced hypertrophic scar formation
Diabetes Foundation (2008-2011): Heme oxygenase as a novel target in the prevention of vascular complications in type 2 diabetes mellitus
ZonMW-AGIKO stipendium (2009-2013): Heme oxygenase: a novel pharmacological target in the treatment of sepsis

Wound healing around implants

Title of Grant
Technology Foundation STW (2006-2011): Nanostructured biomaterial Services
NWO-Smartmix (2007-2012): Translational Regenerative Medicine (TeRM)
NWO-SRON (2007-2012): Real-time investigation to the effects of multi-factorial mechanical stimuli on cell behavior
ITI-Foundation (2007-2011): Gene delivery for bone repair
Osteology Foundation (2008-2011): ALP enhanced guided tissue regeneration
KNAW-China Exchange (2008-2012): Gene therapy for bone regeneration
KNAW-PSA (2008-2013): Nanoscale materials for bone regeneration
IOP-Senter Novem (2008-2012): Self-healing composites for bone substitution
KNAW-China Exchange (2009-2013): Reconstruction of periodontal tissues by tissue engineering
Robert Mathys Foundation (2009-2012): Periodontal tissue regeneration using injectable calcium phosphate cement/ paste loaded with rhPDGF-BB and rhIGF-1
EC- Marie Curie (2009-2013):Training multidisciplinary scientists for Tissue Engineering and Regenerative Medicine
Biomedical Materials (BMM) (2010-2014): Bone-IP
IOP-Senter Novem (2010-2014): Development of self-healing gels based on stimulus-responsive crosslinking of bio-inspired, calcium-binding polymers
Netherlands Initiative Regenerative Medicine (NIRM) (2011-2015): Bioinspired materials
KNAW China Exchange (2011-2013): Multi-factorial mechanical stimuli on cell behavior
EC- Marie Curie (2011-2013): Molecular design of biologically inspired soft materials for hard tissue regeneration

Dental hard tissue disorders

Title of Grant
Borrow Foundation, UK (2006-2011): Fluoridated milk with and without sugar: its effect on caries progression or regression in enamel and dentine, and on the concentration of calcium and fluoride in plaque and its acidogenicity.
Europees Fonds voor Regionale Ontwikkeling (2008-2010): Oral Care Aopliance
Vereniging Frisdranken, Waters, Sappen. (2009 - 2011): Soft drinks and erosion.
National Institutes of Health (2010-2014): Biofilm composition and secondary caries in situ and in vivo
College voor Zorgverzekeringen (2011): Indicators for severe dental wear.
Duchenne Parents Project (2011-2012): Chewing ability in Duchenne patients.

People

Etiology of dental & craniofacial phenotypes

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Wound healing around implants

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For more information about our researchers and their activities please visit our Linkedin group *Dentistry*. Here you will find the C.V.'s and thought-provoking discussions of our faculty.

Dental hard tissue disorders

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Highlight on results of Imagination

Line 1
Etiology of dental & craniofacial phenotypes

Mignon Ackermans

Vitamin A and Cleft Palate

Nutrition Reviews 69(10),613–624.2011

Vitamin A and clefting: putative biological mechanisms.

Orofacial clefts are the most common craniofacial birth defects in humans. These disorders are caused by impaired fusion of one or more orofacial structures in the embryo. The Department of Orthodontics and Craniofacial Biology of the Radboud University Nijmegen Medical Centre studies genetic and environmental factors that are involved in the etiology of orofacial clefting. In the era of food fortification and dietary supplements, the maternal diet has become a popular research topic. Nutritional factors such as vitamin intake also contribute to the etiology of cleft palate. Vitamin A is a crucial regulator of embryonic development. Excess vitamin A can cause congenital malformations such as spina bifida and cleft palate. Therefore, preventive nutritional strategies are required to reduce the risk of these malformations. This review identifies putative biological mechanisms underlying the association between maternal vitamin A intake and cleft palate.

The secondary palate is formed between weeks 6 and 12 of human development. The inner parts of the maxillary processes develop bilateral shelf-like outgrowths that grow downward on either side of the developing tongue (Figure 1A). As palatogenesis progresses, the palatal shelves move upward and grow towards the midline. After contact, the opposing processes adhere and form a midline epithelial seam (Figures 1B and 1E). As soon as the midline epithelial seam disappears, the two shelves become confluent (Figures 1C and 1F). Fusion spreads from the middle third of the palate in anterior and posterior directions and is completed by week 12 of development. Subsequently, the ossified hard palate forms out of the anterior two-thirds of the palate, while the posterior one-third of the palate forms the soft palate (Figures 1D and 1G).

Animal studies show that excess vitamin A may disturb all three stages of palatogenesis (Figure 2): 1) during shelf outgrowth, it may decrease cell proliferation and thus prevent tissue development; 2) it may prevent shelf elevation by affecting extracellular matrix composition and hydration; and 3) during shelf fusion, it may affect epithelial differentiation and apoptosis, which precludes the formation of a continuous palate. In general, high doses of vitamin A affect palatogenesis through interference with cell proliferation, and growth factors such as transforming growth factor β and platelet-derived growth factor.

Epidemiological studies on nutritional exposure to vitamin A are scarce. Only a few studies clearly describe the dosage used and have an acceptable statistical power. In summary, these studies suggest a U-shaped dose-effect curve with harmful effects for vitamin A deficiency (≤375 µg), possible protective effects in the range of the recommended daily allowance (RDA) of 770 µg, and harmful effects at high doses (≥4,500 µg).
In the light of the limited number of available studies, the question remains whether slight nutritional overexposure to vitamin A contributes to clefting in humans. Theoretically, this might increase the risk of clefting in genetically predisposed individuals with specific polymorphisms of enzymes or other proteins involved in vitamin A metabolism. However, as for folate, such interactions have not yet been definitely established.

Future research should focus specifically on the effects of slight nutritional overexposure of vitamin A to improve the dietary recommendations to pregnant women or those who want to become pregnant, thereby reducing the risk of cleft palate in offspring.

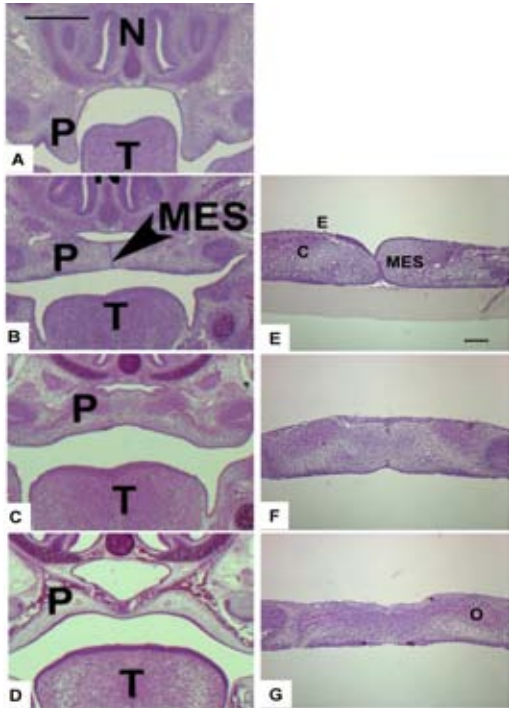


Figure 1 (A-G)
The secondary palate is formed between weeks 6 and 12 of human development. The inner parts of the maxillary processes develop bilateral shelf-like outgrowths that grow downward on either side of the developing tongue (Figure 1A). As palatogenesis progresses, the palatal shelves move upward and grow towards the midline. After contact, the opposing processes adhere and form a midline epithelial seam (Figures 1B and 1E). As soon as the midline epithelial seam disappears, the two shelves become confluent (Figures 1C and 1F). Fusion spreads from the middle third of the palate in anterior and posterior directions and is completed by week 12 of development. Subsequently, the ossified hard palate forms out of the anterior two-thirds of the palate, while the posterior one-third of the palate forms the soft palate (Figures 1D and 1G)

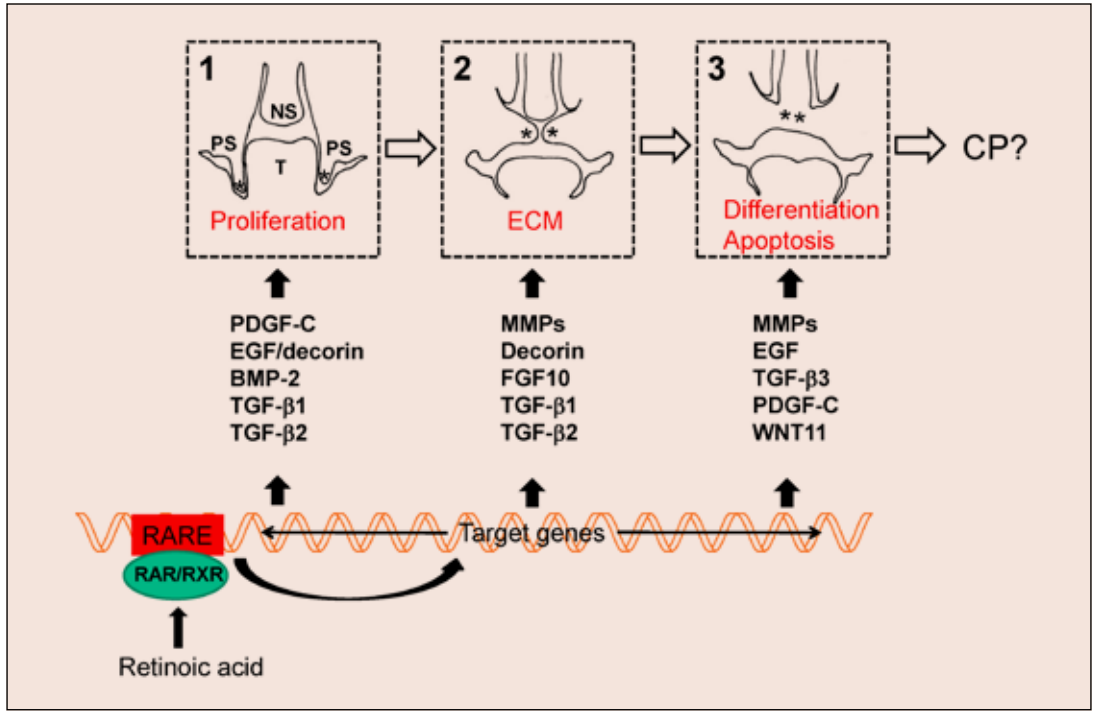


Figure 2
Animal studies show that excess vitamin A may disturb all three stages of palatogenesis (Figure 2):
1) during shelf outgrowth, it may decrease cell proliferation and thus prevent tissue development;
2) it may prevent shelf elevation by affecting extracellular matrix composition and hydration; and
3) during shelf fusion, it may affect epithelial differentiation and apoptosis, which precludes the formation of a continuous palate.

Rania Nada

Voxel based superimposition of cone beam computed tomography models on the anterior cranial base and the zygomatic arches

PLoS ONE 6(2): e16520. 2011

Superimposition of cone beam computed tomography models for three dimensional evaluation of treatment effects.

Three-dimensional digital records are becoming more and more popular among orthodontists and maxillofacial surgeons as the specialties progress towards a three dimensional (3D) virtual representation of the patient for diagnosis, treatment planning and simulation. Cone Beam Computed Tomography (CBCT) scans have been well established as a valuable tool in the orthodontist's and surgeon's 3D toolkit. A single scan not only provides an overlap-free 3D visualization of the skull but also allows detailed evaluation of the maxillofacial structures in thin axial, coronal and sagittal slices. Close comparison of radiographs taken before and after treatment, or in other words the superimposition of serial radiographs has been traditionally used for assessment of growth and treatment effects or stability over a certain time interval. Nowadays, superimposition of CBCT scans allows a three dimensional visualization of these effects.

In this study we tested the accuracy and reproducibility of the voxel based superimposition of CBCT scans registered on two different regions: the anterior cranial base and the left zygomatic arch (Figure 1). Voxel-based image registration is a recently developed semi-automated registration technique whereby CBCT scans are superimposed by comparing the grey values in a defined volume of interest in two scans to compute the rotation and translation required to align the two scans. We evaluated the accuracy of the superimpositions by calculating the mean absolute distances between the two models at four different anatomic regions: the anterior cranial base, the forehead, the left and the right zygomatic arches. The cranial base region was chosen to test alignment errors in the vertical direction, the forehead region for the antero-posterior direction, while the right and left zygomatic arches were chosen for the transverse direction (Figures 1 and 2).

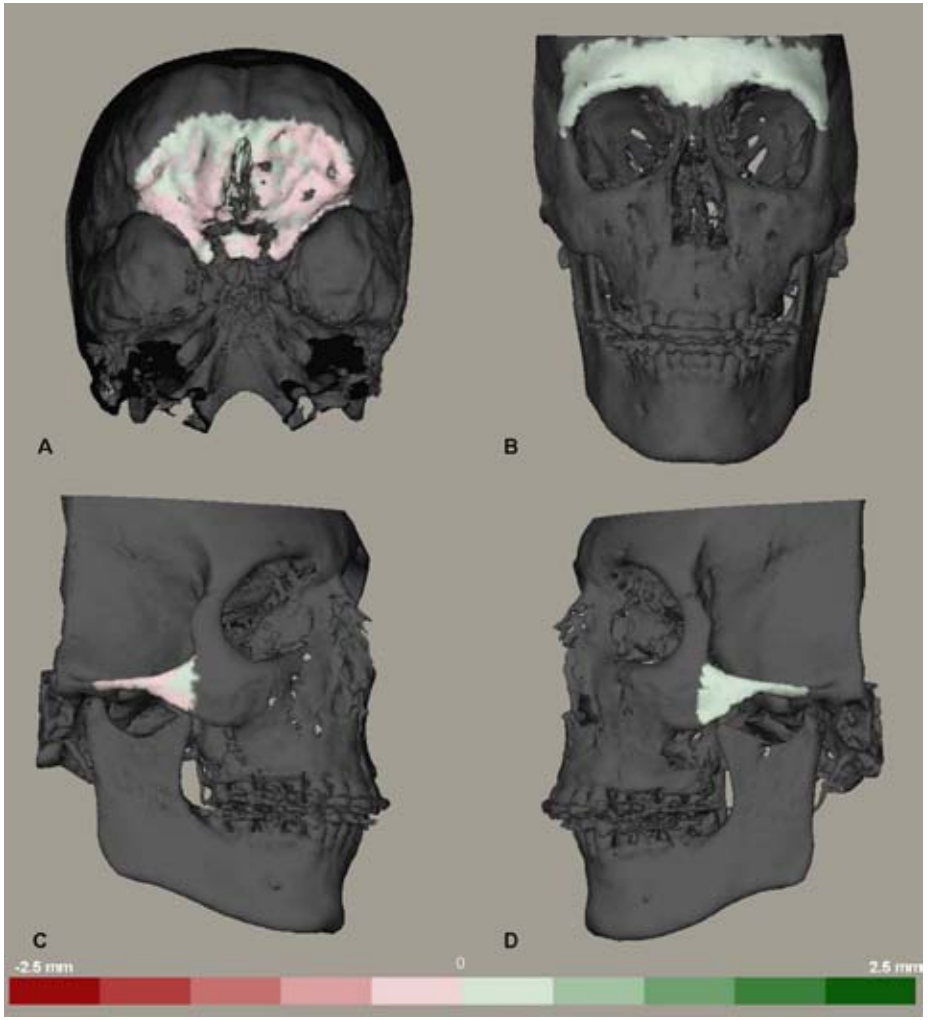


Figure 1
Distance maps to visualize the distances between two models registered on the anterior cranial base. Color coded distance maps to visualize the distances between two superimposed models registered on the anterior cranial base. The green color indicates that the superimposed model is in front of the original model and red color indicates the opposite. Each color graduation is 0.5 mm. (A) anterior cranial base. (B) the forehead region. (C) the right zygomatic arch. (D) the left zygomatic arch.

The zygomatic arches are clearly visible and easily isolated as a region of interest in CBCT scans. With the growing concern about the radiation dosage from CBCT scans, they could offer an added advantage as they are clearly visible in a scan with smaller field of view (FOV) or reduced scan height (13 cm) compared to the anterior cranial base which requires an extended field of view (22 cm). Smaller FOV examinations are associated with significant radiation dose reductions and less tissue radiation especially to the eyes. When the registration was performed on the left zygomatic arch, the distances between the two superimposed models were slightly larger at the anterior cranial base, the forehead and the right zygomatic arch but were smaller on the left zygomatic arch when compared to superimpositions registered on the anterior cranial base. The mean difference ranged between 0.12 to 0.19 mm. While these differences were found to be statistically significant they are too small to be considered clinically relevant.

Our results showed that voxel based image registration is an accurate and a reproducible semi-automated technique for superimposition of 3D CBCT models. This technique could be used as a accurate tool for 3D assessment of treatment outcome and documentation of treatment changes.

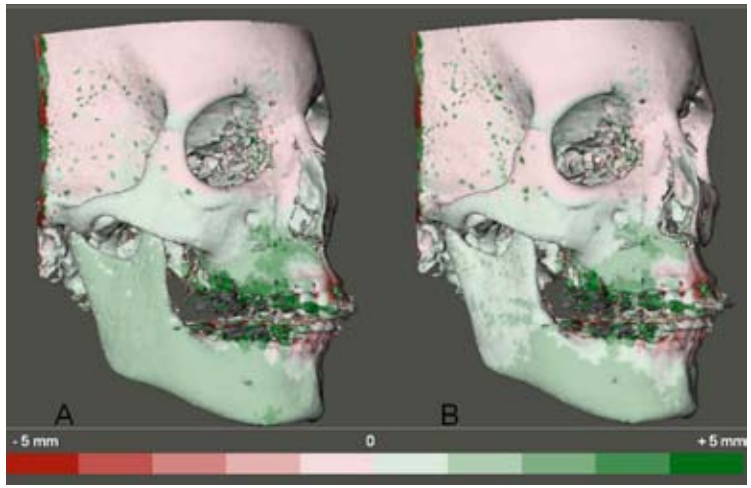


Figure 2
Color coded distance maps to visualize treatment changes following two CBCT scans superimposition. The green color indicates that the superimposed model is in front of the original model and red color indicates the opposite. Each color graduation is 1 mm. (A) models registered on the anterior cranial base. (B) same models registered on the left zygomatic arch.

Line 2
Wound healing around implants

Matilde Bongio

Biomimetic modification of synthetic hydrogels: in vitro evaluation of cell behavior

Eur Cell Mater. 2011 Dec 17;22:359-76

Biomimetic modification of synthetic hydrogels by incorporation of adhesive peptides and calcium phosphate nanoparticles: in vitro evaluation of cell behavior

Conventional treatment approaches for bone loss and injuries are limited by a significant donor-site morbidity. A promising regenerative medicine approach to address this issue is the development of injectable hydrogels as cell carrier systems that can sustain cellular activities and promote functional bone tissue recovery. The current study presents a combinatorial approach that integrates synthetic hydrogels consisting of oligo(poly(ethylene glycol)fumarate) (OPF) matrices, cell binding peptides, i.e. the three- amino acid peptide sequences RGD, and calcium phosphate (CaP) nanoparticles in the form of hydroxyapatite, as inorganic components of natural bone tissue. The biological performance of rat bone marrow derived osteoblast-like cells (OBLCs) encapsulated within these biomimetic hydrogels were assessed in vitro. We hypothesized that (i) RGD peptides affected cell spreading and hence cell viability, (ii) CaP nanoparticles stimulated OBLCs to mineralize their environment, and (iii) the combination of these two biomimetic cues increased the osteogenic capacity of cells encapsulated within these synthetic scaffolds even further.

Four groups were included in this study as outlined in Table 1. In brief, OBLCs (10 million/ml) were encapsulated in OPF hydrogels either modified with RGD (2μmol/ml), CaP nanocrystals or combinations thereof, and cultured in osteogenic medium. Cell survival, cell spreading, proliferation and mineralized matrix formation were determined via cell viability assay, histology (Von Kossa staining) and biochemical analyses for DNA, alkaline phosphatase and calcium content measurements, respectively.

Live/dead assay showed a 2-fold increase in cell viability in RGD-modified OPF compared to unmodified gels (87% ± 8 versus 41% ± 7) during the first days of culture (Figure 1). Nevertheless, cells failed to proliferate in any of the groups. ALP-activity measurements revealed a significant continuous increase for CaP-free gels until day 12 and a decline thereafter. In contrast, OBLCs encapsulated in CaP-enriched gels showed a minimal ALP-activity until day 12, and an increase thereafter. No significant change in calcium content for CaP-free gels was observed over the entire

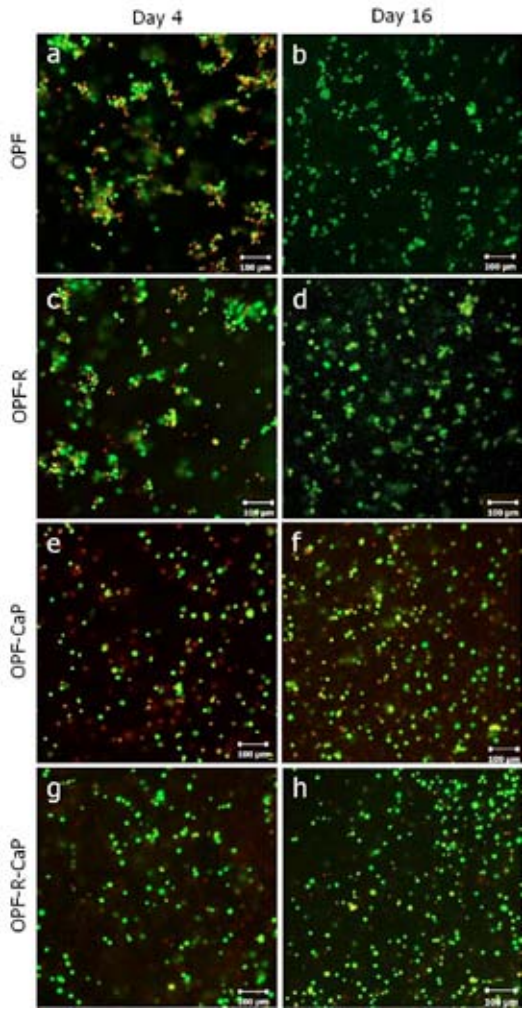


Figure 1.
Cell survival in OPF hydrogels 4 and 16 days after encapsulation by LIVE/DEAD assay. Confocal imaging was utilized to visualize the distribution of live cells in green and the nucleus of dead cells in red in (a,b) OPF, (c,d) OPF-R, (e,f) OPF-CaP, and (g,h) OPF-R-CaP, respectively. (Scale bar = 100μm).

Groups	Biomimetic cues: RGD	Biomimetic cues: CaP nanoparticles
1) OPF	-	-
2) OPF-R	+	-
3) OPF-CaP	-	+
4) OPF-R-CaP	+	+

Table 1.
Experimental groups included in this study

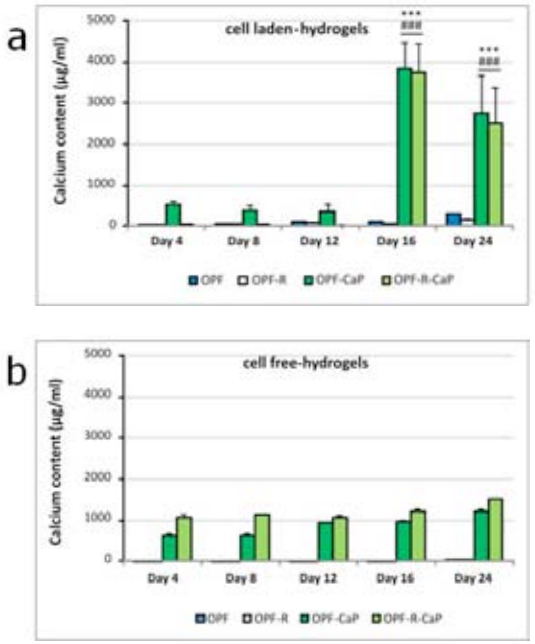


Figure 2.
*Calcium content per sample for OBLCs in (a) cell laden-hydrogels and (b) cell-free hydrogels at different time points of culture. ***p<0.001 relative to OPF hydrogels. ### p<0.001 relative to OPF-R hydrogels. Error bars represent means±standard deviation.*

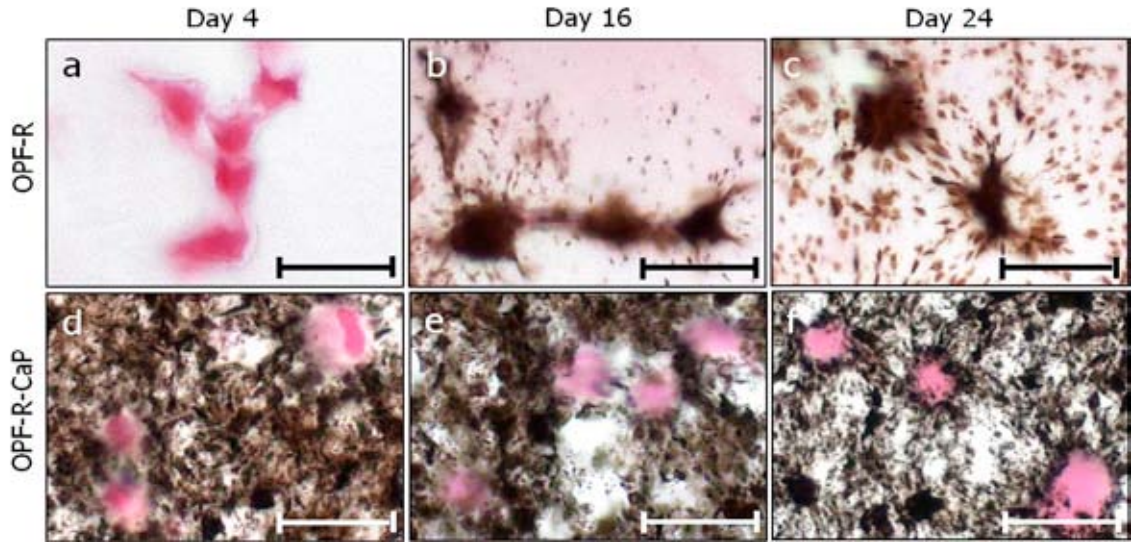


Figure 3.
Cell morphology analyzed with light microscopy of Von Kossa-stained paraffin sections of OBLCs encapsulated in OPF-R (a-c) and OPF-R-CaP (d-f) hydrogels at day 4, 16 and 24 of culture.

culture period, while a drastic increase in calcium deposition was observed for both CaP-enriched gels at late stages compared to the earlier time points and to the corresponding cell-free hydrogels (Figure 2). Cytological observation and roundness index measurement demonstrated cell morphological changes only in the presence of RGD peptides (Figure 3).

These results confirmed the role of RGD peptides to support cell spreading and viability within synthetic hydrogels, although cell proliferation was not observed in these groups. The remarkable increase of cell-mediated hydrogel mineralization in CaP-enriched hydrogels corroborated the potential role of CaP nanoparticles to enhance cell differentiation into the osteogenic lineage. More interestingly, RGD peptide and CaP nanoparticles together seemed to elicit a better biological response than that of the individual components, showing both sustained cell viability and mineralized matrix production mediated by encapsulated OBLCs.

The data presented in this study demonstrated the ability of OPF-CaP hydrogels to promote cell-mediated mineralization in vitro and hence their capability to provide a suitable microenvironment for mineralization. This stimulus for mineral nucleation by encapsulated cells within synthetic materials makes these novel hydrogel-based composites promising candidates for bone tissue engineering and regenerative medicine applications.

Huanan Wang

A bottom-up approach towards preparation of injectable gels for soft and hard tissue regeneration by exploiting attractive interactions between oppositely charged biopolymer nanoparticles

Adv Mater 2011;23(12):H119-24

Oppositely charged gelatin nanospheres as building blocks for injectable and biodegradable gels.

Current gel-based materials for regeneration of soft and hard tissues exhibit a poor capacity to present multiple signaling molecules at programmed time-points and release rates. Colloidal gels, on the other hand, have recently been identified as a promising “bottom-up” strategy for design of functional scaffolds by employing micro- or nanoscale particles as building blocks to assemble into shape-specific bulk materials. To this end, interparticle interactions such as electrostatic forces, magnetic forces, hydrophobic interactions and steric hindrance can be used to induce self-assembly of micro- or nanoparticles into integrated scaffolds. By incorporation of bioactive agents (e.g. enzymes, growth factors) into these particulate building blocks of variable biodegradability, injectable materials can be formed that offer a virtually unlimited degree of freedom with respect to programmed drug release of multiple biomolecules at predetermined release rates. So far, colloidal gels have been made of polymers functionalized with charged groups, but their lack of cell attachment sites and need for additional functionalization has compromised the biological performance of these gels.

On the contrary, gelatin is well-known for its excellent biocompatibility, controllable biodegradability and non-immunogenicity. Consequently, it has found widespread applications in various biomedical areas. Gelatin gels that can be injected at body temperature, however, are not available yet. Gelatin is a cheap product that is commercially available in both positive (gelatin A) and negative (gelatin B) charge without the necessity of additional functionalization. In the current study, injectable gelatin gels have been formed by using oppositely charged gelatin nanospheres as building blocks. Upon mixing of oppositely charged gelatin nanospheres, it was possible to form elastic and self-healing colloidal gels.

Dynamic light scattering was used to provide direct evidence for the formation of cohesive aggregates of several micrometers in size due to the attractive electrostatic interaction between oppositely charged gelatin nanospheres under diluted conditions. At higher solid contents, elastic gels were formed owing to electrostatic self-assembly between the nanospheres (see Figure 1). The shear-thinning behavior of the gels allowed injection through conventional medical syringes (see Figure 2), while gel elasticity was maintained at ionic strengths comparable to physiological fluids. Owing to their favorable clinical handling, ease of biomolecule loading and cost-effectiveness, these gels show great potential as injectable gels for tissue regeneration.

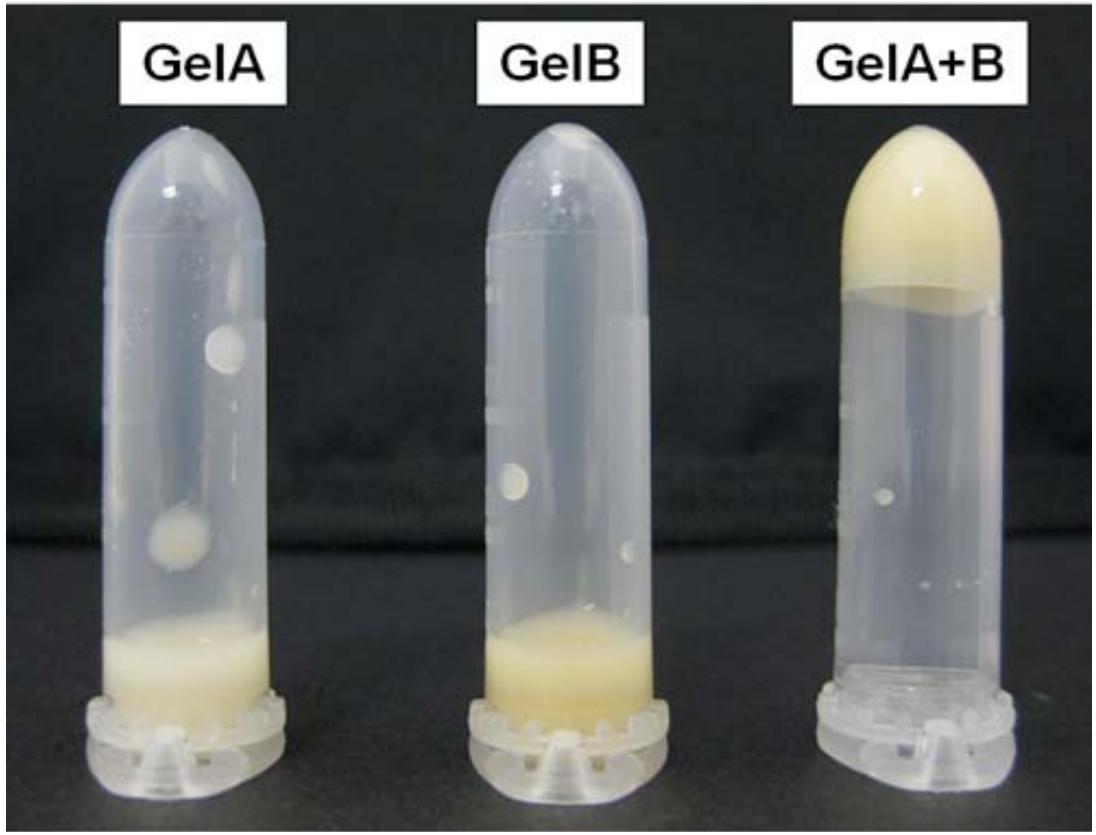


Figure 1:
Photographs of nanosphere dispersions (5 w/v% solid content) of oppositely charged (Gelatin A + B) and similarly charged (GelA or GelB) nanospheres after an inverted-vial test.

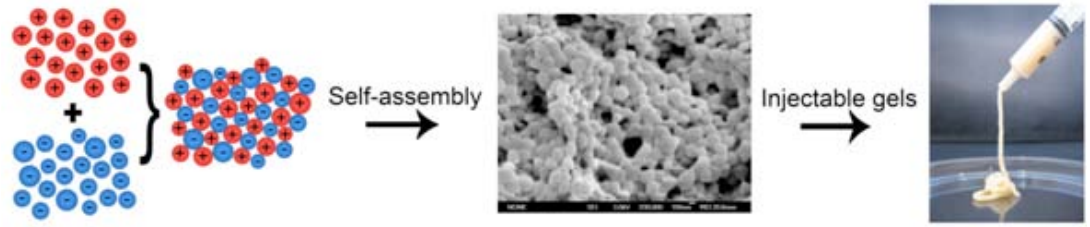


Figure 2:
Electrostatic interactions between oppositely charged gelatin nanospheres results into self-assembling colloidal gels that are elastic, cohesive and injectable through narrow syringes.

Line 3
Dental hard tissue disorders

Danielle Matos de Menezes Abreu

Pain related to dental treatment in children

Journal of Oral Sciences 2011; 119(2): 163-8

Pain experience after conventional, atraumatic, and ultraconservative restorative treatments in 6- to 7-yr-old children

Figure 1.
Children of the study

Pain and dental anxiety are potential distressing conditions that may make it difficult, or even preclude the performance of conventional restorative treatment, especially in paediatric dentistry. The use of burs and drills, and that of injection needles are often pointed out as the main reasons for manifestations of dental anxiety related to dental restorative treatment. The Atraumatic Restorative Treatment (ART), is considered to be less invasive than conventional restorative techniques for treating cavitated dentine carious lesions, as it uses only hand instruments to remove the soft decayed tooth tissues. The ART approach also brings a concept of being 'atraumatic' to the person having to undergo restorative dental care, in a way which could minimize the apprehension related to the use of burs and drills. Moreover, as local anaesthesia is hardly needed to perform ART restorations, pain related to administering an injection is also reduced. However, no clinical trial had been carried out to investigate the above mentioned observations from the field.

Figure 2.
Dental chair side assistant presented the Wong-Baker FACES Pain Rating Scale to the child after completion of the treatment. The child points to the score that reflected the level of pain she had experienced during treatment.

The present study is one of six that have investigated whether the use of the ART treatment protocol would lead to lower levels of pain and dental anxiety in children compared to the conventional restorative treatment protocol and an ultra-conservative treatment protocol. In the latter group, small cavities were treated using the ART approach and medium- and large-sized cavities were kept clean through tooth brushing/toothpaste. This treatment protocol is new and its effectiveness is topic of investigation in a parallel study.

The hypothesis, tested in the present study, was that children's pain level following the conventional restorative treatment is higher than for children treated using the atraumatic restorative treatment (ART) and an ultra-conservative treatment. The sample consisted of 244 children, aged 6-7-yr, from a socially deprived area of Brasilia, the Capital of Brasil (Figure 1). These children needed to have at least 2 teeth with dentine carious lesions in primary teeth for inclusion in the study. Before the first treatment session, in which one of the carious teeth was treated according to one of the treatments, the level of dental anxiety (FIS Tx-1) was assessed using the Facial Image Scale (FIS). The child reported the intensity of pain experienced during the procedure using the Wong-Baker FACES Pain Rating Scale (Wong-Baker), immediately after completion of the treatment (Figure 2). When conventional restorative treatment was used more children needed local anaesthesia administered. Analyses excluding the data of children that had local anaesthesia administered, showed no treatment group effect on the Wong-Baker score, a FIS Tx-1 effect on the Wong-Baker score and a statistically significant correlation between FIS Tx-1 and Wong-Baker scores. There was no significant difference in the pain levels of children treated in accordance with the conventional restorative treatment, the atraumatic restorative treatment and an ultra-conservative treatment. Local anaesthesia had to be administered more frequently in children from the conventional restorative group than in those from the other two treatment groups. These outcomes suggest that the use of ART should receive wider attention among dentists.

Rutger Sonneveld

BMC Health Services Research, 2011 Oct 11;11(1):263

The estimation of patients' views on organizational aspects of a general dental practice by general dental practitioners: a survey study

Considering the changes in dental healthcare, such as the increasing assertiveness of patients, the introduction of new dental professionals, and regulated competition, it becomes more important that general dental practitioners (GDPs) take patients' views into account. The aim of the study was to compare patients' views on organizational aspects of general dental practices with those of GDPs and with GDPs' estimation of patients' views.

Two survey studies were combined. In the first study, after a literature search, three focus group meetings, and a pilot test in a general dental practice, two questionnaires were developed: one for patients and one for GDPs. The questionnaires contained a list 41 organizational aspects of a general dental practice. A final question was added to document the 10 most important aspects (out of the 41). In the second survey study, a questionnaire was developed for GDPs based on the patient questionnaire in the first survey. GDPs estimated what percentage they thought the patient would give for each answering category. To avoid large time constraints, we decided to only ask the GDPs about the top 20 aspects mentioned by patients from the first study in the second study, as shown in Table 1.

In the first study, the questionnaire was sent to 5000 dental patients divided over 100 general dental practices, and 500 GDPs. In the second study, the questionnaire was sent to 400 GDPs.

For the analyses of the GDPs' estimation of patients' views, we categorized the findings as follows: (a) GDPs estimated the patients' views well and the patients' views were similar to those of the GDPs; (b) GDPs estimated the patients' views well, but the patients' views differed from those of the GDPs; (c) GDPs estimated the patients' views poorly, but the patients' views were the same as those of the GDPs; and (d) GDPs estimated the patients' views poorly and the patients' views differed from those of the GDPs. If an answering category of patients' views and GDPs' estimation of patients' views differed by more than 10%, we concluded the aspect to be answered differently. Table 1 shows that for 4 of the 20 aspects, patients and GDPs had the same views, and GDPs estimated patients' views reasonably well: 'Dutch-speaking GDP', 'guarantee on treatment', 'treatment by the same GDP', and 'reminder of routine oral examination'. For 2 aspects ('quality assessment' and 'accessibility for disabled

patients') patients and GDPs had the same views, although the GDPs underestimated the patients' views. Patients had higher views than GDPs for 7 aspects and lower views than GDPs for 8 aspects.

GDPs could use the results of this study in their general practice to organize the dental care more to meet the preferences of their patients. For policy makers, this information could be used for the development of guidelines. The outcomes show the aspects that will have consensus or reveal potentially conflicting areas of dental care. Looking at the aspect 'treatment by same GDP' it can be concluded that GDPs estimate the views of patients well, and the views of patients and GDPs do not differ. The implementation of a guideline on that aspect will experience little resistance.
On most aspects GDPs and patient had different views, except for social desirable aspects. Given the increasing assertiveness of patients, it is startling the GDP's estimated only half of the patients' views correctly. The findings of the study can assist GDPs in adapting their organizational services to meet more the preferences of their patients and in improving the communication towards patients.

Table 1.
Distribution (%) of the answers on the organizational aspects of a general dental practice given by patients, by GDPs' estimation of patients' views, and by GDPs

Rank (estimation)*	Aspect	Patients	GDPs' estimation	GDPs
1	**Accessibility by telephone**			
(d)	directly	5.1	10.5	2.0
	within 15 sec	20.6	25.7	32.9
	15–30 sec	30.1	37.0	36.5
	30–60 sec	28.9	18.2	21.3
	more than 60 sec	4.5	3.5	3.3
	does not matter	10.8	5.1	4.0
2	**Continuing education dentist**			
(d)	yes, 0–8 hours	5.4	7.9	4.3
	yes, 8–24 hours	17.5	19.1	29.8
	yes, 24–40 hours	10.6	22.0	21.2
	yes, more than 40	3.5	11.6	6.6
	yes, but any length is ok	62.4	36.8	37.7
	no	0.7	2.6	0.3

Rank (estimation)*	Aspect	Patients	GDPs' estimation	GDPs
3	**Dutch-speaking dentists**			
(a)	yes	97.7	91.3	98.7
	does not matter	2.2	7.3	1.0
	no	0.1	1.4	0.3
4	**In office waiting times**			
(d)	none	1.4	9.0	2.3
	1–5 min	18.5	28.1	22.2
	6–10 min	48.3	33.0	34.4
	11–15 min	25.5	19.9	31.5
	16–20 min	5.9	8.3	8.6
	more than 20 min	0.5	1.6	1.0
5	**Information about dental services***			
(b)	written	48.0	42.2	72.9
	internet	37.2	34.8	41.9
	oral	48.7	51.3	80.5
	does not matter	18.2	15.0	11.6
6.1	**Availability of appointments (waiting lists)**			
	routine oral examination			
(d)	directly	0.4	3.2	0.0
	same day	1.0	3.9	2.3
	within 2 days	4.4	6.9	1.3
	within 1–2 weeks	42.4	55.5	36.4
	within 2–4 week	40.7	24.5	52.3
	longer than 4 weeks	11.1	6.0	7.6
6.2	***broken tooth***			
(d)	directly	6.5	1.8	1.7
	same day	26.9	9.7	11.6
	within 2 days	33.7	47.6	51.3
	within 1–2 weeks	30.3	35.4	32.1
	within 2–4 week	1.7	4.8	3.3
	longer than 4 weeks	0.8	0.7	0.0

Rank (estimation)*	Aspect	Patients	GDPs' estimation	GDPs
6.3	***pain complaints***			
(b)	directly	18.4	23.0	14.2
	same day	61.3	60.4	78.5
	within 2 days	15.0	16.2	6.0
	within 1–2 weeks	3.7	0.4	0.3
	within 2–4 week	0.6	0.0	1.0
	longer than 4 weeks	1.0	0.0	0.0
7	**Guarantee****			
(a)	filling	61.4	63.5	64.4
	crown	80.4	72.9	69.3
	prosthesis	69.5	66.6	57.4
	does not matter	7.8	9.1	12.5
	no	2.2	3.4	16.5
8	**Quality assessment**			
(d)	once	2.9	11.7	4.5
	every 6 months	6.3	10.8	0.7
	every year	36.8	31.1	9.2
	every 2 years	47.7	30.6	45.2
	does not matter	4.5	14.0	21.6
	no	1.8	1.8	18.8
9	**Check-up of perishable goods**			
(d)	yes	97.0	82.4	83.8
	does not matter	2.5	13.3	8.9
	no	0.5	4.2	7.3
10	**Treatment by same dental therapist**			
(a)	by the same person	74.2	67.7	68.1
	by someone with the same education	8.9	14.3	4.4
	according to same treatment plan	10,5	10.0	21,8
	does not matter	5.5	5.1	3.4
	no	1.0	2.9	2.3

Rank (estimation)*	Aspect	Patients	GDPs' estimation	GDPs
11	**Specialties in dental practice**			
(b)	yes	41.1	37.9	22.3
	does not matter	40.0	42.8	29.9
	no	18.9	19.3	47.8
12	**Information on tasks of staff**			
(d)	yes	70.8	83.3	89.4
	does not matter	26.2	13.5	10.0
	no	3.0	3.2	0.7
13	**Working according to professional standards**			
(b)	yes	58.0	64.9	82.1
	what is a professional standard?	41.5	33.7	17.5
	no	0.6	1.4	0.3
14	**Information on dental bill****			
(b)	treatment	95.2	80.3	95.4
	date	76.4	73.3	96.0
	amount	85.9	85.0	96,7
	payment terms	47.9	48.3	91.4
	name dental professional	38.8	30.4	51.8
15	**Reminder of routine oral examination**			
(a)	yes	61.4	61.8	58.9
	does not matter	20,5	23,4	17.8
	no	18.1	14.8	23.2
16	**Opening hours in the evening and/or weekends**			
(d)	only in the evening	15.2	19.2	3.7
	only in the weekend	5.5	8.9	0.7
	evening and weekend	18.4	31.0	4.7
	does not matter	16.5	17.8	7.0
	no	44.4	23.1	84.0

Rank (estimation)*	Aspect	Patients	GDPs' estimation	GDPs
17	**Practice accessibility**			
(d)	less than 2 km	14.3	16.6	1.0
	2–5 km	39.9	28.7	11.3
	5–10 km	27.4	32.8	20.0
	more than 10 km	2.9	7.1	7.7
	does not matter	15.5	14.9	60.0
18	**Accessibility for disabled patients**			
(c)	yes	88.2	66.3	86.8
	does not matter	9.3	23.3	6.6
	no	2.5	10.4	6.6
19	**Parking spaces**			
(d)	does not matter	23.9	26.3	13.6
	1–2 places	23.0	32.3	51.5
	more than 3	53.1	41.4	34.9
20	**Working according protocols and guidelines**			
	yes, always	52.7	n/a	33.0
	yes, but diverge considered	29.4	n/a	60.3
	does not matter	3.8	n/a	2.0
	unfamiliar with protocols and guidelines	13.6	n/a	2.7
	no	0.6	n/a	2.0

* *Estimation: (a) GDPs estimated the patients' views well and the patients' views were similar to those of the GDPs; (b) GDPs estimated the patients' views well, but the patients' views differed from those of the GDPs; (c) GDPs estimated the patients' views poorly, but the patients' views were the same as those of the GDPs; and (d) GDPs estimated the patients' views poorly and the patients' views differed from those of the GDPs*

** *More answers are possible*

Spotlight on Grants

Diabetes Fonds

Heme oxygenase as a novel target in the prevention of vascular complications in type 2 diabetes mellitus

Frank Wagener/Paul Smits

Background

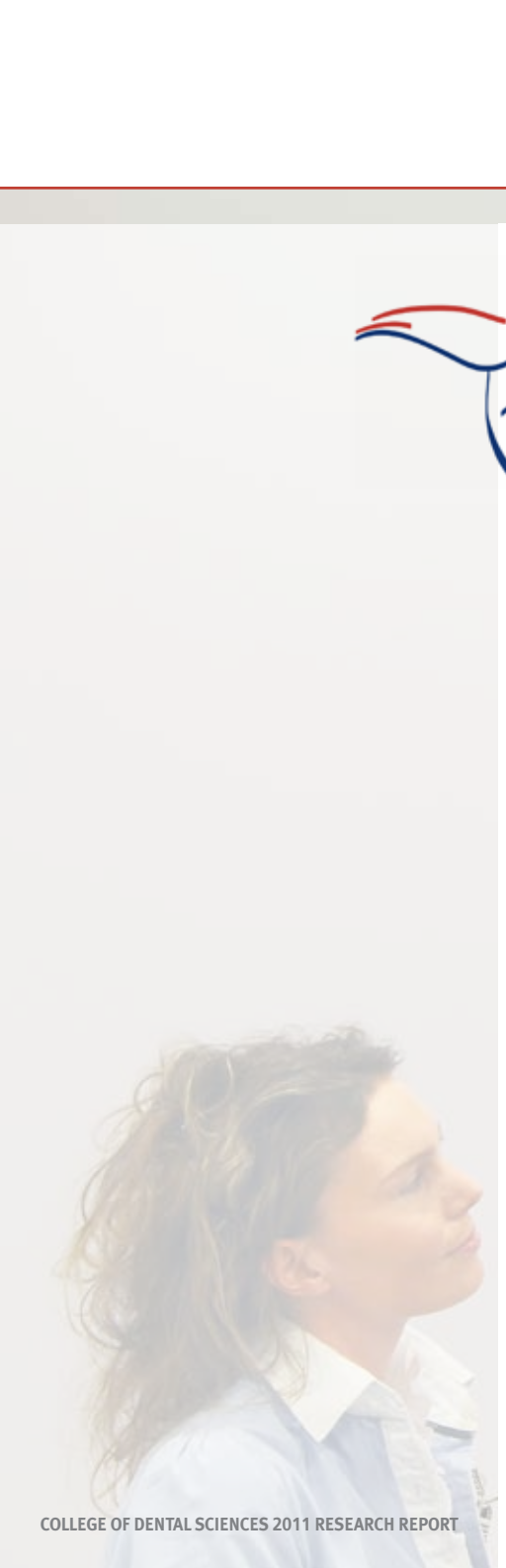
The prognosis of type 2 diabetes mellitus is largely determined by the development of micro- and macrovascular complications. In this project, we will investigate whether the enzyme Heme Oxygenase (HO) is a relevant molecular target for the prevention and treatment of the macrovascular complications. In type 2 diabetes, the production of radical oxygen species (ROS), the expression of inflammatory adhesion molecules and the resulting leukocyte binding and vascular injury have been attributed to the chronic state of hyperglycemia, dyslipidemia and elevated blood pressure.

Objective

One of the protective mechanisms is the activity of the enzyme HO, which breaks down heme into the strong anti-oxidants biliverdin/bilirubin and the potent vasodilator molecule carbon monoxide (CO). In general, the versatile HO-products strongly protect against these vascular insults by reducing oxidative stress, inflammation, proliferation and apoptosis. However, hyperglycemia itself has been observed to inhibit HO-activity, thereby impairing protective mechanisms against vascular dysfunction in type 2 diabetes.

Methods and Results

In an epidemiological study using a cohort of the Nijmegen Biomedical Study (NBS), we found that not only high bilirubin levels were associated with protection against vascular dysfunction, but also that low bilirubin levels form a risk factor for developing cardiovascular disease. However, despite the promising features of HO-1 induction and administration of its effector molecules, translation towards the human setting has been limited. In an attempt to translate the beneficial effects of HO-activity to the human setting, we used heme arginate, a well-known inducer of HO-1 in preclinical studies, as inducer of HO1 in metabolic syndrome patients and assessed its effects on vascular function and insulin sensitivity.



Unfortunately, heme arginate administration did not result in significant HO-1 induction in PBMC, did not increase serum bilirubin levels, and had no effect on vascular functioning. Heme arginate seems therefore not suitable for inducing HO-mediated cytoprotective effects in humans.
Interestingly, people with the syndrome of Gilbert have a polymorphism in the UGT1A1 promoter and are significantly better protected against cardiovascular complications. This polymorphism results in slower glucuronidation and therefore diminished excretion of bilirubin, leading to elevated bilirubin levels. As a next strategy, we wished to experimentally induce mild hyperbilirubinemia to mimic the positive effects seen with the Gilbert syndrome. Atazanavir, a HIV protease inhibitor, inhibits UGT1A1 activity, and has been demonstrated to result in hyperbilirubinemia. In a double-blind, placebo-controlled crossover design, we used this "hyperbilirubinemic side-effect" as a therapeutic to study the role of bilirubin on oxidative stress and inflammation-induced vascular dysfunction in type 2 diabetes mellitus patients. Indeed, we found significant amelioration of vascular function and an improved redox status following induction of mild hyperbilirubinemia in this clinical setting.

Conclusions

These results support a role for bilirubin as endogenous vascular regulator and stresses the potential power of bilirubin as novel medicine for inflammatory diseases. Although unlikely, it is possible that these observed protective effects are not mediated by bilirubin, but by atazanavir itself or other molecules that are influenced by hampered glucuronidation. In addition, the bilirubin level that offers maximum protection should be sought for. We are therefore currently investigating alternative means of hyperbilirubinemia by parenteral administration of bilirubin that was made suitable for human use. We have already been able to achieve reproducible mildly increased bilirubin levels following administration of bilirubin in volunteers. We hope that these exciting "first in human" data showing clinically significant protective effects of HO-effector molecules in humans strongly encourages more translational research towards the protective properties of HO and its effector molecules in diabetes mellitus.

What's next?

We recently applied for a follow up grant from the diabetes foundation entitled: "Heme oxygenase as a novel target in the prevention of diabetes-induced congenital anomalies and perinatal death"

Line 2 - *Wound healing around implants*

Netherlands Institute of Regenerative Medicine

Principal Investigator
NIRM research line 2 "Musculo-Skeletal Tissue/Disease", workpackage "Bioinspired materials"

Prof. John A. Jansen, DDS PhD
Dr. ir.Sander Leeuwenburgh, PhD

Partners
Nanomi, Feyecon, Encapson, Bender Analytical Holding, RUNMC, UMC Utrecht, UTwente, Wageningen University

Summary
The Netherlands Initiative for Regenerative Medicine (NIRM) is an innovative and integrative life sciences research and development program comprised of two strong BSIK consortia – Stem Cells in Development and Disease (SCDD) and the Dutch Program for Tissue Engineering (DPTE). NIRM was formed to 'Build' the scientific knowledge base and provide synergy in the advances from cutting-edge research in stem cell biology with advances in tissue engineering, so as to improve existing and create novel regenerative medical treatments. Together, these biomedical research fields involving cells and biomaterials will lead to innovative approaches to promote the regeneration of damaged or diseased tissues and organs.
NIRM research lines are organized by major tissue/disease areas. The five focus tissues are Cardiovascular, Musculo- Skeletal, Blood, Neuronal and Internal Medicine.

Within NIRM research line 2 "Musculo-Skeletal Tissue/Disease", workpackage "Bioinspired materials" is dedicated to development of novel instructive materials for regeneration of musculoskeletal tissues (i.e. bone, cartilage and meniscus tissue). To achieve this ambitious goal, academic and industrial partners have joint forces to develop novel polymeric materials of improved functionality that can be applied as injectable gels, pre-made scaffolds, membranes, glues, or particles.

College voor zorgverzekeringen

Development of indicators for care provision within the 'basic health insurance', in cases of severe dental wear.

CVZ, NL
Participating groups (both UMC St Radboud):
IQ healthcare: dr Mariëlle Ouwens, dr Mirjam Harmsen
College of Dental Sciences: dr Bas Loomans, prof dr Marie-Charlotte Huysmans

In clinical dentistry there is an increase in the prevalence of tooth wear. It is recognized that tooth wear has two main etiological causes: 1) erosion by chemical etching of the enamel and dentine by acids from either extrinsic, e.g., soft drinks, or intrinsic, gastric, sources, and 2) mechanical wear by grinding tooth contacts or food particles. Severe tooth wear may lead to functional problems, difficulty with chewing and pain during eating and speaking and esthetical problems, due to shortening of front teeth. Some patients have relatively a 'mild' tooth wear, but have severe functional problems (Fig. 1); on the contrary, some patients have a 'severe' tooth wear, but do not have any functional problems (Fig. 2).

Patients with severe generalized pathological tooth wear present a complex problem in dentistry and a challenge for the general dental practitioner. Loss of tooth tissue due to caries leads to lesion progression and cavities, which are usually restored with direct 'fillings', the most common dental restorative procedure. In tooth wear the outer surface of the tooth is lost, including the morphological and functional features. The restoration of the morphological form and function of the worn dentition is often highly complicated by the fact that these worn teeth are much shorter and smaller, which has resulted in a loss of vertical dimension of occlusion (VDO). Therefore, to restore form and function, an increase of vertical dimension of occlusion is necessary (the distance between the jaws has to be increased to provide space for the restorations).
To cover the cost of this treatment a special claim can be made on the 'basic health insurance'.

At this moment there is need to uniform and standardise the procedure to write an insurance application. Therefore, the aim of this study was to develop a set of diagnostic indicators, to score the severity of tooth wear and to determine the level of functional problems. This list can also be used by the dental examiner of the insurance company to test if a claim can be made on the 'basic health insurance'.

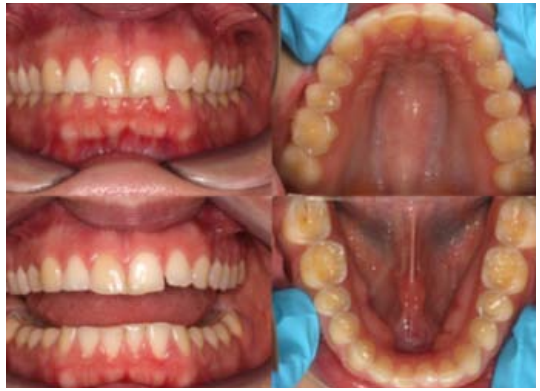


Figure 1.
Patient (31 years) with a 'mild' tooth wear, reflux disease and severe functional problems due to extreme sensitivity of all teeth.

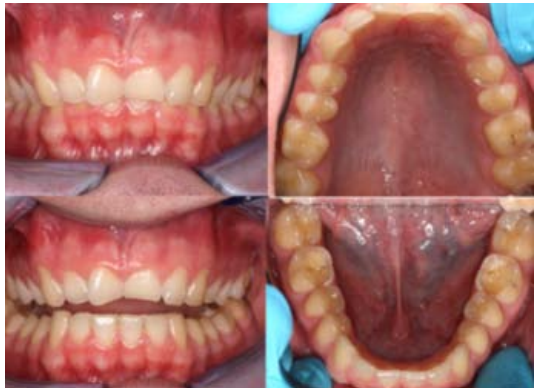


Figure 2.
Patient (27 years) with a 'severe' tooth wear, but who does not have any functional complaints.

List of papers
published in 2011

List of papers

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