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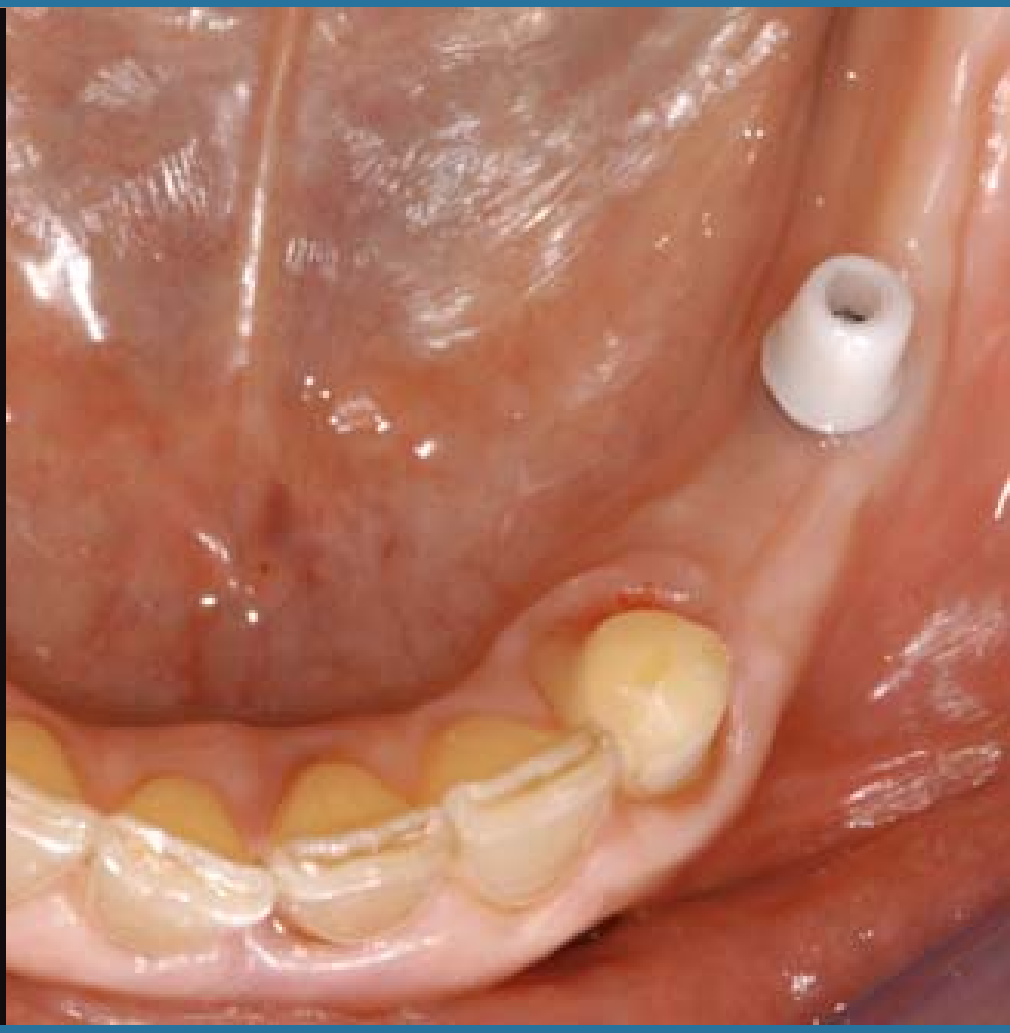

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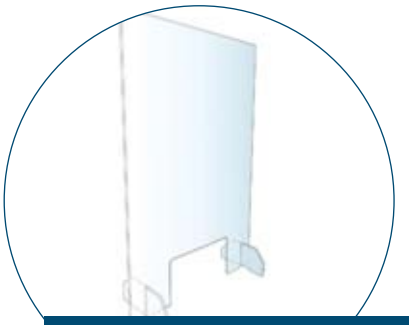

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"Once around the world ..." Unsolicited congress invitations via e-mail

For some years now, scientifically active people have been the recipients of e-mails that advertise for their participation in two-, three- and sometimes even four-day conferences. It is not uncommon for the recipients to be offered the opportunity to attend as speakers or chairpersons. Specialist literature on this topic can easily be overviewed, as it is rather limited [1–10, 13, 17, 18, 20, 21, 23–26, 29–35]. For most publications, short articles, such as editorials or letters to the editors, are involved. There are very few data-based analyses of this phenomenon [6, 27]. In the only article in the field of dentistry to date, the British periodontist Peter Heasman describes his experiences with the organizers of such meetings [17].

In order to get an overview of the extent of this nuisance from a dental point of view, the e-mails received at my address <jens.tuerp@unibas.ch> (including spam folder) between the 1st and 31st of January 2020 were collected and assessed.

Results

In the reporting period, 38 mails were received. These messages referred to 32 congresses which one should attend or at which one should hold presentations. The remaining 6 mails were inquiries ("we have contacted you before [...]").

The 32 events took place or are taking place in 23 cities which are attractive to tourists in 16 Asian, European and North American countries (Tab. 1).

Three out of four e-mails were not related to the subject (Table 2), i.e., only 8 of the conferences were related to dentistry (Table 3). Each of these events is organized by a different company.

The participation fees are high, as documented in Table 3 using the example of holding a lecture ("[academic] speaker registration").

Assessment

It is noticeable that most e-mails refer to conferences that have nothing to do with dentistry. Other authors reported similar findings [6, 27]. The dermatologists Jakhar and Kaur

Country	Number	City
Japan	5	Osaka (4), Tokyo
Italy	4	Rome (2), Milan, Venice
China	3	Dalian (2), Chengdu
Canada	3	Vancouver (2), Toronto
Spain	3	Barcelona (2), Valencia
Germany	2	Berlin
Portugal	2	Lisbon
USA	2	Dallas, Las Vegas
England	1	London
France	1	Paris
Greece	1	Thessaloniki
Malaysia	1	Kuala Lumpur
Poland	1	Cracow
Czech Republic	1	Prague
Singapore	1	Singapore
Thailand	1	Bangkok

Table 1 The 16 host countries and their respective cities, ranked by the number of conferences

Translation from German: Cristian Miron
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therefore rightly ask: "What will a dermatologist gain out of a petrochemical conference?" [18].

Offering conferences in popular cities seems to be a profitable business model for the organizers, despite the high fees they charge. According to its own statement, the website of Conference Series LLC Ltd[1], which is the largest organizer of such events and a subsidiary of OMICS Publishing Group[2], lists an impressive number of events held in Europe, Asia as well as North and South America. The titles of the congresses presented often contain adjectives such as "International," "World," and "Global."

Nevertheless, doubts seem to be justified with regards to the organizers. All 8 organizers of the dental conferences are on the "Questionable Conferences" list of the library of the renowned California Institute of Technology (Caltech Library)[3]. Among these is an Indian publishing group which was sentenced to a fine of over 50 million US dollars by the District Court in Nevada in April 2019 because "they made deceptive claims to academics and researchers about the nature of their conferences and publications, and hid steep publication fees" [14].

The investigative journalist (and medical layman) Peter Onneken has documented on film how such conferences take place [28]. He pretended to be the research director of a (non-existent) Cologne "Institute for Diet and Health." With a biography modified for this purpose and a bumpy, apparently unreviewed congress abstract ("The impact of Salvia hispanica L. enhanced nutrition on breast cancer prevention"[4]), he managed to easily give a "scientific" lecture at the "7th World Congress on Breast Cancer" in Frankfurt am Main in May 2018. In the film, you can see how Onneken prepares his presentation the evening before his lecture:

Conference Title
11th Neurotalk's Brain Health Conference
International Conference on Neurology & Neuro Disorders
International Conference on Alzheimer's Disease & Dementia
3rd International Conference on Addiction Therapy and Clinical Reports
International Conference on Emergency and Critical Care Medicine
World Congress on Geriatrics and Palliative Care
Orthopedics and Rheumatology World Forum
World Conference on Osteoarthritis and its Complications
World Congress on Pain Research & Management
39th Annual The European Society of Regional Anaesthesia & Pain Therapy (ESRA) Congress
World Congress on ENT
Global Congress on Nephrology & Urology
Preventive Medicine and Healthcare Congress
13th Annual World Cancer Congress
3rd Edition of Nursing & Healthcare
Nursing, Practice and Care
International Conference on Cell Science & Tissue Science
Association for Molecular Pathology (AMP) Europe 2020 Congress
11th Annual World DNA and Genome Day-2020
4th International Conference on Biological Information and Biomedical Engineering
8th Annual Conference of AnalytiX-2020
4th Global Summit on Nanotechnology
Nano Science and Technology-2020
Global Conference on Plastic Aesthetic and Reconstructive Surgery

Table 2 The titles of the 24 conferences unrelated to dentistry

1. www.conferenceseries.com (last access: April 6, 2020)
2. www.omicsgroup.org (last access: April 6, 2020)
3. Caltech: Open Access / Predatory Publishers / Questionable Conferences: Home. Last updated: April 3, 2020. https://libguides.caltech.edu/c.php?g=512665 (last access: April 6, 2020)
4. Abstract: www.omicsonline.org/conference-proceedings/1948–5956-C2–125–004.pdf (last access: April 6, 2020)

6th Global Summit and Expo on Dental and Oral Health	Cracow	Scientific Federation, India	March 23–24, 2020	$699 – $799 – $899 (early bird, standard, on spot registration)
3rd International Conference on Dentistry, Implantology and Oral Health	Berlin	Cientific Group, Singapore	March 18–19, 2020	$ 699
International Conference on Dentistry and Integrated Medicine	Osaka	Ology Mavens, Canada/India	April, 29–30, 2020	$699 – $799 – $899 (early bird, standard, on spot registration)
IDF-2020: Transforming the Face of Dentistry	Lisbon	Innovinc Intcon Pvt Ltd, India	June 15–17, 2020	$699 – $799 – $899 (early bird, mid-on, final registration)
Global Conference on Clinical Dentistry and Oral Health	Dallas	Moraft Corporation, USA	June 11–12, 2020	$599 – $699 – $799 (early bird, standard, event day)
International Congress on Clinical Dentistry and Practice	Vancouver	Peers Alley Media, Canada	July 20–21, 2020	$599 – $699 – $799 (early bird, standard, event day)
Annual Congress on Oral Care & Dentistry	Tokyo	Conference Series LLC LTD (OMICS Publishing Group) India	September 16–17, 2020	$650 – $740 – $830 (early bird, standard, final call)
World Congress on Dentistry and Oral Health	Singapore	Axiomatic Conferences, England	March 25–26, 2021	$799 – $899 – $999 (early bird, standard, on spot)

Table 3 The 8 dental conferences with their respective title, city, organizer, date, and cost of the event

"I'm something like the headliner for day two. I am giving the opening speech. I'm speaking on the role of Salvia hispanica in breast cancer prevention. Now I'm copying Wikipedia."

Shortly before his presentation he goes on to record:

"And now I have to see how far I can go with my copy-paste speech, which I made last night."

And he continues:

"Now it's the time to keep my cool. And then I'll just read from Wikipedia. Word for word. More bad than good. Nobody says anything. And the rest of my speech is also generalizations. Or a copied-together article. The congress participants seem to find it normal. I did it! And the professor even has praise for me."

For his research, Onneken was awarded the journalist prize "Evidence-Based Medicine in Media" from the German Network for Evidence-Based Medicine (DNEbM) in 2019.

Similar reports from participants of such conferences can be found on the Internet [12, 16, 22].

However, this does not mean that the presentations at these events are without exception of poor quality, although Eduardo Franco (McGill University, Montreal) noted [16]:

"Some of our junior faculty and respected senior professors attended these conferences because they thought they were in bone fide, but once they got there, they realized how small and Mickey Mouse they were."

Conclusions

The available evidence suggests that the organizers of such "congresses" are not concerned with scientifically acceptable content or scientific exchange, but with profit maximization: "Predatory conferences are thought to primarily seek profits, in a pay-to-play model where researchers give money to speak at the event. Consequently, predatory conference organizers may have little concern for the quality or rigor of the abstracts they accept or the speakers they invite" [6].

"Like predatory journals, predatory conferences may undermine our science and clinical practice through the dissemination of questionable information or presentation to an inappropriate audience."

Annette M. Bourgault, editor of the magazine "CriticalCareNurse" [4]

The following tips offer a good indication of whether or not a conference is a predatory conference. Not all points will necessarily be relevant to the conference in question; what decisive is is the overall impression.
1. You have never heard of this conference.
2. You are invited to the conference via e-mail, possibly even to hold the keynote lecture.
3. Neither you nor anyone in your field has ever attended the conference.
4. Searching online for "predatory conference <conference name>" or "predatory conference <organizer>" results in hits and reviews.
5. The conference website on the Internet looks unprofessional; important information is not provided.
6. The fees given deviate substantially from the average; they are often well hidden.
7. The title of the conference is extremely vague.
8. The program details of the conference have no clear structureor are incomplete.
9. A beautiful conference setting is adverised (sometimes holiday destinations or cruise ships).
10. Prominent figures, for example Nobel Prize Laureates, are listed in advertissements.
11. The conference is backed by a multitude of particularly renowned sponsors, often with no relation to the conference topic.
12. There is the promise of extrtemely fast acceptance processes for the conference contributions or abstracts.
13. There are no clear information on the peer review process or on the publication of conference contributions.
14. Publications resulting from the conference in previous years cannot be found in any of the usual scientific sources.

Table 4 Checklist "Predatory Conferences" of the Jülich Research Center [15]
(Courtesy of Jülich Research Center()

Striking features which typically recur in connection with such events include (besides the characteristics listed in Table 4) (cf. [3, 6, 8, 24, 29]:

- invitation to a conference in a different field
- markedly polite, flattering letters ("a celebrated leader in the field")
- offer to appear as a speaker, keynote speaker and/or member of the organizing committee (without the usual waiver of participation fees for legitimate congresses)
- striking similarity of the conference titles with those of scientifically honest conferences
- conference organization by companies without reference to or participation of professional societies or universities
- the use of names and photographs of scientists on the website to promote the conference without their permission or knowledge
- hardly any information about the members of the congress committee
- no direct contact persons listed on the website
- linguistically incorrect texts in e-mails and/or on the website
- minimal or inexact information about the congress program
- no information about the exact venue in the city in question (usually a hotel)
- high participation fees (some of which are not fully disclosed until after participation has been confirmed)
- unusually rapid acceptance of conference abstracts, regardless of their quality
- obvious lack of qualitative appraisal of the submitted texts
- inadequate on-site organization
- announcement of speakers, but their lack of appearance
- low number of participants
- participants who only appear for a short time and disappear relatively quickly
- largely unknown speakers
- unusually broad, sometimes multidisciplinary range of lecture topics
- parallel congresses on different topics at the same location[5]
- merging of conferences from different fields, which take place simultaneously in the same location, into a single event

Bogus conference
Dubious conference
Fake conference
Flaky conference
Fraudulent conference
Hijacked conference
Predatory conference
Sham conference
Sketchy conference
Questionable conference
Vanity conference

Table 5 English terms for questionable conferences ("fake conferences")
(Tab. 1–3 and Tab. 5: Türp)

- excessive awarding of "awards"
- no refund of congress fees in case of cancellation of participation or cancellation of the event
- publication of conference contribution without the speakers' permission and knowledge

"I strongly recommend that all researchers and clinicians from all countries avoid these meetings."

Peter A. Heasman, Professor Emeritus of Periodontology, School of Dental Sciences, Newcastle upon Tyne, England [17].

The common English terms used to characterize such events are summarized in Table 5. In German one speaks of "Scheinkonferenzen" or "Raubkonferenzen".

Recommendation

Participation at these conferences, or more precisely, at these commercially-oriented fake meetings with seminar character, can negatively influence one's scientific career [4]. Education is therefore necessary [19], particularly because the Internet does not forget anything [11]. In addition to the suggestions given under "Conclusions," the "Checklist Predatory Conferences" [15] published by the Jülich Research Center can serve as an aid in order to identify shady, profit-driven events in advance (Table 4) and thus prevent the waste of money, time, and reputation.

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(Photo: J. C. Türp)

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Healthcare avoidance – A phenomenon in (dental) medical care

Introduction

A considerable proportion of the population avoids healthcare [8, 14, 16], even when people may be aware of the need for treatment [17]. This well-known problem applies to dentistry as well, as about 7–10 % of the total German population avoids visiting the dentist [5].

The research field of "Healthcare Avoidance" (HCA) deals with the problem of patient avoidance or delay of examinations or treatments. HCA is an interdisciplinary field of research involving medicine, social science and psychology, in which the causes of avoidance behavior, the early identification of risk patients and possible concepts for improving the current situation are examined.

The following text presents an overview of literature relating to this phenomenon.

Statement

A review of literature shows that the topic of HCA has been much more frequently investigated in general medical subjects than in dentistry. There is a large number of available studies that explore the causes of HCA, yet research which deals with approaches to solving the problem of HCA is still relatively rare. Due to the high number of factors related to HCA and the associated difficulty in identifying affected patients or groups, research related to attaining a concept for early identification is crucial.

Qualitative interviews are often used to determine the reasons of physician avoidance. The most commonly used variant is the semi-structured interview; in this case, the areas to be investigated are defined on the basis of key questions, yet the interviewer or respondent can still elaborate on topics or thoughts [6]. Questions regarding physician avoidance are also often part of large-scale studies, such as the Health Information National Trends Survey (HINTS) in the USA, which can serve as a foundation for other investigations [8, 12, 16, 17]. The 5th German Oral Health Study (DMS V) also examines the oral health attitudes and behaviors of German citizens [7]. The aim of the investigations is to create a scheme which facilitates the identification of affected patient groups and individuals in order to reveal areas in healthcare that need improvement.

Studies in general medicine

A large number of studies on discipline-specific diseases highlight the problem of HCA. The problem of HCA was emphasized in the study performed by the research group Moser and Kimble et al. (2006) on the topic of delayed treatment of patients with acute coronary syndrome, on the one hand, and acute stroke on the other; they point out the importance of social, cognitive and emotional factors in both cases, which can only be ascertained by means of interviews or questionnaires, thus making it rather challenging to collect and classify data [10].

In a meta-study, Bish et al. (2005) investigated the reasons for the delayed presentation of women with breast cancer and found that higher age, the type of symptoms, lack of trust in the family physician and fear of cancer treatment led to delays [3]. A study by Rogers et al. (2011) showed that patients with oropharyngeal carcinomas usually presented themselves late to the physician due to their lack of awareness of the associated clinical symptoms; in this case, going to the doctor or dentist was perceived less of a barrier by the patients [13]. Persoskie et al. (2013) also demonstrated a strong emotional factor by linking the fear of cancer and the self-assessed risk of cancer with doctor avoidance. Interestingly, the combination of existing fear and increased cancer risk was found to lead to increased avoidance of medical treatment for respondents aged 50 years and older [12].

These examples illustrate the high variety of reasons for avoiding doctors in relation to each specific general medical discipline. In the USA, regional differences were presented by Spleen et al. (2014). The researchers reported an increased incidence of physician avoidance among participants of the male sex, of younger age, having no health insurance, having little trust in their general family physician or having no general physician at all as well as among the rural population [16]. Similarly, Ohl et al. (2010) found a correlation between rural popu-

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lations and a delayed onset of treatment, which consequently resulted in an increased mortality rate among HIV patients [11]. By interviewing 4162 patients aged 65 and older, Rupper et al. (2004) investigated whether or not self-disclosure with regard to delayed healthcare treatment due to doctor avoidance is a general predictor of an increased mortality rate; no correlation between doctor avoidance and increased mortality could be determined [14].

Dental studies

Research in dentistry mainly focuses on dental anxiety, which is an important aspect that possibly leads to dental treatment avoidance and the associated problems in healthcare.

In this field, Armfield et al. (2015) showed that two thirds of all respondents with a pronounced fear of dental treatment tend to delay visits to the dentist [1]. According to a study by Enkling et al. (2006), younger people are more often affected by dental anxiety than older people, and women more often than men. The reasons for anxiety are painful experiences during treatment and fear of needles in 67 % and 35 % of cases, respectively [5]. Berggren et al. (1993) addressed this topic early on after finding a direct link between pronounced dental anxiety and dental care avoidance and poorer oral health; in their investigation, they reported social and emotional effects on affected patients and found that the majority of these patients reported negative effects on social life, including loneliness and social isolation [2].

A correlation between parental dental care avoidance behavior and an increased caries prevalence in 5-year-old children was found by Wigen et al. (2009). They showed that children who were not regularly taken to the dentist by their parents were more likely to develop carious lesions [18].

McGrath et al. (2007) demonstrated a significant influence of socioeconomic status on the neglect of oral health [9]. Similarly, the DMS V (Jordan et al., 2016) also found that, in a group of younger adults (35 to 44-year-olds), those with a low social status tended to visit the dentist irregularly and mainly in a manner which was complaint-oriented; conversely, patients with a high social status tended to visit the dentist in a prevention-oriented manner [7].

Concept developments

In order to determine an interdisciplinary categorization for patients who avoid visits to the doctor, Taber et al. (2014) conducted a study with 1369 participants in which 3 main categories were identified: 33.3 % of the respondents mentioned that they were late to visit the doctor because of "unfavorable evaluations of seeking medical care", which included factors such as the trustworthiness and expertise of the doctor, long waiting times and communication problems; 12.2 % of respondents reported a low perceived need to see a physician because they underestimated symptoms for instance, while 58.4 % reported "traditional barriers to medical care" such as high costs, no health insurance and time constraints as reasons for avoiding the physician. Limitations of this study are seen as the lack of question "depth" in relation to medical treatments, fear of serious illness and the association of doctors with death. Further limitations were seen in the demographic distribution of the respondents [17].

The team of Kannan et al. (2014) used a classification scheme based on 8 reasons to which 81 % of all physician avoiders can be assigned: Fear of serious illnesses (34 %), discomfort during physical examinations (33 %), costs (19 %), time constraints (16 %), thoughts of death (13 %), lack of sympathy or trust towards doctors (8 %), fear of treatments involving medication (3 %) or the preference for self-treatment or alternative medical treatments (3 %). The authors described different possible interventions that could help to reduce the frequency of doctor avoidance. Firstly, health-conscious behavior should be encouraged. Information which tries to reduce the fear of examinations, treatments and diagnoses could aid in increasing patient motivation; this information should be individualized so as to be relevant to the motivations of different groups of people. Also, it is recommended that more educational work should be done to eliminate misconceptions such as the idea that obesity is exclusively genetically determined.

Kannan et al. also proposed media and communication campaigns that portray the desired patient behavior. Another possibility could be the introduction of the concept of a proactive attitude on the part of the patient, in which the patient actively and committedly engages himself/herself for his/her health. Another important intervention according to the authors involves the closer cooperation between doctors and insurers on the one hand, and between doctors and patients on the other. In this way, more patient compliance, understanding and satisfaction could be ensured [8].

According to Enkling et al. (2006), people surveyed in the field of dentistry stated that they wished for detailed communication with regards to treatment, a sensitive dentist and painless treatment [5].

One possible strategy that was developed by Skaret et al. (2003) and was presented as being very promising involves the use of a questionnaire, followed by a motivational telephone interview, in order to reduce dental treatment avoidance [15].

Summary

Healthcare avoidance is a widespread, multidisciplinary problem in health care which is linked to the doctor-patient relationship as well as administrative, demographic and personal factors such as distrust of doctors and/or science, health beliefs, insurance status or socioeconomic status [4]. Methods which can identify patients or groups at risk allow for a more accurate representation of the complex motivations behind HCA. It has been shown in many specialist areas that personal factors, particularly, play a major role in avoidance behavior. In order to adequately determine these factors, a standardized concept that can be applied in ideally both, general and dental practice, would be desirable so that patients at

risk can be identified and appropriate therapeutic measures can be taken. In dentistry, there are already studies on the handling of anxiety patients; however, the development of a concept which is applicable to other aspects relating to HCA is still pending. Communication strategies, such as intensive doctor-patient communication, appear to be particularly important in addressing avoidance behavior and increasing patient compliance.

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Hanoverian prevention concept to improve (self-responsible) home-based oral hygiene

Caries and periodontitis are biofilm associated diseases with multifactorial causes. In addition to regular visits to the dentist and dietary control, the efficient removal of oral biofilm plays a major role in the prevention of these diseases. The removal of biofilm should not only be the concern of the dental professional, but rather that of the patient who should routinely employ home-based oral hygiene measures [10]. Therefore, self-responsible, home-based oral hygiene is an important pillar for maintaining oral health.

The awareness with regard to oral health of the German population has increased significantly in recent years. In the Fifth German Oral Health Study (DMS V), depending on the age group, between 70–85 % of the survey respondents were convinced that they could contribute "very much" or "much" to maintaining or improving their oral health [23]. Thus, patients are certainly aware of the fact that plaque/biofilm removal as part of self-responsible, home-based oral hygiene is of great importance in the prevention of caries and periodontitis. Especially in the age group of young seniors (65 to 74-year-olds), a significantly increased awareness of their own oral health was observed in DMS V [23]. However, DMS V also shows that a relatively large number of patients are still affected by caries (particularly root and crown margin caries) and inflammatory periodontal disease. Nowadays, successful prevention concepts combined with advances in the field of restorative dentistry have made it possible to preserve natural teeth for much longer or even until the end of life [26]. Hence, there is a clear trend towards "tooth preservation in old age" (significant reduction in tooth loss) [23]. However, the longer that teeth are preserved, the more they are exposed to the risk of periodontitis or caries. The causes of increased susceptibility to root or crown margin caries in older people is multifactorial (e.g. increased proportion of exposed root surfaces or crown margins, extensive prosthetic restorations, insufficient removal of plaque, reduced salivation [caused by medication], previous periodontal therapies) [1, 7, 20, 29].

In relation to periodontal health, DMS V shows that 75.4 % of younger seniors (65 to 74-year-olds) suffer from moderately severe (one in two; 50.8 %) or severe periodontitis (one in four; 24.6 %) and that 80.6 % of older seniors (75 to 100-year-olds) suffer from moderately severe (one in two; 50.5 %) or severe periodontitis (one in three; 30.1 %), thus suggesting that periodontitis is still widespread [23]. Given that periodontitis increases with age, the demographic trend implies that the need for treatment should be expected to increase in the future.

Meanwhile, ample evidence from epidemiological, clinical and experimental studies has suggested that periodontal infections are not only influenced by systemic factors, but that they themselves can also exert systemic effects [24]. Oral health, which can be defined as the unrestricted functionality and symptom free from inflammation and discomfort, is an important component of general health together with a healthy diet and it has a close link to the quality of life [8, 36]. The saying "health begins in the mouth" is indeed true when a well functioning and well maintained masticatory system is present. The effectiveness of a good home-based oral hygiene combined with regular prophylactic visits to the dental professional for the prevention of caries and periodontitis has been proven in studies [2, 6]. The sole removal of biofilm by qualified dental personnel in the context of professional tooth cleaning is not sufficient for the prevention of caries and periodontitis. Rather, it should be regarded as an individual prophylactic component in a more comprehensive prophylaxis concept [38]. In addition to needs-based plaque removal, a thorough prophylaxis concept should also focus on teaching practical skills for optimal home-based oral hygiene, as well as, foster

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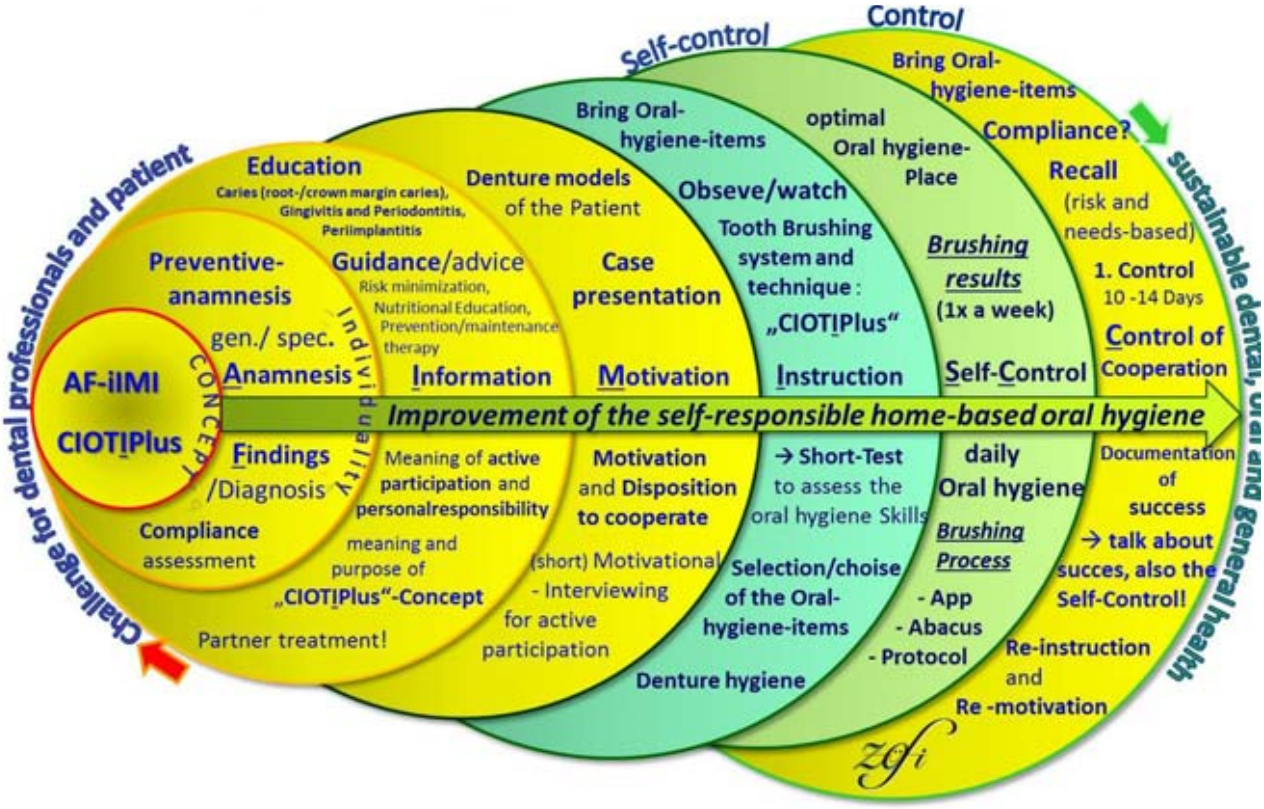


Figure 1 Hanoverian prevention concept to improve self-responsible, home-based dental and oral hygiene

health-promoting and health-preserving behavior patterns through education, instruction and motivation [30].

At the Clinic for Conservative Dentistry, Periodontology and Preventive Dentistry in Hannover, we have developed a practicable prophylaxis concept which consists of different interlinking and overlapping components: "anamnesis and findings – individual information, motivation and instruction (**AF-iIMI**)", "the **CIOTIPlus** tooth brushing system and technique", "**self-control of oral hygiene**" and "**compliance assessment**" (Fig. 1). The effectiveness of each individual component has already been investigated and confirmed in several studies and pilot projects [13–18, 25]. The combination and integration of each component into an overall concept should lead to an improvement in self-responsible, home-based oral hygiene and oral hygiene self-control, specially in risk groups, hence ensuring sustainable dental, oral and general health. Each components of the Hanoverian prevention concept are presented below.

Components of the Hanoverian prevention concept

AF-iIMI (**a**namnesis, **f**indings, **i**ndividual **i**nformation, **m**otivation and **i**nstruction) is the main component of the prophylaxis concept. However, it should not only be understood as pure oral hygiene training.

A

In the beginning, a general, specific and prevention **anamnesis** (including dietary anamnesis) is recorded. On the one hand, this allows conclusions to be drawn regarding compliance (health awareness and behavior, individual significance of oral hygiene, motivation for change), while on the other hand, it also provides clues as to whether interdisciplinary cooperation is needed as part of **o**ral **h**ealth **c**are **p**romotion **i**nterdisciplinary (OHCP-i) (e.g. cooperation with diabetologists, general physicians, family physicians).

F

After this, in order to evaluate the risk, determine the need for treatment and establish the current level of oral hygiene, oral (tooth, implant, periodontal, peri-implant and mucosa) **findings** and quantitative plaque indices for the smooth and proximal surfaces of teeth are collected. The degree of gingival inflammation is checked using the index "Bleeding on Probing" (BoP) and the need for periodontal treatment is determined using the "Periodontal Screening Index" (PSI). The *bleeding* and *plaque indices* are suitable for quantifying and monitoring the current *oral hygiene status* of the patient. For better visualization, plaque staining agents are applied to make plaque visible for the patient, while keeping in mind to differentiate between "old" and "new" plaque. The results of a plaque index, where only a yes or no decision is made with regard to the presence of plaque, is often less suitable for motivating the patient than an index that assesses plaque quantitatively (e.g. Quigley-Hein-Index – QHI). Hardly any patient is able to achieve complete plaque free within the framework of home-based oral

Figure 2 Using a magnifying mirror, problem areas are revealed to an 89-year-old female patient based on the AF-iIMI framework

Figure 3 Education regarding AF-iIMI of the same patient

hygiene. The value of a plaque index with a simple qualitative yes or no decision may change only marginally in the course of follow-up examinations, despite a significantly reduced amount of plaque. Therefore, this type of index does not track changes in plaque levels thoroughly enough and could result in patient demotivation. Similar to the QHI, which assesses the extent of plaque on smooth surfaces, we have suggested an index to assess the extent of plaque in approximal areas (mAPI) [15]. Under optimal lighting conditions and with the help of magnifying mirrors, the patient is shown "problem or weak areas" in the mouth (Fig. 2). Individual denture models or intraoral images of the patient's mouth can also be helpful here. The presentation of the patient's specific case using, for example, X-rays, photos (not only current, but also previous ones, if available) as part of a "case presentation" individualizes the possibly existing problem and should act to sensitize the patient with regard to his/her dental and oral hygiene and self-responsibility. For patients with removable dentures, a demonstration is necessary to point out any existing plaque on the denture, as denture hygiene is also a component of dental and oral hygiene.

il

Based on the anamnesis and findings, each patient receives **individualized** needs-oriented education and **information** regarding, for example, caries (root surfaces and crown margins), gingivitis, periodontitis and peri-implantitis, as well as advice on possibilites of risk minimization, prevention, treatment and maintenance therapy (recall). Supplementary dietary recommendations for (dental) health should also include advice on foods that promote and inhibit inflammation. Moreover, the function of mastication and the necessity of intensive chewing needs to be explained (Fig. 3). When periodontal treatment is required, it is essential that the patient understands the meaning and purpose of "partner treatment". In this step, the relevance of being "self-responsible" and active participation for his/her dental and oral health should also be clarified. Furthermore, the effect of regular and effective home-based dental and oral hygiene on oral health should also be explained while not forgetting to emphasize the importance of employing a systematic approach (e.g. the CIOTIPlus system or technique).

M

An important prerequisite for subsequent **motivation** is to first determine the extent to which the patient can be motivated and is willing to cooperate. Depending on the patient, different models (e.g. the preventive intervention or transtheoretical models) can be used for support. Based on the categorization of the patient, *individualized motivation* then follows, which should include the principles of "motivational interviewing" (MI) for active participation. In order to make this session strictly individualized for the patient, the motivational interview should make use of aids in the form of denture models of the patient, X-rays, photographs and the documented findings of the plaque and inflammation indices which present the patient's own case. If the need for treatment was identified at the time of diagnosis, it is vital that the patient is first given a "*whole mouth therapy concept*" before following any further instructions on oral hygiene measures; this is done in order to minimize iatrogenic irritation factors and establish hygiene ability. It is imperative to avoid standardized, ordinary, and boring routine explanations when familiarizing patients with the AF-iIMI approach! The patient must have the feeling of receiving personalized individually care! It is recommended not to resort to any repetition of well-known slogans (e.g. "Don't forget to brush your

teeth twice daily after meals!") in preventive care, as only individualized health counseling can shape health-conscious behavior [19]. In order to ensure consistent professional thinking using the same language, the dental professional and the office staff must discuss the office's prophylaxis concept as a team and update it regularly with new findings (very important: joint continuous internal and external training). Motivational Interviewing (MI) is another evidence-based method for positively influencing patient behavior in dentistry [37]. Based on the "preventive intervention model" according to Weinstein et al. (1989), the patient's perception of risk ("recognizing having a problem") and willingness to cooperate (willingness to work on the problem) are the basic prerequisites for successful prophylaxis [35]. The reasons for failure in the area of motivation and instruction usually have 3 different causes: lack of knowledge, lack of skills or lack of motivation. A thorough behavioral analysis before starting motivation and instruction should therefore establish whether the problems are connected to knowledge, skill or motivation. Accordingly, in several small steps, either knowledge can be imparted (for problems on the knowledge level), skills can be trained (for problems on the skill level) or work can be done on problems with motivation [11]. In any case, the patient must be aware of their own responsibility. In order to successfully motivate a patient, his/her willingness to cooperate should be assessed in advance. Although originating from health psychology, a classification using the "transtheoretical model" can also be of help in dentistry [9].

Figure 4a Observation of a 71-year-old patient through a venetian mirror in a special oral hygiene place while she performs oral hygiene in the context of AF-iIMI

Figure 4b Observation-oriented oral hygiene instruction using a model for the same patient at a special oral hygiene place within the context of AF-iIMI

I

As part of **instructions**, the patient should first demonstrate how he/she performs home-based oral hygiene with his/her personal *oral hygiene tools* brought from home. Beforehand, the plaque should be made visible to the patient with a plaque staining agent. Instructions must be observation-oriented (Fig. 4a and b) and dependent on individual abilities as well as the intraoral status of the patient. It is advisable to perform this step together with the patient in special oral hygiene places with "bathroom-like equipment" (mirror, washbasin, magnifying mirror with a light source, opportunity to sit). The patient is asked to demonstrate his/her daily dental and oral hygiene routine with own oral hygiene tools brought from home. Firstly, it should

be evaluated if the tools already being used by the patient allow for sufficient oral hygiene or whether small changes in the application of these tools could lead to hygiene improvement. Depending on the individual abilities and motivation of the patient, various other oral hygiene tools can be recommended and training with them should occur on site with the patient. Oral hygiene recommendations for older people, in particular, should be formulated as simple as possible and tailored to their individual abilities and motivation, while simultaneously paying particular attention to possible age-related functional limitations such as a decline in motor, sensory or mental abilities [36]. In order to objectively verify the motor, sensory and mental abilities of a patient, various "*short tests*" can be used (e.g. the money counting test and the neck grip left/right, and if necessary, the fist/fingertip test) [31]. The results of the various tests can then be used to decide which oral hygiene tools (hand and electric toothbrushes [oscillating/rotating or sonic]) can be used for home-based oral hygiene. Often, "modifications" of oral hygiene tools can be useful. For example, if patients are no longer able to grip or guide a manual toothbrush properly, an individualized "gripping aid" for the toothbrush handle may help them. Changing to an electric toothbrush, which has a more compact and easier to grip handle, and which also requires no movements from the wrist joint, may also be beneficial. In case of decreased eyesight we recommend wearing reading glasses during oral hygiene and using a magnifying mirror with an integrated light source. An opportunity for seating gives the patient the chance to take sufficient time for oral hygiene.

For patients with removable dentures, advice regarding the importance of regular and effective denture hygiene for oral health should not be overlooked. The plaque (biofilm) on removable dentures represents a source of microorganisms. Therefore, careful cleaning and, if necessary, disinfection of the dentures is as important as brushing natural teeth and implants. The tools and procedure for cleaning the dentures should also be shown and explained.

Many dental professionals recommend the "modified bass technique" for mechanical plaque removal using a toothbrush [5]. However, this technique is difficult to learn. There is no evidence in literature indicating that this technique is superior to, for example, the "horizontal scrubbing technique" for plaque removal [12, 27, 34]. It is generally agreed that it is probably more important to follow a brushing system than to follow a specific technique when using both hand and electric toothbrushes [12]. The regular use of a certain system is intended to prevent teeth or tooth surfaces from being overlooked during home-based oral hygiene [28]. For this reason, we recommend, explain and demonstrate the "CIOTIPlus" system and technique to the patient as part of the instructions [16]. According to this system, the patient first brushes the **c**hewing, followed by the **i**nside and **o**utside surfaces, with a toothbrush. Afterwards, the **t**ongue and **i**nterdental spaces are cleaned with interdental hygiene tools. Subsequent to this cleaning procedure, the patient re-applies the same pea-sized amount of fluoride-containing toothpaste evenly across all tooth surfaces and uses the toothbrush to systematically brush the tooth surfaces and gums using circular or rotating movements ("**plus**"). In order to clearly demonstrate the advantage of the system's "plus" step to the patient, it is useful to make the plaque visible again before and after the "plus" step. The plaque is made visible to the patient a total of 3 times: before the instruction, after performing the "CIOTI" system and after the "plus" step. In this manner, the patient can see and be convinced that a further reduction of plaque can be achieved by the "plus" step. This system does not literally denote "double" brushing, as the entire cleaning process is not repeated in the same way [16]. By applying the fluoride-containing toothpaste once more, the tooth surfaces are mechanically cleaned again on the one hand, while on the other hand, additional fluoride administration occurs. Fluoride appears to be more effective on clean, plaque-free tooth hard tissue [22]. The aim of "CIOTIPlus" system is to achieve both a more effective plaque reduction (removal of supragingival [visible] and achievable subgingival [non-visible] plaque from the tooth surface) and improved fluoride availability to the tooth surface. In addition, the periodontium is also stimulated by mechanical stimuli (plus function), which is intended to promote blood flow to the epithelium and subepithelial connective tissue and to strengthen the periodontal tissue. The effectiveness of CIOTIPlus has already been proven in several studies [13, 15, 17, 25]. In older patients that had undergone periodontal therapy, the use of the CIOTIPlus system not only increased the removal of plaque on smooth and proximal surfaces [13, 15, 17, 25], but combined with efficient regular supportive periodontitis therapy, it even minimized the formation of new root surface and crown margin caries and stabilized or improved the periodontal conditions [15]. Yet, in order to identify "problem sites" in the area of plaque control, and thus successfully prevent caries and periodontal disease, individualized and observation-oriented dental and oral hygiene advice, information and instruction (AF-iIMI), as well as regular re-instruction and re-motivation are absolutely essential for every patient. Following the oral hygiene training, a professional tooth cleaning is performed.

SC

In order to achieve the best possible results in self-responsible, home-based oral hygiene, a patient should be able to evaluate and control the cleaning process and cleaning result alone.

Self-control of the cleaning process (daily):

It appears that many patients have difficulties with the regular implementation of a specific daily dental and oral hygiene system. Numerous possibilities exist for patients to perform the self-control of the cleaning process or system. In the digital age, computer programs or apps may offer the possibility to support patients in their daily dental and oral care [21]. However, the fact that

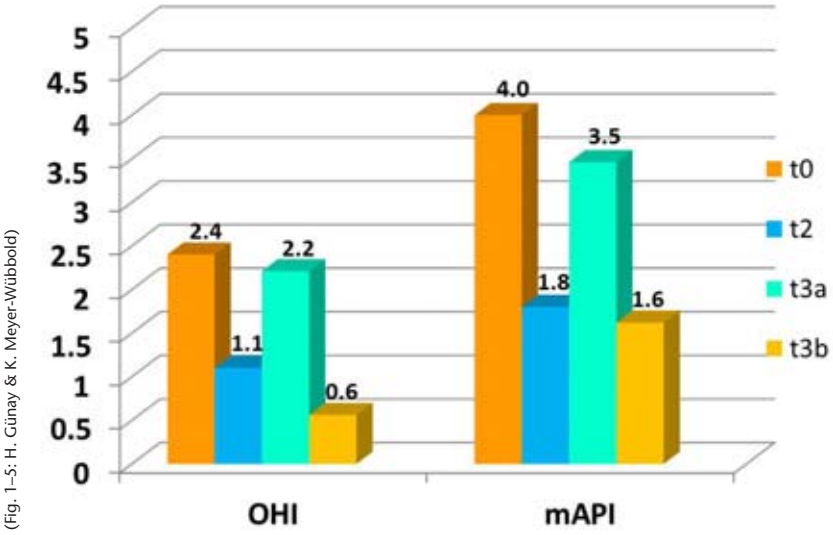
Figure 5a 72-year-old patient, condition before the start of AF-iIMI

Figure 5b The same patient, status before the start of AF-iIMI, plaque made visible with a plaque-staining agent (t0) (QHI: 2.4; mAPI: 4.0)

Figure 5c The same patient, status 3 weeks after AF-iIMI, plaque made visible with a plaque-staining agent (t2) (QHI: 1.1; mAPI: 1.8)

Figure 5d The same patient, status 6 months after AF-iIMI, plaque made visible with a plaque staining agent (t3a) (QHI: 2.2; mAPI: 3.5)

Figure 5e The same patient, status 3 weeks after Fig. 5d, plaque made visible with a plaque-staining agent (t3b) (QHI: 0.6; mAPI: 1.6)



(Fig. 1–5: H. Günay & K. Meyer-Wübbold)

Figure 5f Smooth and proximal surface plaque index values of the 72-year-old patient at different times

computer programs or apps are not suitable for everybody should be considered. Particularly, many older people use newer technical devices less than younger ones. The reasons for this are manifold. First, older people barely have any contact with new technologies because they did not grow up with them and thus lack an understanding of how modern technology works [31, 32]. Moreover, physical challenges occurring in older age, such as visual or hearing impairments, limitations in fine motor skills and cognitive limitations, can also be a hurdle [31, 32]. In a survey, 41 % from 1000 people over the age of 65 stated that they found it difficult to operate modern technical devices [31, 32]. In order that these patients also have the possibility to self-control their oral hygiene at home, our working group "oral health care promotion" has developed an initial "oral hygiene protocol" in which the patient can document the system he/she has used on a daily basis. We evaluated the use of these protocols in a study and it could be shown that such protocols are well suited for the self-monitoring of the cleaning process for a short period of time and that they do indeed improve oral hygiene [15]. However, such simple protocols are frequently not very attractive for patients in the long run. Thus, we have additionally developed an abacus ("CIOTIPlus-Abacus"). With this tool, it is very easy for the patient to document the "CIOTIPlus" brushing system and technique on a daily basis in a playful way, which also increases the motivation to use this tool for documentation and self-control. At the same time, this tool allows the patient to test his/her cognitive and motor skills. Unfortunately, the success of the tool was not evaluated over a longer time period and this is why we developed an app/computer program. The use of the CIOTIPlus-App and the CIOTIPlus-Abacus were tested in a pilot study; it was shown that dental and oral hygiene could be significantly improved by self-controlling the cleaning process with an app or abacus in senior citizens [18].

Self-monitoring of the cleaning result (once weekly):

Many patients find it difficult to objectively evaluate their own cleaning result. A pure visual check, even with magnifying aids and optimal lighting conditions or a "tongue feel test" to identify any plaque-affected areas that may still be present is insuffi-

cient and cannot reveal hidden "problem or weak areas" (e.g. interdental spaces, the inside surfaces of the teeth and the areas around the gum line) particularly well. We therefore recommend that patients use plaque staining agents (e.g. staining [chewing] tablets or rinsing solution) at least once weekly during their home dental and oral hygiene in order to visualize plaque. Plaque staining agents that make a distinction between "new" and "old" plaque are also useful. Patients should make plaque visible both before starting and after completing home-based oral hygiene. The initial staining serves as a guide for performing oral hygiene by allowing one to concentrate directly on the "problem or weak areas". The second staining is then used to check the cleaning result. Studies have shown that a second staining after tooth brushing is advisable; the plaque staining agents in any remaining plaque are partially washed out or bleached by the cleaning process and the ingredients in toothpaste (e.g. surfactants), thus making plaque less visible to the patient [13]. Visualization of plaque helps patients to evaluate and optimize their own oral hygiene [3, 4]. Before recommending that the patient self-monitors the cleaning result, however, it is necessary to demonstrate and explain to the patient from the perspective of the dentist how the "coloring agents" are used and which spatial requirements or additional tools (e.g. mouth mirror, telescope magnifying mirror with light source) are necessary for doing this. The self-monitoring of cleaning results by visualizing plaque gives patients the chance to recognize their own problems and weaknesses, and thus, to continuously improve their cleaning system or technique! Most patients falsely appraise their own oral hygiene as being considerably better in the absence of plaque visualization [18]. Patients' self-evaluation after the demonstration of plaque staining correlated well with the objective findings of the plaque indices.

The patient should therefore be made conscious of the need for self-control of oral hygiene at home. First of all, the necessary home conditions should be discussed (optimization of the site for home-based oral hygiene by means a telescope magnifying mirror with a light source and possible seating).

C

All good intentions fade with time. In this respect, success in terms of patient **cooperation** is rather short-term [4]. Figures 5a–f illustrate a patient case. The patient was re-examined 3 weeks after "AF-iIMi" and a clear improvement in home-based dental and oral hygiene was observed based on the smooth and proximal surface plaque index values. After 6 months, the same patient was re-examined again. However, the plaque index values of the smooth and proximal surfaces were found to have returned to the initial values. In order to successfully prevent caries and periodontal disease in the long-term, in addition to the AB-iIMI (including implementation of the system/technique CIOTIPlus) and self-control in home-based oral hygiene, patient cooperation should be regularly monitored in terms of re-instruction and re-motivation. It is advisable to schedule the patient for a (success) **control** 10–14 days after the first AF-iIMI in order to clarify possible questions, to control if the given recommendations for home dental and oral hygiene were fulfilled and to re-instruct and re-motivate the patient. During recall sessions, the patient is again shown possible weak and problem areas related to his/her home-based oral hygiene. However, caution should be exercised in order to avoid demotivating the patient.

In this appointment, the patient is once again asked to bring his/her own oral hygiene tools and an objective evaluation can be made based on plaque and inflammation indices. During the appointment, the next recall appointments should then be scheduled needs-based (risk-oriented). Depending on the patient's needs, ¼-, ⅓- or ½-yearly intervals are chosen. The recall appointment procedure is also individualized and needs-oriented and includes all the elements of the concept.

Conclusion

The improvement of home-based oral hygiene for risk groups is a challenge both for the dental professionals and teams as well as for the patient. The presented concept can help to contribute to sustainable dental, oral and general health in these groups.

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Digital treatment planning and prosthetic rehabilitation of a patient suffering from generalized tooth wear

Introduction: Implant supported fixed reconstructions in patients with massive tooth wear often require an increase of the vertical dimension of occlusion (VDO) and can be considered complex in terms of material selection and the treatment procedures. In order to reduce clinical and laboratory efforts as well as the need of adjustments it is nowadays possible to implement several hard- and software tools to acquire and process three-dimensional data. Along with prosthetic backward planning, the final outcome might be improved with such technologies. However, according to the recent literature, there are no evidence-based treatment guidelines available for patients with massive tooth wear, impeding selection of long-term reliable materials and a specific treatment procedure.

Treatment Methods: A 68-year-old patient presented clinically insufficient prosthetic reconstructions in a partially edentulous arch in combination with massive tooth wear, that finally resulted in a deep bite. He aimed for aesthetically pleasing and functional reconstructions. Due to massive and generalized loss of dental hard tissues, adequate treatment was only possible by increasing the VDO, which included provisionalization for 6 months. Before bite registration, the position of the maxilla was three-dimensionally determined. Furthermore, a scan of the face as well as an intraoral scan were performed. Based on the acquired data, a prosthetic-backward planning was performed and the ascertained vertical height was transferred to a noninvasive splint in the upper jaw as well as to temporary eggshell restorations in the lower jaw. During 6 months of provisionalization, guided implant surgery in the region of former teeth 23 and 24 was performed. After the provisional phase, maxillary teeth were prepared and direct temporary restorations were inserted. Subsequently, impressions were taken using an intraoral scanner and a polyether material. Finally, monolithic ZrO_2 crowns and bridges were adhesively luted to the abutment teeth. After the treatment, a Michigan splint was designed and milled using CAD/CAM (computer aided design/ computer aided manufacturing).

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Results: By increasing the VDO in the provisional phase, it was possible to achieve an adaptation of the stomatognathic system before incorporating the final reconstructions. The digital workflow contributed to increasing time efficacy.

Conclusion: The presented treatment describes a predictable and efficient method to rehabilitate patients with massive tooth wear.

Keywords: therapy planning; digital workflow; backward planning; bite elevation; CAD/CAM

1. Introduction

Fixed, implant-prosthetic rehabilitation of patients with massive tooth wear require vertical readjustment in multiple cases and often go along with a non-invasive provisional testing phase as well as higher planning and time expense. In order to reduce the clinical and laboratory expense as well as the necessity of intraoral fittings to a minimum, a variety of hard- and software are available for data acquisition, processing and therapy planning. Examples of this are the intra- and extraoral surface scanners, digital volume tomographies as well as appropriate software-solutions to link the generated data and computer aided designs (Computer-aided design, CAD) of the dentures. By creating a three-dimensional face scan, the laboratory software can show the physiognomy of the face. This process enables a prosthetically oriented "backward planning" before implantation and allows an increased planning security in regards to functionality and aesthetic. Due to the lack of evidence-based treatment guidelines, the correct selection of the material as well as the planning of treatment processes is impeded [1, 17].

2. Case report

2.1 Initial diagnosis

A 68-year old patient presented himself in the Department of Prosthodontics, Geriatric Dentistry and Craniomandibular Disorders of the Charité Center for Dental, Oral and Maxillary Medicine with an insufficiently restored dentition, generalized tooth wear, a resulting deep bite in the anterior region and the desire for aesthetically and functionally pleasing restorations. The general medical history did not show pathological findings. After extensive clinical examination several edentulous spaces and insufficient prosthetic reconstructions in combination with a multifactorial (bruxism, attrition, erosions) loss of vertical dimension that resulted in a deep bite, could be reported. The teeth 18, 15, 22, 23, 24, 26, 28, 38, 36, 46 and 48 were missing. A slight generalized bone loss of < ⅓ of the root length in the region of the upper posterior teeth and of ⅓ to ⅔ in the upper front could be determined periodontally (Fig. 1). The removable partial denture that replaced the teeth 22, 23, 24 and 26 has been worn in the upper jaw since 2007 and didn't show retention due to the generalized tooth wear. The gaps in region 36 and 46 were not restored prosthetically. Abrasion facets were diagnosed on all teeth (Fig. 2a, 2b, 3). Especially the teeth 25 and 47 showed a high degree of attrition due to extensive tooth wear. A downsized lower third of the face was shown from an extraoral perspective. A functional screening on painful CMD was performed based on the groundwork of CMD summary report after Jakstat and Ahlers [2]. The probability for the development of a CMD was categorized as unlikely in this context. The derived diagnoses from the mentioned findings are listed in Table 1. The categorization of tooth wear was based on the modified tooth wear index after Donachie and Walls [9]. Because adequate prosthetic rehabilitation only seemed reasonable in combination with a bite elevation, a provisional phase of 6 months was implemented to test out the aspired bite elevation.

2.2 Integration of bite registration and maxillo-mandibular relationship in digital workflow

The necessary bite elevation was determined with regard to the planned prosthetics in the lab and the speaking distance was clinically checked. Prior to the bite registration the patient was asked to wear a hydrostatic relaxation splint for 30 minutes (Aqualizer, Dentatrade International, Cologne, Germany) (Fig. 4). This supposedly reduced the risk of occupying a potentially neuromuscular forced bite. After removing the relaxation splint, a laboratory-fabricated registration aid composed of light-curing plastic sheets (C-Plast, Candulor, Rielasingen-Worblingen, Germany) was used to register the prospectively aspired occlusion position (Fig. 5). First, a relining of the base with Bis-GMA (Luxatemp, DMG chemical pharmaceutical plant, Hamburg, Germany) occured in the lower jaw. The impressions of the teeth were shortened in the plastic state of the relining material down to the impressions of the cusp tip and incisal edges. After fixing the lower jaw, the step-by-step relining of the upper jaw took place: First, the incisal edges of the middle upper incisors were relined and the impressions were shortened to a minimum. This registration was tested multiple times on reproducibility of the bite in the following. Afterwards, the posterior upper teeth were relined and the definitive bite was fixed.

The PlaneSystem (Zirkonzahn GmbH, Pustertal, Italy) was used to gather the position of the upper jaw in relation to the so-called natural head position (NHP). It consists of the PlaneFinder, the virtual and real

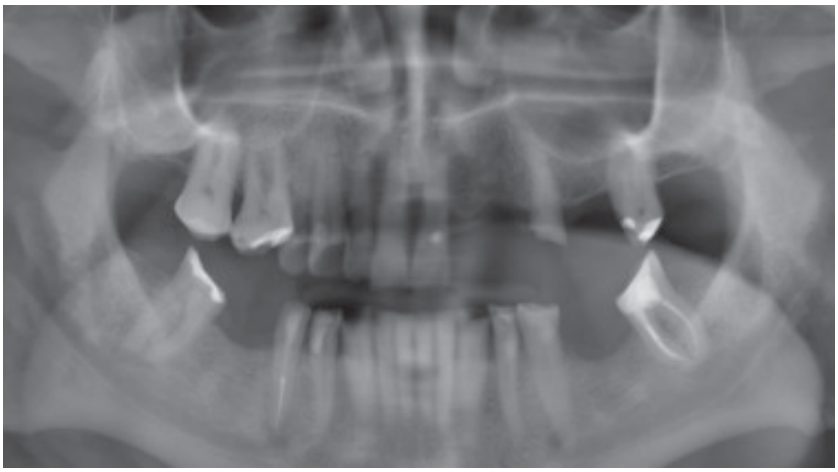


Figure 1 Panoramic tomographic image of the initial situation. Radiologically, an apical radiolucency is visible on tooth 47.

articulator PS1, the PlanePositioner as well as the PlaneSystem software. This allows the acquisition of individual patient differences of the natural head position as well as the angle of inclination of the occlusal level of the registered position (Fig. 6). The models can be positioned above the PlanePositioner in the articulator PS1 using the determined angle, which simulates the individual patient's rotation-, sliding- and closing movements of the jaw. In order to enable the allocation of the acquired data and coordination in three-dimensional space, the position of the articulated models was gathered in a PS1 articulator using the stripe-light scanner S600 ARTI and was integrated using the PlaneSystem software (Zirkonzahn.Modellier, Zirkonzahn GmbH, Pustertal, Italy) and transferred into a virtual integrated articulator in the software. Collecting the physiognomy of the face took place using an extraoral scanner (Face Hunter, Zirkonzahn), which enabled the axis-related positioning of the face in a virtual articulator by gathering a 3D face scan (Fig. 7).

2.3 Creation of a digital wax-up and intraoral fitting in form of a mock-up

After acquiring the three-dimensional relation of both jaws and an axis-related positioning of the face scan, a set-up of both jaws was created in a

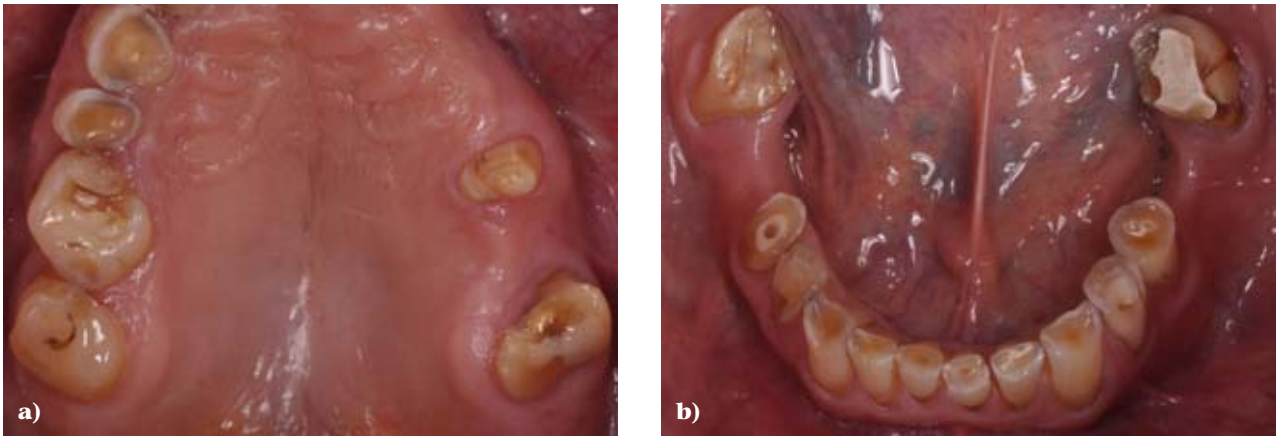


Figure 2a and 2b The intraoral findings resulted in partially edentulous adult arches with insufficient prosthetic and preservative restorations. The massive tooth wear can especially be seen on the occlusal surfaces of the molars, as well as the palatal surfaces of the upper incisors and the incisal edges of the lower incisors.

Figure 3 Due to tooth wear, a significant reduction of vertical dimension occurred, which clinically resulted in the form of a deep bite.

Figure 4 Prior to the bite registration the patient was asked to wear a hydrostatic relaxation splint for 30 minutes in order to reduce the risk of occupying a potentially neuromuscular forced bite.

computer-aided design (CAD) (Zirkonzahn.Modellier, Zirkonzahn) and printed (Form 2, Formlabs, Somerville, USA) (Fig. 8). The printed models enabled the creation of a transfer key made out of transparent silicone (Hardglass, Ichem, Palosco, Italy), and evaluated the created set-up in form of a mock up regarding phonetics and aesthetics (Fig. 9). After testing the mock up, the definitive prosthetic restoration was planned as follows:

- monolithic ZrO_2 crowns in region 17, 16, 15, 13, 12, 11
- monolithic ZrO_2 bridges in region 24–26, 34–37, 44–47
- screwed, implant-supported monolithic ZrO_2 extension in region 22–24

Diagnosis	tooth/region/value
modified tooth wear index (TWI) category 1	17
modified tooth wear index (TWI) category 2	16, 11, 21, 34–43
modified tooth wear index (TWI) category 3	14–12, 25, 27, 37, 35, 44, 45, 47
insufficient fillings	16, 27, 37, 34, 44, 45
insufficient prosthetic treatment	22, 23, 24, 26
periodontal screening index (PSI)	1, 1, 1, 1, 1, 1
apical periodontitis	47
deep bite	11, 21, 31, 32, 41, 42

Table 1 Listing of the diagnoses derived from the above findings.

2.4 Testing of the aspired occlusion position and bite elevation

As things developed, the digital set-up served as a template to produce a polycarbonate splint (Multistratum, Zirkonzahn) according to Edelhoff et al. [10] in the upper jaw as well as a template for temporary eggshell restorations made out of polymethylmethacrylate (Premiotemp Multi PMMA, primotec, Bad Homburg, Germany) in the lower jaw (Fig. 10a, 10b). After selective preparation of the teeth 37, 35, 34, 44, 45 and 47, the insertion of temporary eggshell restorations, as well as the dental colored polycarbonate splints, the new bite elevation was tested for 6 months prior to definitive restoration. During this, the bite in the anterior region was elevated by a total of 5 mm.

Figure 5 The fixation of the bite occurred through relining of a laboratory registration aid.

2.5 Preservative pretreatment

During the temporary phase of the bite elevation the lower incisors were reshaped based on the digital wax-up using Ceram X Duo (Dentsply Sirona, York, USA) (Fig. 11). The teeth 25 and 47 were treated with root canal procedures for prosthetic reasons and fiberglass pins during the course of treatment.

2.6 Digital implantation design

Before implantation, a three-dimensional planning of the aspired implant position was completed and for this a DVT was necessary (Veraview-epocs 3D, J. Morita, Tokyo, Japan). In terms of a prosthetic oriented backward planning the DICOM data set of the DVT was overlapped with the STL data set of the upper jaw diagnostic model with the help of a planning software (SMOP, Swissmeda, Baar, Switzerland). Afterwards, the STL data set of the antagonistic jaw and the created set-up were read in. Because these data sets were exported in the same coordinate systems, no new alignment was necessary. In the end the optimal implant positions in region 23 and 24 were determined (Fig. 12ac). Based on the SMOP-planning, a dentally-supported implantation splint was printed and guiding sleeves were attached. These were tested on the patient to ensure a wobble-free fit before implantation.

2.7 Implantation

The implantation was performed with local anesthesia and mid-crestal incision from region 21 to region 25 as well as the preparation of a muco-periosteal flap. There was no vertical relieving incision. After inserting 2 implants (Camlog Screw Line, Camlog, Wimsheim, Germany) with a diameter of 3,8 mm and 11 mm in length, a saliva-proof wound closure

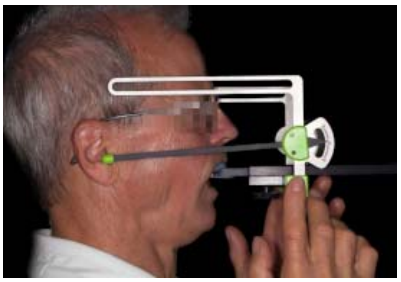


Figure 6 Acquisition of the position of the upper jaw in relation to the Natural Head Position (NHP) occurred with the PlaneSystem.

Figure 7 An extraoral scan was performed in order to determine the face physiognomy.

Figure 8 After determining the three-dimensional relation of both jaws as well as the axis-related positioning of the face scan, a set-up of both jaws were digitally designed and printed.

Figure 9 After production of a transfer key, the digitally created set-up was transferred intraorally as a mock up.

with a horizontal mattress suture as well as lateral sutures were performed (Fig. 13). After a healing period of 3 months the implants were exposed surgically. For this, another mid-crest incision was chosen and a mucoperiosteal flap was prepared. The cover screws were replaced by 2 gingiva formers (height 4 mm) and the mucosa was adapted to the gingiva formers using single button sutures.

2.8 Preparation, direct temporary restorations of the upper jaw and impressions

The preparation occurred selectively based on the overlapping data of wax-up and initial model. With digital measurement it was possible to determine the difference between wax-up and diagnostic casts. Many teeth already showed a difference of 0,8 mm due to loss of hard tooth structure compared to the wax-up, causing that the minimum layer thickness of zirconium dioxide could be kept without any or only minimal preparation (Fig. 14, 15a, 15b). It should be noted that a preparation reserve for the restorations should be taken into account at all times. The impressions of the preparation were done digitally and conventionally using individual, open impression trays and a polyether (3M Impregum Penta, 3M-Germany, Neuss, Germany). In conventional impressions, the double cord technique was used. In order to analyze the deviations between digital data of the intraoral scan and the conventional model, the conventional model was additionally scanned (Scanner S600 ARTI, Zirkonzahn) and overlapped with the digital set of data in the CAD/CAM software Zirkonzahn.Modellier. After preparation and taking impressions direct temporary restorations were manufactured (Fig. 16). The bite registration was performed in 2 steps to maintain the vertical alignment. For this, the provisions of the 1. and 4. quadrant were removed and the bite was scanned in centric occlusion contralaterally, or rather, fixed with silicone (Futar D, Kettenbach, Eschenburg, Germany). The same procedure occurred in the 2. and 3. quadrant.

2.9 Bite registration control

Based on the bite registration, a precise registration was manufactured in the laboratory, which was used in a follow-up appointment for bite check occlusion control analogue to the bite registration in section 2.2. In order to correct the imprecisions while taking impression of the implant positions, the impression posts were interlocked with Pattern Resin LS (GC, Tokyo, Japan) after model creation. The interlocking was separated with a thin saw cut, which was sealed intraorally with Pattern Resin LS after screwing the impression posts.

2.10 Completing and production of a Michigan splint

The CAD/CAM manufactured crowns and bridges were milled from monolithic zirconium dioxide (Katana Zirconia STML, Kuraray, Chiyoda, Japan) and sintered in the lab. Before integration, the restorations were sandblasted with aluminium oxide powder (1 bar, 50 µm grain size) and the teeth were cleaned with rotating brushes and polishing paste [12]. The implant bridge in region 22–24 was screwed intraorally with 20 Ncm and

the screw canal was sealed with teflon tape and a low viscosity composite. The crown and bridge constructions were bonded adhesively with Panavia F2.0 (Kuraray, Chiyoda, Japan) (Fig. 17a–e). In order to obtain a permanently stable prosthetic result as well as the modified functional model, the upper and lower arch were scanned (Trios, 3Shape, Kopenhagen, Denmark) again after integration and a Michigan splint for nightly use was designed digitally and then milled (Fig. 18a, 18b).

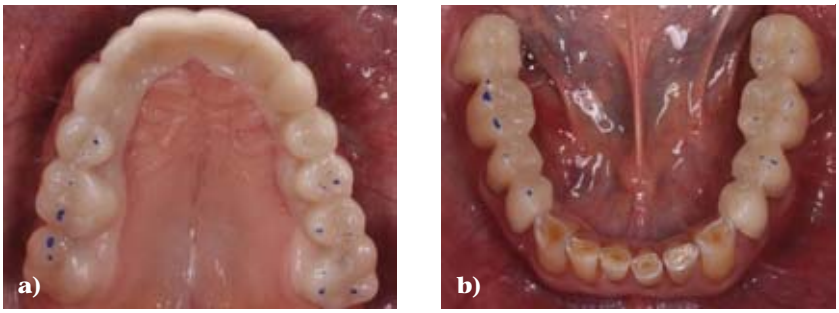


Figure 10a and 10b The bite elevation occurred in the temporary phase using a non-invasive splint in the upper arch and temporary eggshell restorations in the lower jaw.

Figure 11 During the temporary phase of bite elevation the tooth wear in the lower arch incisor region was built up directly using composite and made possible by the vertical space gained.

3. Discussion

In general, 3 reasons can be listed for a non-caries loss in tooth substance. These include erosions due to extrinsic (e.g. with increased consumption of acidic drinks or foods) and intrinsic processes (e.g. bulimia or reflux). Another cause of pathological loss of teeth substance is abrasions and attritions. Contrary to abrasions, where tooth wear occurs based on external factors, attritions where loss occurs by parafunctions in the stomatognathic system and tooth wear patterns result on teeth due to increased antagonistic tooth-to-tooth contact [8]. In that, bruxism is a frequent cause of attrition. Bruxism is defined as the parafunctional abrasion of antagonistic teeth in the form of an "oral habit" by unwilling rhythmic or spastic non-functional abrasion or pressing, whereas these movements are not in connection with the comminution of food [11]. The loss of vertical dimension can therefore lead to a compensatory growth of the alveolar process or to an increased interocclusal distance, which can then have a massive impact on the masticatory function, aesthetics and the occlusal levels [16]. According to the S3-guidelines on bruxism, definitive occlusal measures can be considered for functional-aesthetic or prosthetic reasons so that the consequences of such tooth wear can be compensated. The use of implants in patients with bruxism for prosthetic rehabilitation is controversially discussed in literature. Even though latest meta analyses [6, 7, 13, 20] showed an increased risk of implant loss, bruxism is not seen as a contraindication for implantation to date. The increased vertical burden of implants in this case is seen as cause for peri-implant bone loss and implant fractures, which is why bruxism is nonetheless a contraindication for

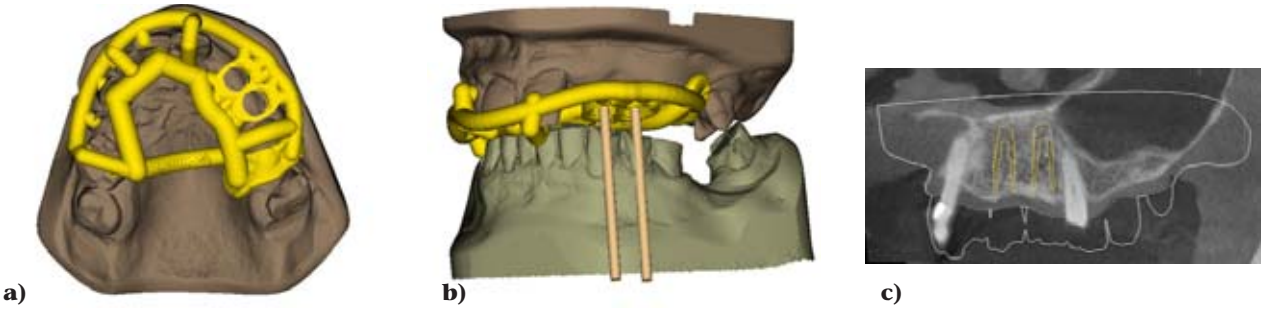


Figure 12a–c The planning of the ideal implant positions occured by prosthetically oriented backward planning. With the software SMOP the scanned diagnostic model, the wax-up, as well as the DVT were overlapped to determine an ideal implant position. Based on the plan, the implantation splint, portrayed yellow in the software, was printed and guides were stuck in.

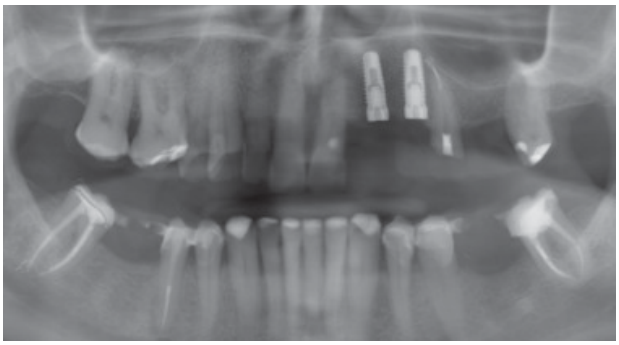


Figure 13 The postoperative radiological control of the implant position occurred with a panoramic tomographic image.

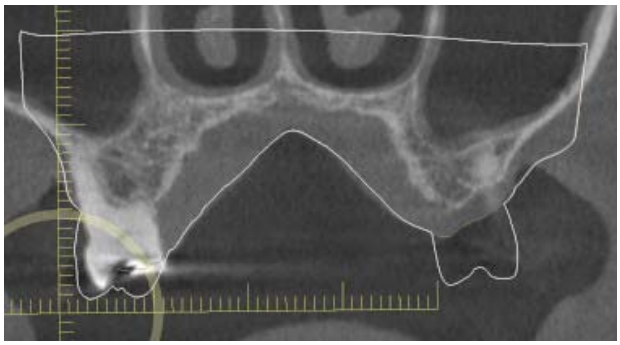


Figure 14 An additional control on the necessary reduction of tooth structure during preparation was done by the digital measurement of the wax-up and diagnostic casts in the DVT and the determination of the difference.

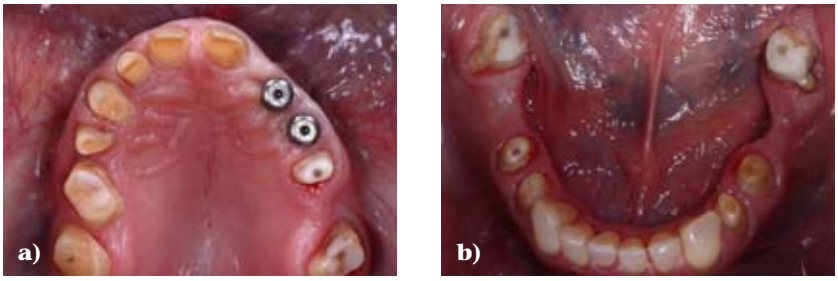


Figure 15a and 15b A chamfer preparation with a minimum reduction of 0.8 mm took place for the restorations with monolithic zirconium dioxide crowns and bridges.

Figure 16 The direct temporaries were created based on the digitally created wax-ups and transferred intraorally with a laboratory-fabricated molded part.

implants for many dentists [14]. A correlation between an increased implant loss and bruxism could not be found in other systematic reviews to date [5, 14, 15].

A digital planning of the implant positions was made for the implantation mentioned above in region 23 and 24. The base of digital implant planning was formed with the possibility of overlap of three-dimensional data from radiological imaging examination (DICOM data), the surface data of diagnostic casts and the data of the digital set-ups (STL format) [18]. Within the implantation planning the overlap of the individual data sets occurred using the software SMOP (Swissmeda, Baar, Switzerland). The digital set-up created a first orientation of optimal anatomic and aesthetic positioning of implants. Afterwards, the definitive determination of the implants' positions were transferred in vivo using implantation splints. Regarding the precision of the navigated implantations, Vermeulen [19] could determine statistical significant differences compared to precision of free-hand implantations.

The material selection of the planned prosthetics presents the treating dentist with a challenge. In literature, the question on the lasting probability of e.g. all-ceramic restorations in patients with bruxism could not be cleared up conclusively, because patients with bruxism are excluded in a multitude of studies. The question if monolithic zirconium oxide is an appropriate alternative in patients with bruxism cannot be answered at this point in time. According to the patient in the case report, the direct provisions made out of Bis-GMA already led to a significant reduction of the muscular activity due to a new adjustment of the bite elevation. This only resulted in 2 fractured provisions during the provisional phase of the bite elevation. A significant reduction of muscular activity by elevating the vertical dimension was also found electromyographically by Carlsson et al. [4].

Other than the careful selection of the materials, the treatment process should also be planned systematically. However, even though extensive prosthetic cases in com-

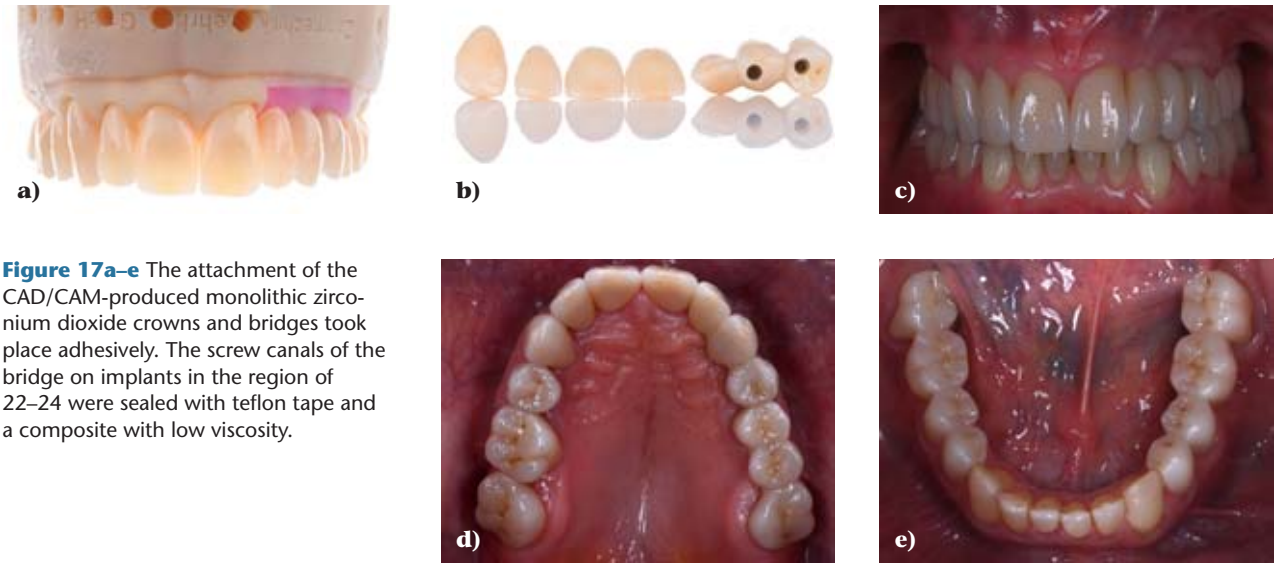


Figure 17a–e The attachment of the CAD/CAM-produced monolithic zirconium dioxide crowns and bridges took place adhesively. The screw canals of the bridge on implants in the region of 22–24 were sealed with teflon tape and a composite with low viscosity.

bination with a bite elevation are subject of a complex treatment plan, there are no existing evidence-based guidelines which are helpful in choosing the right treatment approach. In the S3-guidelines "diagnosis and treatment of bruxism", recommendations in "management of bruxism through definitive dental treatments" are expressed [17]. Abduo [1] was able to formulate some treatment recommendations and specifies in this context, that for adaptation to the new vertical dimension before integration of the definitive prosthetic restorations, a provisional phase of at least 1 month should be adhered to. The bite elevation was supposed to occur on all remaining teeth in the upper and lower jaw. Fixed temporary dental restorations led to a more rapid adaptation and was experienced as a more pleasant wearing comfort in comparison to removable splints.

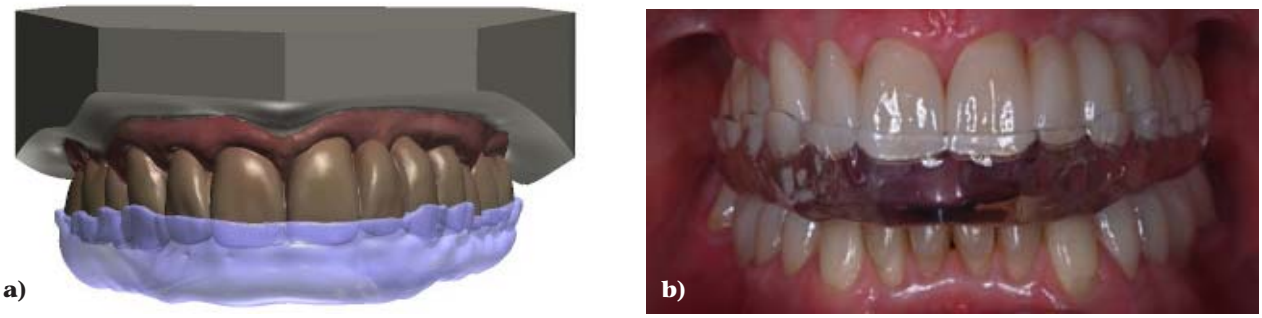
Upon completion of the outlined therapy, a digital Michigan splint was designed and then milled. The field of indication of a Michigan splint is not only to protect teeth from further attrition, but also in the modification of a functional model of the masticatory system as well as stabilization of the mandibular joints. In preparation of the Michigan splint the concept of "freedom in centric" was used, where a freedom of mandibular joint movement of 0.5–1.0 mm was aspired before the posterior teeth discluded [3].

4. Conclusion

The lack of evidence-based guidelines makes the choosing of the appropriate restoration materials and the therapy approach rather difficult, which shows the necessity for further studies in connection to bruxism and material behavior in crowns, bridges and implant materials. A significant simplification of the complex treatment demand can be achieved by using digital technologies. A three-dimensional acquisition of intra- and extraoral surfaces enables a precise, functional and aesthetic wax-up in the present treatment, which was maintained in the sense of a "backward planning" until integration of the final restorations and therefore made repeated fittings obsolete. Because prosthetic planning as well as treatment process in patients with generalized tooth wear and a resulting loss in vertical dimension is based only on expert opinion to date, an extensive after-care program should be ensured that sustainably guarantees the adaptation of the stomatognathic system to the new bite elevation.

Conflicts of interest:

The co-author (PD Dr. F. P. Strietzel) received third-party funding and



(Fig. 1–18, Tab. 1: B. Spies)

Figure 18a and 18b A Michigan splint was digitally designed and milled after integrating the restoration.

travel expenses from the Camlog Foundation (now Oral Reconstruction Foundation) in the context of research projects. In the context of student education, third-party funds for hands-on courses were raised by Camlog.

The other authors declare that there is no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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(Photo: M.-E. Jennes)

(Photo: B. Spies)

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Cells from granulation tissue of intra-bony periodontal defects reveal neurogenic and angiogenic differentiation potential and express the embryonic transcription factors NANOG, OCT4 and SOX2

Introduction: Aim of the present study was to assess if potent mesenchymal stem cells reside in the granulation tissue of intra-bony periodontal defects (IPD). The regeneration of IPD requires formation of new blood vessels and nerve fibers to ensure the neurovascular supply of the regenerated periodontal tissues (alveolar bone, periodontal ligament, root cementum). The main focus was to investigate the expression of osteogenic markers (BMP2, BMP4) and embryonic pluripotency factors (NANOG, OCT4, SOX2) during neurogenic and angiogenic differentiation.

Methods: Cells from granulation tissues of 5 systemically healthy subjects (mean age: 44.04 ± 5.73 years; range: 35 to 49 years) were used for the present investigation. The expression of mesenchymal (CD73, CD90, CD105, CD146, STRO1), hematopoietic (CD34, CD45) and embryonic stem cell markers (SSEA4, NANOG, OCT4 and SOX2) was analysed using flow cytometry. Neurogenic and angiogenic differentiation was induced with respective differentiation media for 5 weeks. Cultures grown in the maintenance medium without differentiation substances were used as negative controls. Changes in cell morphology were documented with an inverted microscope. The mRNA-expression of proteins characteristic for neurons (NEFL, NCAM1, ENO2), endothelial cells (ANGPT1, VEGFR1, VEGFR2, PECAM1), osteoblasts (BMP2, BMP4), and embryonic stem cells (NANOG, OCT4, SOX2) was analysed using qRT-PCR.

Results: The data of flow cytometry revealed a very high expression of CD73 (97.66 ± 1.92 %) and CD90 (98.87 ± 0.93 %), a high expression of CD105 (78.02 ± 12.81 %) and CD146 (80.64 ± 23.87 %) and a low expression of STRO1 (5.29 ± 3.62 %). The pluripotency factors demonstrated a very high expression of OCT4 (94.60 ± 1.95 %) and SOX2 (98.27 ± 0.36 %) and a lower but significant expression of NANOG (52.09 ± 6.98 %) and SSEA4 (29.76 ± 12.38 %). The neurogenic and angiogenic differentiation was documented

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through morphologic changes towards a neuron- and endothelial cell-like phenotype and through the continuously increasing mRNA-expression of neuronal (NEFL, NCAM1, ENO2) and endothelial markers (VEGFR1, VEGFR2, PECAM1). The expression of BMP2 and NANOG was significantly up-regulated and the expression of BMP4 and SOX2 was significantly down-regulated in cells grown in both differentiation media. OCT4 did not significantly change, but there was a clear down-regulation in 3 out of our 5 donors.

Conclusions: The granulation tissue of IPD contains cells with properties of mesenchymal stem cells. Therefore, it is a possible source for regenerative therapeutic applications. The embryonic pluripotency factors NANOG and SOX2 were influenced by differentiation media and seem to be involved in the regulation of multipotency and differentiation in mesenchymal stem cells from inflamed periodontal granulation tissue.

Keywords: inflamed periodontal granulation tissue; mesenchymal stem cells; neurogenic differentiation; angiogenic differentiation; bone morphogenic proteins; embryonic pluripotency factors

Introduction

The ultimate goal of regenerative periodontal surgery is the structural and functional regeneration of tissues that have been lost due to periodontal diseases. Histological examinations have shown that the sole removal of the microbial biofilm results in the formation of a long junctional epithelium along the mechanically debrided root surfaces. This is known as reparative healing [8]. A regenerative healing can only be achieved through the application of specific surgical techniques, like the guided tissue regeneration or the bio-modification of the root surfaces with enamel matrix derivatives [18, 38, 47]. There is consensus in the scientific literature that periodontal regeneration also requires the presence of progenitor cells. These cells differentiate under the influence of growth and differentiation factors into osteoblasts for the regeneration of the alveolar bone, into fibroblasts for the regeneration of the periodontal ligament, and into cementoblasts for the regeneration of the root cementum [22]. All these periodontal tissues originate from the ectomesenchyme of the neural crest [10]. Therefore, mesenchymal stem cells can be regarded as ideal progenitor cells for periodontal regeneration.

Intra-bony periodontal defects resulting from inflammatory periodontal diseases represent the most frequent indication for regenerative periodontal surgery. These defects are characterized by the formation of intra-bony pockets, in which the healthy periodontal tissues are replaced through an inflammatory granulation tissue. This tissue has been assumed to negatively influence the treatment outcome and is generally resected during regenerative periodontal surgery [11]. The granulation tissue preservation technique (GTPT, Fig. 1) was introduced 2013 by our group and has led to promising results from a clinical and radiographic perspective [20]. Possible explanations are

1. the preservation of the blood vessel network favoring the initial wound healing,
2. the preservation of an endogenous matrix as soft tissue support, and
3. the preservation of multipotent mesenchymal stem cells, which are required for the regeneration of the periodontal tissues.

Mesenchymal stem cells can be found in many healthy tissues of the oral cavity, but they are also present in inflamed tissues. Thus, cells isolated from the pulp of teeth with irreversible pulpitis as well as from granulation tissue of intra-bony periodontal defects were shown to have properties of mesenchymal stem cells [30, 31, 33]. Granulation tissue of intra-bony periodontal defects is easily accessible through a simple minimally invasive surgical intervention. Therefore, it is a useful source for the extraction of mesenchymal stem cells. The isolation of mesenchymal stem cells from inflammatory granulation tissue, their *ex vivo* expansion and finally their replantation in an increased number, is far away from being routine in regenerative periodontal surgery. However, it seems likely that the increased number of undifferentiated progenitor cells may have a positive influence on the regeneration of periodontal defects.

During periodontal regeneration, the formation of nerve fibers and blood vessels is required to ensure the neurovascular supply of the regenerated periodontal tissues. Therefore, aim of the present study was to assess the neurogenic and angiogenic differentiation potential of inflamed human periodontal ligament stem cells (ihPDLSCs). Special attention was given to the expression of bone morphogenic proteins and embryonic transcription factors. Bone morphogenic proteins (BMPs) belong to the transforming growth factor β superfamily. In addition to postnatal bone formation, BMPs participate in several non-osteogenic developmental processes, like neurogenesis and angiogenesis [9, 16, 37]. The pluripotency factors nanog homeobox (NANOG), octamer-binding transcription factor 4 (OCT4) and SRY (sex determining region Y)-box 2 (SOX2) are known to regulate the processes of self-renewal and differentiation in embryonic stem cells [29, 46]. There is growing evidence that they may play a similar role in

multipotent mesenchymal stem cells. Our experiments intended to examine how the osteogenic markers BMP2 and BMP4 as well as the pluripotency factors NANOG, OCT4 and SOX2 are expressed by ihPDLSCs during cultivation in neurogenic and angiogenic differentiation media.

Material and methods

Isolation and cultivation of ihPDLSCs

Five systemically healthy subjects with a mean age of 44.04 ± 5.73 years (range: 35 to 49 years), who suffered from advanced chronic periodontitis, were selected as donors. Before surgery, all patients received a comprehensive periodontal treatment consisting of professional dental cleaning, oral hygiene instructions and non-surgical periodontal treatment (scaling and root planning). In cases of a residual periodontal defect exhibiting a probing pocket depth > 6 mm, bleeding on probing and a radiographically evident intra-bony component ≥ 3 mm, regenerative periodontal surgery was performed. The granulation tissue preservation technique, comprehensively described by Günay et al. [20], was applied in all cases. Aim of this technique is to preserve as much granulation tissue as possible during mobilization of the mucoperiosteal flaps. The residual granulation tissue was harvested from the bottom of the intra-bony defect and used for the present *in-vitro* investigation. The exposed, defect-related root surfaces were mechanically debrided using sonically-driven scalers (SONICflex, KaVo, Biberach, Germany) and hand curettes. Consecutively, the regenerative procedure consisting of the application of 24 % EDTA gel (PrefGel, Straumann, Freiburg, Germany), irrigation with sterile isotonic sodium chloride solution and application of enamel matrix derivatives (Emdogain, Straumann) was conducted. At the end of surgery, the mucoperiosteal flaps with the adherent granulation tissue were repositioned and fixed with interrupted sutures.

Immediately after harvesting, the granulation tissue was sliced into the smallest pieces possible using sterile scissors and scalpel blades. The enzymatic digestion was performed for 1 hour at 37 °C using alpha minimal essential medium (α-MEM, Gibco, Grand Island, NY, USA) supplemented with 3 mg/ml collagenase type I (Gibco/Life Technologies, Paisley, Scotland) and 4 mg/ml dispase II (Sigma Aldrich, Steinheim, Germany). Afterwards, the mixture was passed through a strainer with a pore size of 70 µm (EASYstrainer, Greiner bio-one,

Figure 1a–h Representative case presentation of the granulation tissue preservation technique (GTPT) on teeth 14 and 15: Clinical aspect before (**a, b**) and during surgery (**c, d**): Note the intra-bony defects at the distal areas of teeth 14 and 15 as well as the preserved granulation tissue at the interdental papillae. Clinical aspect after surgery immediately following wound closure with interrupted sutures (**e, f**). Radiological aspect before treatment. Note the calcified deposits and the intra-bony defects at the distal areas of teeth 14 and 15 (**g**). Radiological aspect 16 months after surgery. Note the bone fill at the former intra-bony defects (**h**).

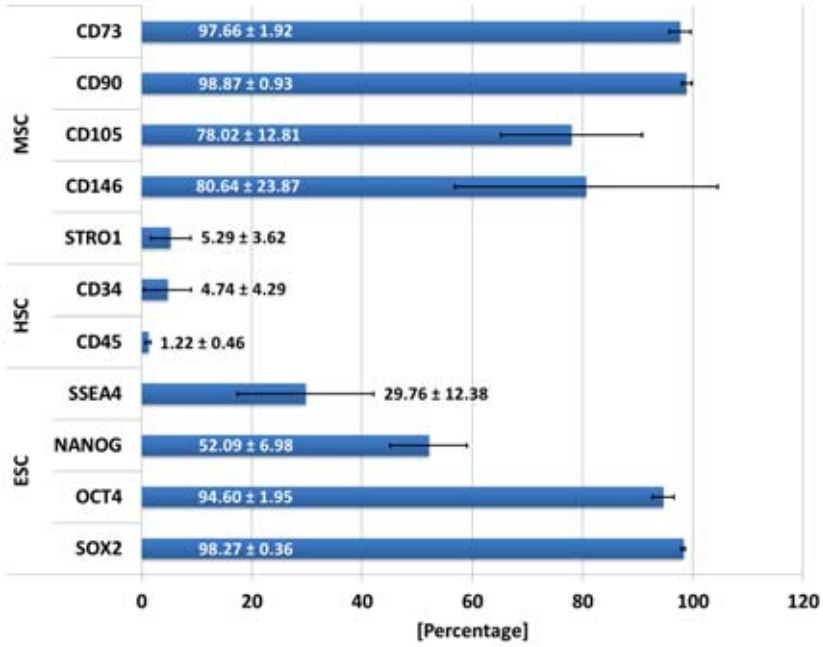


Figure 2 Summarized data of the immunophenotypic characterization using flow cytometry: Expression of markers characteristic for mesenchymal stem cells (MSC: CD73, CD90, CD105, CD146, STRO1), hematopoietic stem cells (HSC: CD34, CD45) and embryonic stem cells (ESC: SSEA4, NANOG, OCT4, SOX2) of all donors (n = 5).

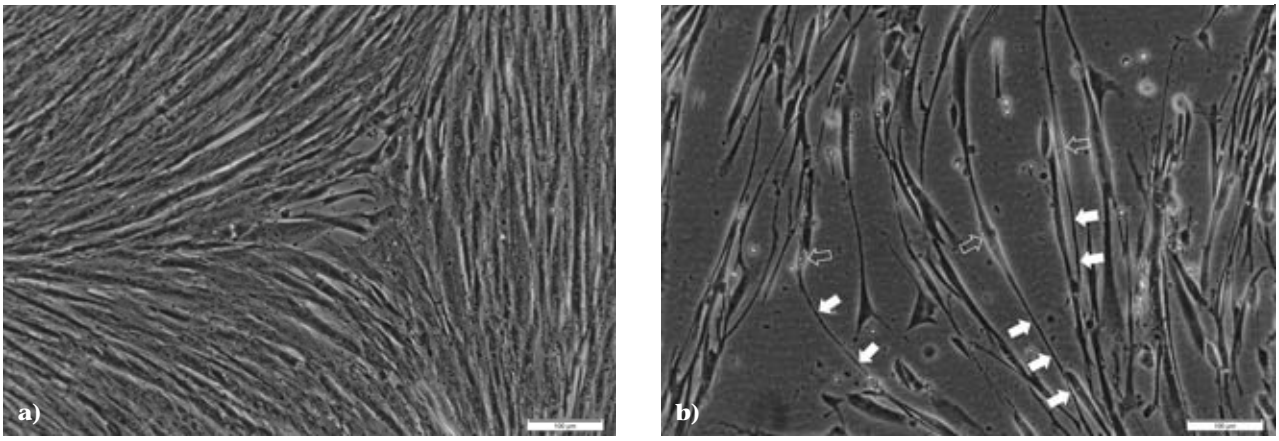


Figure 3a and b Histomorphologic changes occurring during neurogenic differentiation: Representative microscopic images recorded during culture in (**a**) CCM and (**b**) NDM 7 days after seeding. Note the strung-out cell body (open arrow) and the dendrite-like extensions (white arrows) in cells grown in NDM.

Frickenhausen, Germany) and re-suspended in complete culture medium (CCM) consisting of α-MEM supplemented with 15 % fetal bovine serum (FBS, Biochrom, Berlin, Germany), 100 U/ml penicillin, 100 µg/ml streptomycin (both from Biochrom), 2.5 µg/ml Amphotericin B (Capricorn Scientific, Ebsdorfergrund, Germany) and 100 µM L-ascorbic acid phosphate (Sigma-Aldrich). The resulting single cell suspension was transferred to culture flasks and expanded under humidified atmosphere at 37 °C and 5 % CO_2. Cells of the passages 2–4 were used for the experiments.

The present study was approved by the ethical committee of Hannover Medical School (ethics vote no. 1096). All donors were informed – verbally and in writing – about the intended use of the tissue samples and the goals of the study. All participants signed a consent form.

Characterization of cells using flow cytometry

The cells were seeded into 75 cm^2 culture flasks and expanded in CCM until they reached confluency. Subsequently, the cells were detached from the culture vessel via trypsinization, washed with phosphate buffered saline (PBS) and re-suspended in FACS buffer consisting of PBS, 1 % bovine serum albumin and 0.1 % sodium azide. Each sample contained 1× 10^6 cells/100 µl FACS buffer. Unspecific binding sites (Fc receptors) were blocked through incubation with 1 µg of human IgG (Sigma-Aldrich) for 15 min on ice. For extracellular staining, the cells were incubated for 25 min on ice in the dark with the fluorochrome-conjugated antibodies STRO1-FITC (fluorescein isothiocyanate), CD146-PE (phycoerythrin), CD105-APC (allophycocyanin), CD90-FITC, CD73-FITC, CD45-PE, CD34-APC, and SSEA4-FITC (all from BioLegend, Fell, Germany). For intracellular staining, the cells were fixed using paraformaldehyde-containing buffer (fixation buffer, BD Biosciences, Heidelberg, Germany), permeabilized using saponin-containing buffer (perm/wash buffer, BD Biosciences) and incubated with the fluorochrome-conjugated antibodies NANOG-PE, OCT4-Alexa Fluor 647 and SOX2-PE (all from BD Biosciences) for 25 min on ice in the dark. The flow cytometry analyses were performed using a BD LSR II Flow Cytometer (BD Biosciences). For each sample, 100,000 events were read. The analyses of the raw data were performed using the Summit 5.1 Software (Beckman Coulter, Fullerton, USA). The described procedure was conducted at least thrice for each donor.

Induction of neurogenic differentiation

Cells were seeded into six-well plates coated with 0.1 % gelatin (Sigma-Aldrich) at 1× 10^5 cells/well. Cells were cultivated for 5 weeks in neurogenic differentiation medium (NDM) consisting of neurobasal A medium (Gibco) supplemented with B27 supplement (2 % v/v, Gibco), 2 mM L-glutamine (Gibco), 20 ng/ml epidermal growth factor (EGF, Biochrom), 40 ng/ml recombinant human basic fibroblast growth factor (rh-bFGF, Biochrom), 100 U/ml penicillin, 100 µg/ml streptomycin and 2.5 µg/ml amphotericin B. Morphological changes towards a neuron-like phenotype were observed using an inverted microscope (Olympus Optical Co. Ltd., Tokyo, Japan). Expression of the neuronal marker proteins neurofilament light polypeptide (NEFL), neural cell adhesion molecule 1 (NCAM1) and enolase 2 (ENO2), of the osteogenic marker proteins BMP2 and BMP4 and of the embryonic transcription factors NANOG, OCT4 and SOX2 were assessed using quantitative reverse transcriptase polymerase chain reaction. These investigations were conducted at days 0, 3, 7, 14, 21, 28 and 35. Cells grown in CCM were used as negative control. NDM and CCM were changed every 2–3 d.

Induction of angiogenic differentiation

Cells (1× 10^5) were seeded into six-well plates coated with collagen I (Santa Cruz Biotechnology, Heidelberg, Germany) and expanded in CCM until they reached confluency. Afterwards, CCM was replaced through the angiogenic differentiation medium (ADM), which consisted of M199 medium (Gibco) supplemented with 5 % FBS,

	QuantiTect Primer Assay	Protein/enzyme (abbreviation)	Catalogue number	Detected transcript(s)
Neurogenic	Hs_ENO2_1_SG	Enolase 2 (ENO2)	QT00084889	NM_001975 (2423 bp)
	Hs_NCAM1_1_SG	Neural cell adhesion molecule (NCAM1)	QT00071211	NM_000615 (5977 bp) NM_001076682 (4944 bp) NM_001242608 (4831 bp)
	Hs_NEFL_1_SG	Neurofilament, light polypeptide (NEFL)	QT00096369	NM_006158 (3854 bp)
Angiogenic	Hs_ANGPT1_1_SG	Angiopoietin 1 (ANGPT1)	QT00046865	NM_001146 (4338 bp) NM_139290 (2379 bp)
	Hs_PECAM1_1_SG	Platelet and endothelial cell adhesion molecule 1 (PECAM1)	QT00081172	NM_000442 (6831 bp) XM_005276880 (4006 bp) XM_005276881 (3972 bp) XM_005276882 (3966 bp) XM_005276883 (3943 bp) XM_006721944 (2438 bp) XM_006721945 (2452 bp)
	Hs_FLT1_1_SG	Fms-related tyrosine kinase 1 (FLT1) or vascular endothelial growth factor receptor 1 (VEGFR1)	QT00073640	NM_002019 (7123 bp)
	Hs_KDR_1_SG	Kinase insert domain receptor (KDR) or vascular endothelial growth factor receptor 2 (VEGFR2)	QT00069818	NM_002253 (6055 bp)
Osteogenic	Hs_BMP2_1_SG	Bone morphogenic protein 2 (BMP2)	QT00012544	NM_001200 (3150 bp)
	Hs_BMP4_1_SG	Bone morphogenic protein 4 (BMP4)	QT00012033	NM_001202 (1957 bp)
Embryonic	Hs_NANOG_1_SG	Nanog homeobox	QT01025850	NM_024865 (2103 bp) NM_001297698 (2055 bp)
	Hs_POU5F1_1_SG	POU class 5 homeobox 1 (POU5F1)/octamer-binding transcription factor 4 (Oct4)	QT00210840	NM_001173531 (1589 bp) NM_002701 (1430 bp) NM_203289 (2075 bp) NM_001285986 (2300 bp) NM_001285987 (2075 bp)
	Hs_SOX2_1_SG	SRY (sex determining region Y)-box 2 (Sox2)	QT00237601	NM_003106 (2520 bp)

Table 1 QuantiTect primer assays (Qiagen) used for the qRT-PCR analyses

100 U/ml penicillin, 100 µg/ml streptomycin, 2.5 µg/ml amphotericin B, 50 µg/ml heparin (Sigma-Aldrich), 1 µg/ml hydrocortisone (Sigma-Aldrich), 60 µg/ml endothelial cell growth supplement (ECGS, PromoCell, Heidelberg, Germany), 10 ng/ml EGF (Biochrom), 25 ng/ml rh-bFGF (Biochrom) and 50 ng/ml vascular endothelial growth factor (VEGF, Gibco). The cells were cultivated for 5 weeks. Morphological changes towards an endothelial cell-like phenotype were observed using an inverted microscope. Quantitative reverse transcriptase polymerase chain reaction was used to assess the expression of the angiogenic marker proteins vascular endothelial growth factor receptor 1 and 2 (VEGFR1, VEGFR2), angiopoietin 1 (ANGPT1), and platelet endothelial cell adhesion molecule 1 (PECAM1), expression of the osteogenic marker proteins BMP2 and BMP4 and expression of the embryonic transcription factors NANOG, OCT4, and SOX2. These investigations were con-

Housekeeping genes	Hs_RRN18S_1_SG	18S ribosomal RNA (RRN18S)	QT00199367	X03205 (1869 bp)
	Hs_ACTB_1_SG	Actin, beta (ACTB)	QT00095431	NM_001101 (1852 bp)
	Hs_B2M_1_SG	Beta-2-microglobulin (B2M)	QT00088935	NM_004048 (987 bp) XM_005254549 (424 bp) XM_006725182 (424 bp)
	Hs_GAPDH_2_SG	Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	QT01192646	NM_002046 (1421 bp) NM_001289745 (1513 bp)
	Hs_SDHA_2_SG	Succinate dehydrogenase complex flavoprotein sub-unit A (SDHA2)	QT01668919	NM_004168 (2803 bp) NM_001294332 (2659 bp) XM_005248329 (2245 bp) XM_005248331 (2151 bp)
	Hs_YWHAZ_2_SG	Tyrosine 3-monooxygenase/ tryptophan 5-monooxyge-nase activation protein, zeta (YWHAZ)	QT02321522	NM_001135699 (3020 bp) NM_001135700 (2974 bp) NM_001135701 (3023 bp) NM_001135702 (3042 bp) NM_003406 (3003 bp) NM_145690 (3077 bp) XM_005251060 (3295 bp) XM_005251061 (3390 bp) XM_005251062 (3165 bp) XM_005251063 (3152 bp)

Table 1 Continuation: QuantiTect primer assays (Qiagen) used for the qRT-PCR analyses

ducted at days 0, 3, 7, 14, 21, 28 and 35. Cells grown in CCM were used as negative control. ADM and CCM were changed every 2 to 3 d.

Quantitative reverse transcriptase polymerase chain reaction

The expression changes occurring during neurogenic and angiogenic differentiation were investigated on transcriptional level using a two-step reverse transcriptase polymerase chain reaction. Briefly, total RNA was isolated using the RNeasy Plant Mini Kit (Qiagen, Hilden, Germany). Genomic DNA was eliminated through on-column DNA digestion (RNase-free DNase Set, Qiagen). The RNA concentration was measured using a microplate reader (Synergy H1, BioTek, Bad Friedrichshall, Germany). Synthesis of cDNA was conducted using 1 µg of isolated RNA and the QuantiTect Reverse Transcription Kit (Qiagen). Amplification and real-time quantification of the target cDNA were conducted using the QuantiTect SYBR Green PCR Kit, the QuantiTect Primer Assays (Tab. 1) and the Rotor-Gene Q Cycler (all from Qiagen). The PCR reactions involved an initial incubation at 95 °C for 5 min activating the HotStarTaq DNA polymerase and subsequent 40 cycles consisting of denaturation at 95 °C for 5 sec as well as annealing and extension at 60 °C for 10 sec. A melting curve was used to validate the specificity of the reaction products. Baseline correction, determination of the window of linearity and calculation of the PCR efficiency was performed using the software program LinRegPCR [36]. Normalization was conducted using 2 of the following housekeeping genes: actin beta (ACTB), beta-2-microglobulin (B2M), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), 18S ribosomal RNA (RRN18S), succinate dehydrogenase flavoprotein subunit (SDHA2) and tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta (YWHAZ). The two most stable housekeeping genes were identified with the software applet geNorm [44] and used for the normalization of the adjusted PCR data. Fold changes in gene expression were calculated using the delta delta CT method [34].

Statistical analysis

The qRT-PCR data recorded during the differentiation experiments were standardized by logarithmic transformation, mean centring and autoscaling [45]. The software program GraphPad Prism 6.0 (GraphPad Software, Inc.; La Jolla, CA 92037 USA) with one-way ANOVA was applied for the statistical analyses. Dunnett's multiple comparison tests were used as post-hoc tests. The main focus was to detect significant differences in gene expression compared to baseline/reference values at day 0. A value of $p \leq 0.05$ was considered statistically significant.

Results

Characterization of cells using flow cytometry

The mesenchymal stem cell markers CD73 (97.66 ± 1.92 %) and CD90 (98.87 ± 0.93 %) were expressed by almost all uninduced ihPDLSCs. CD146 (80.64 ± 23.87 %) and CD105 (78.02 ± 12.81 %) were expressed by the majority of cells. A low expression was observed for STRO1 (5.29 ± 3.62 %). The hematopoietic

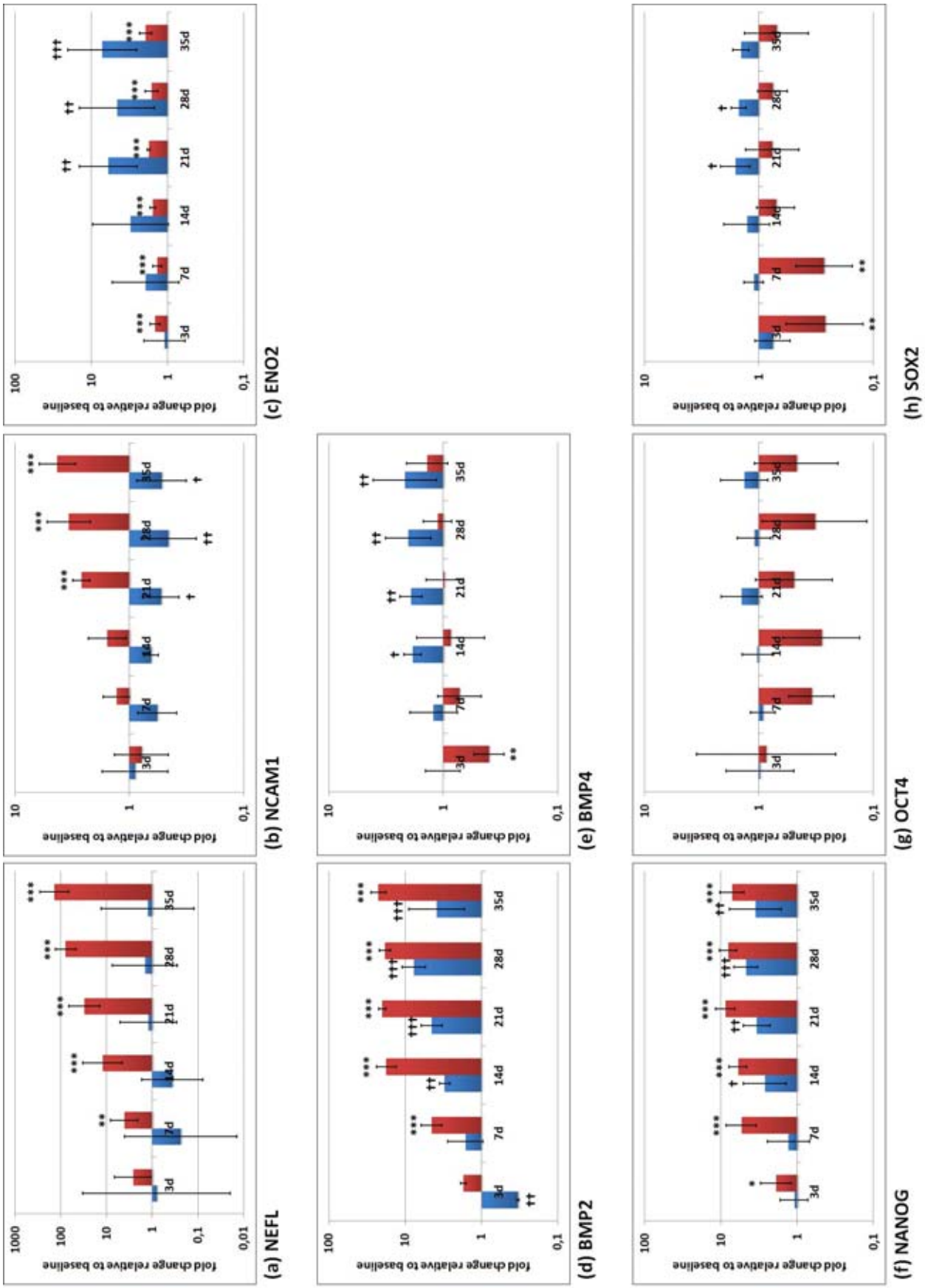


Figure 4a–h Expression of neuronal (NEFL, NCAM1, ENO2), osteogenic (BMP2, BMP4) and embryonic markers (NANOG, OCT4, SOX2) during neurogenic differentiation: The qRT-PCR data are presented as recalculated averages with upper and lower confidence interval (cells grown in NDM: red columns; cells grown in CCM: blue columns). One-way ANOVA with Dunnett's Multiple Comparison Test was used to detect significant differences to the reference value at day 0 (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; †: $p < 0.05$; ††: $p < 0.01$; †††: $p < 0.001$).

stem cell marker CD34 (4.74 ± 4.29 %) showed a low expression as well. Cells expressing the leucocyte common antigen CD45 (1.22 ± 0.46 %) were not detectable in most cases. The embryonic stem cell markers OCT4 (94.60 ± 1.95 %) and SOX2 (98.27 ± 0.36 %) were expressed by almost all cells. NANOG (52.09 ± 6.98 %) and SSEA4 (29.76 ± 12.38 %) showed a medium expression level. The summarized flow cytometry data are given in Figure 2.

Neurogenic differentiation

Cells cultivated in NDM proliferated slowly and showed first morphological changes towards a neuron-like phenotype 3–7 d after seeding (Fig. 3). Thus, cell bodies with elongated shape and dendrite-like extensions occurred. Cells grown in CCM proliferated rapidly and continued showing the fibroblast-specific spindle-shaped morphology. Due to proliferation and multilayered allocation, distinction of cells became more and more difficult at the advanced stages of the experiments. In both media, but in particular in the NDM, a parallel allocation of cells was observed.

Expression of neurogenic markers

In addition to morphological changes, expression of neuron-specific marker proteins was investigated on mRNA level (Fig. 4). Cells grown in NDM showed a continuously increasing expression of NEFL, NCAM1 and ENO2 when compared to cells lysed at day 0. The expression of NEFL was significantly up-regulated at day 7 ($p < 0.01$), 14, 21, 28 and 35 ($p < 0.001$). The expression of NCAM1 was significantly elevated at day 21, 28 and 35 ($p < 0.001$). The expression of ENO2 was significantly increased at day 3, 7, 14, 21, 28 and 35 ($p < 0.001$). In cells grown in CCM, the expression of NEFL did not significantly change, the expression of NCAM1 was significantly down-regulated at day 21 ($p < 0.05$), 28 ($p < 0.01$) and 35 ($p < 0.05$), and the expression of ENO2 was significantly up-regulated at day 21 ($p < 0.01$), 28 ($p < 0.01$) and 35 ($p < 0.001$).

The expression of BMP2 and BMP4 significantly changed in both media. The expression of BMP2 continuously increased in cells grown in NDM with significant values at day 7, 14, 21, 28 and 35 ($p < 0.001$) when compared to day 0. In cells grown in CCM, the BMP2-expression was down-regulated at day 3 ($p < 0.01$) and afterwards up-regulated with significant values at day 14 ($p < 0.01$), 21, 28 and 35 ($p < 0.001$). The BMP4-expression showed a significant increase in cells grown in CCM (day 21, 28 and 35; $p < 0.01$) and a significant decrease in cells grown in NDM (day 3; $p < 0.01$).

Expression of pluripotency markers

The transcription factor NANOG showed a continuously increasing expression in both media. This was significant at day 3 ($p < 0.05$), 7, 14, 21, 28 and 35 ($p < 0.001$) in cells grown in NDM and at day 14 ($p < 0.05$), 21 ($p < 0.01$), 28 ($p < 0.001$) and 35 ($p < 0.01$) in cells grown in CCM. The expression of OCT4 did not significantly change in both media. The expression of SOX2 was significantly down-regulated in cells grown in NDM (day 3 and 7; $p < 0.01$) and up-regulated in cells grown in CCM (day 21 and 28; $p < 0.05$).

Angiogenic differentiation

Cells cultivated in the ADM showed a polygonal endothelial cell-like morphology. This became evident especially at the advanced stages of the experiments (Fig. 5). The allocation of cells changed from a shoal-like to a cobblestone-like pattern. Cells grown in CCM continued showing a spindle-shaped morphology and a shoal-like allocation. The proliferation speed was comparable in both media.

Expression of angiogenic markers

Expression of endothelial cell-specific marker proteins was assessed on the transcriptional level (Fig. 6). A continuously increasing expression of VEGFR1, VEGFR2 and PECAM1 was observed in cells grown in ADM. The expression changes were significant at any time of the assessment. Interestingly, the expressions of VEGFR1 and PECAM1 were also up-regulated in cells grown in CCM. Thus, the expression of VEGFR1 was significantly increased at day 14 ($p < 0.01$), 21, 28 and 35 ($p < 0.001$). The expression of PECAM1 was significantly increased at day 7, 14, 21, 28 and 35 ($p < 0.001$). The expression of ANGPT1 was significantly down-regulated during the entire differentiation experiments in cells grown in ADM ($p < 0.001$) and slightly up-regulated in cells grown in CCM with a significant value at day 35 ($p < 0.05$).

The osteogenic marker proteins BMP2 and BMP4 showed significant expression changes in both media. A continuously increasing expression of BMP2 was observed in both media (significant at any time of the assessment; $p < 0.001$). The expression of BMP4 was significantly down-regulated at day 3, 7, 14, 21, 28 and 35 in cells grown in ADM and significantly up-regulated at day 14 and 35 in cells grown in CCM.

Expression of pluripotency markers

The pluripotency marker NANOG significantly increased in both media ($p < 0.001$ at any time of the assessment). OCT4 did not significantly change in both media. The expression of SOX2 was significantly down-regulated in cells grown in ADM (day 7; $p < 0.05$) and significantly up-regulated in cells grown in CCM (day 21 and 35; $p < 0.01$).

Discussion

Due to their multilineage differentiation potential, mesenchymal stem cells have attracted growing interest in regenerative medicine. Properties of mesenchymal stem cells have been attributed to cell populations isolated from inflamed pulpal [40], gingival [17, 40], and periodontal tissues [30, 31]. The purpose of the present study was to isolate and characterize cells from inflamed granulation tissue of intra-bony periodontal defects. Special focus was given to the neurovascular differentiation potential of the isolated cell populations. The neurogenic and angiogenic differentiation pathways were induced with well-established differentiation media [3, 4]. Changes in the expression of

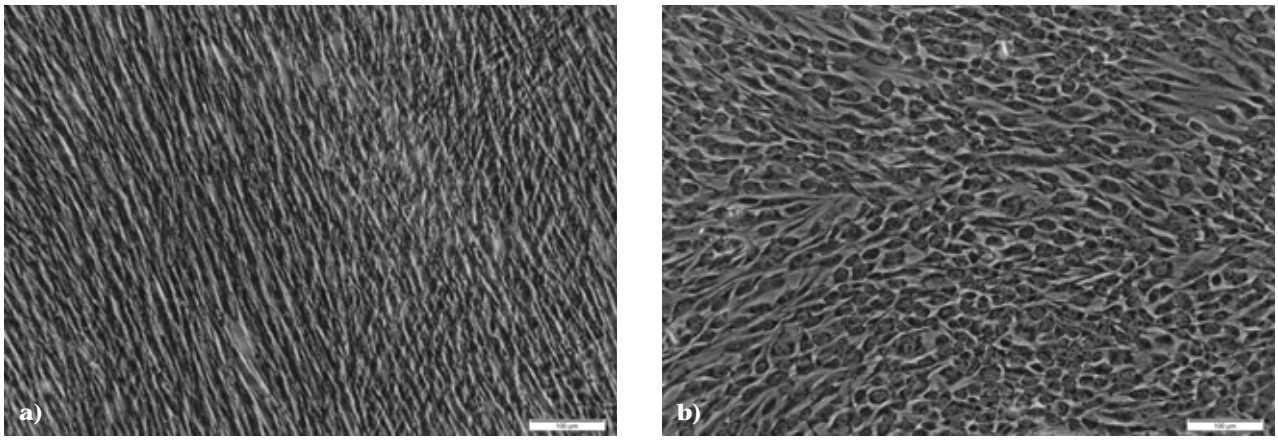


Figure 5a and b Histomorphological changes occurring during angiogenic differentiation: Representative microscopic images recorded during culture in (**a**) CCM and (**b**) ADM 21 days after initiation of the differentiation process. Note the round, polygonal cell morphology and the cobblestone-like arrangement.

the embryonic transcription factors NANOG, OCT4 and SOX2 during these differentiation processes were investigated to provide further insights to their functional role in adult mesenchymal stem cells. Moreover, the functional role of the osteogenic marker proteins BMP2 and BMP4 within the neurogenic and angiogenic differentiation process was evaluated on mRNA level.

Periodontal diseases are mainly caused by anaerobic, gram-negative bacteria, known as periodontal pathogens. Despite the inflamed condition and the presence of periodontal pathogens, harvesting of the periodontal granulation tissues was not associated with any event of microbial contamination during the establishment of our cell cultures. This was due to the non-surgical periodontal pretreatment, which led to a significant reduction of the bacterial load within the periodontal pocket, and due to the supplemented antimicrobials that were used during the enzymatic digestion, cell culture expansion and long-term experiments.

Flow cytometry was used to investigate the expression of epitopes characteristic for mesenchymal stem cells (CD73, CD90, CD105, CD146, SSEA4 and STRO1) and the expression of transcription factors characteristic for embryonic stem cells (NANOG, OCT4 and SOX2). Almost all investigated cells expressed CD73 and CD90 (> 95 %). In addition, the majority of cells expressed CD105 (78 %). CD73, CD90 and CD105 are not only expressed by mesenchymal stem cells, but also by differentiated cells like fibroblasts [28]. Therefore, further markers, like CD146, SSEA4, and STRO1, have been used to prove the presence of mesenchymal stem cells [5, 14, 15, 24, 25]. CD146 (80 %) showed high, SSEA4 (29 %) medium and STRO1 (5 %) low expression in our cell cultures. Recently, comparable results were published for these cell surface molecules [2]. Interestingly, the pluripotency markers NANOG (52 %), OCT4 (94 %) and SOX2 (98 %) were expressed by a large part of our cell populations. This topic will be discussed in more detail at the end of the discussion section. In summary, the flow cytometry data (Fig. 2) suggest that a significant number of mesenchymal stem cells reside in the granulation tissue of intra-bony periodontal defects.

Experiments investigating the neurovascular differentiation potential of ihPDLSCs were used to prove multipotency. Most studies use the osteogenic, adipogenic and chondrogenic pathway to prove multilineage differentiation potential, as proposed by Dominici et al. [12]. Accordingly, Páll et al. [30] demonstrated that cells derived from periodontal granulation tissue are able to generate Alizarin Red S-positive mineralized extracellular matrix, Oil Red O-positive lipid deposits and Alcain Blue-positive chondrogenic micromasses. Aside from osteogenesis, neither adipogenesis nor chondrogenesis is required for the regeneration of tooth-supporting tissues. Therefore, we decided to focus our experiments on the neurogenic and angiogenic differentiation pathways, which are required to warrant the neurovascular supply of the regenerated tissues. During our experiments, we observed the development of a neuron- and endothelial cell-like phenotype (Fig. 3 and 5). Cells grown in NDM exhibited the slowest proliferation rate when compared to cells grown in ADM and CCM. Cells grown in ADM and CCM reached complete confluency on average after 3–7 d. At the same time, there were wide open intercellular spaces in cultures grown in NDM. This phenomenon can be interpreted as prompt modification of the cellular metabolism towards the neurogenic differentiation pathway. In addition, cells grown in NDM immediately started to change their morphological appearance. The elongated cell bodies and the dendrite-like cell protuberances were clearly different from the cell morphologies that were observed in cells grown in CCM. Significant morphological changes induced by ADM were observed later and became obvious after 14–21 d through the development of round-shaped, cobblestone-like arranged cells with a chromatin-rich nucleus. Both differentiation media had a significant impact on the cell

morphology and the pattern of cellular growth. This is an indication that a differentiation process had taken place.

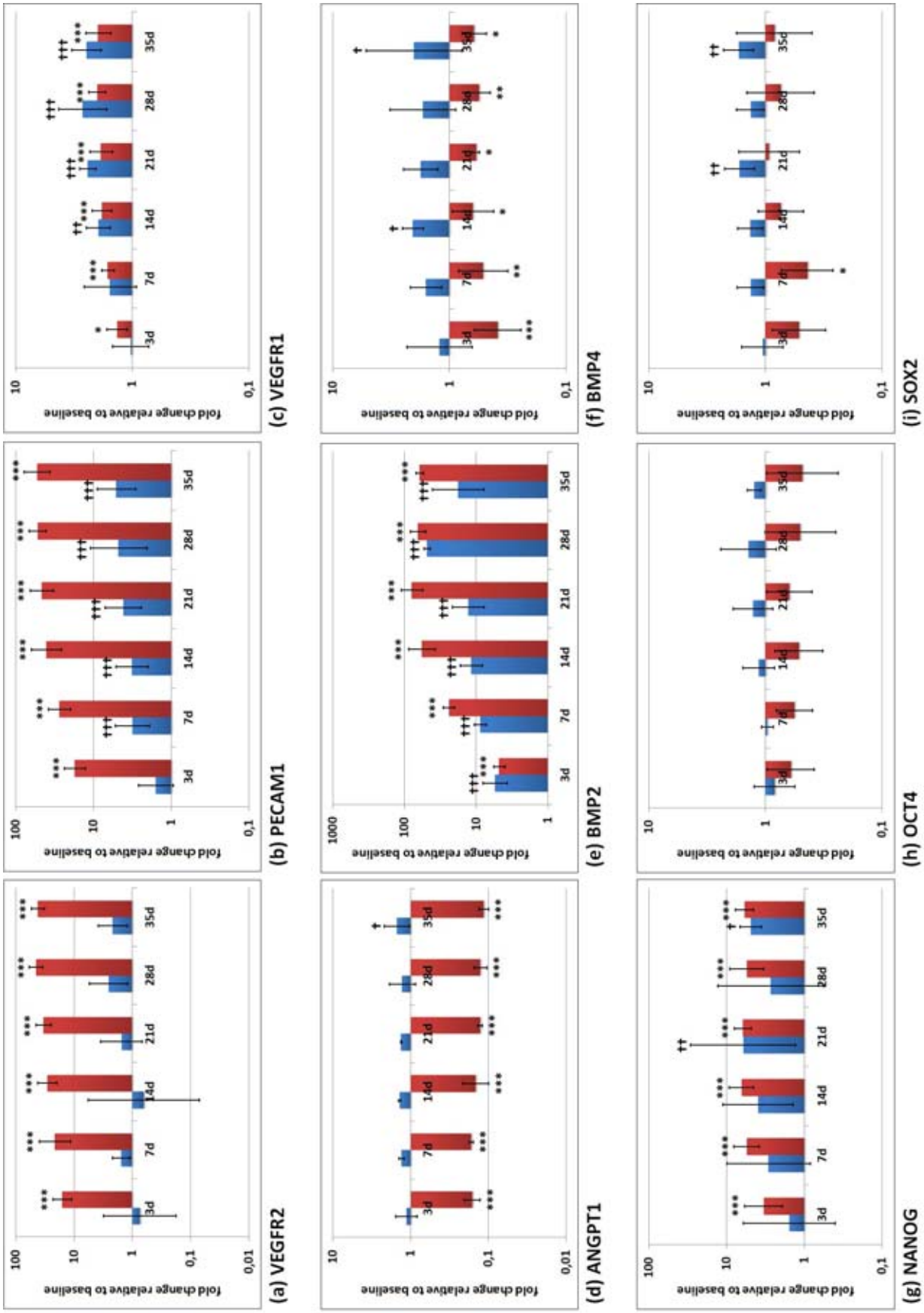
On the transcriptional level, a continuously increasing expression of neuron- (NEFL, NCAM1, ENO2) and endothelial cell-specific marker proteins (VEGFR1, VEGFR2, PECAM1) was observed (Fig. 4 and 6). Interestingly, the expression of ENO2, PECAM1 and VEGFR1 was also increased in cells grown in CCM. These observations suggest that cells grown in CCM show the tendency towards spontaneous differentiation with advanced duration of culture. However, the expression of ANGPT1 was significantly different between cells grown in ADM and CCM, respectively. Whereas a slight increase was observed in cells grown in CCM, a significant decrease was detected in cells grown in ADM. ANGPT1 as an antagonist of ANGPT2 is responsible for the maintenance of vascular quiescence [13]. Branching out of new blood vessels is only enabled when the expression of ANGPT1 is down-regulated, as observed in our experiments when cells were grown in ADM.

Recently, we could show that ihPDLSCs exhibit osteogenic differentiation potential [1]. After induction with osteogenic differentiation medium (ODM), ihPDLSCs showed pronounced matrix mineralization and an up-regulation of alkaline phosphatase and BMP2, which are stage-specific markers characteristic for osteoblastic differentiation. In the present study, we demonstrated that the expression of the osteogenic marker BMP2 is not only increased in cells grown in ODM, but also in cells grown in NDM, ADM and CCM. In cells grown in CCM, this increase can be understood as spontaneous differentiation of ihPDLSCs to osteoblast-like cells, as described by Trivanovic et al. [41]. BMPs are also known to regulate the proliferation and differentiation of neural precursors [37]. Accordingly, Hegarty et al. [21] reported that BMP2 induces neuritogenesis. In addition, BMP2-signaling is involved in vascular development and dysfunction [16]. Benn et al. [6] demonstrated that BMP2 and BMP6 are proangiogenic and induce angiogenesis through binding to specific BMP type I receptors. The results of our study support the hypothesis that BMP2-signaling is involved in neurogenic and angiogenic differentiation.

The expression of BMP4 was significantly down-regulated at the beginning of our neurogenic and angiogenic differentiation experiments. Meyers et al. [27] have shown that an increased expression of BMP4 is associated with reduced neurogenesis and that an inhibition of BMP4-signaling increases neurogenesis. Moreover, BMP4 and VEGF regulate the differentiation of pluripotent stem cells to endothelial cells in a synergistic way [32, 39]. BMP4 is known to convert pluripotent stem cells into mesodermal cells and subsequently VEGF is known to induce the differentiation of endothelial cells. Since ihPDLSCs are cells of mesodermal origin, the expression of BMP4 was not necessarily to be expected and indeed down-regulated during the angiogenic differentiation experiments.

Despite intense research in the field of mesenchymal stem cells, the molecular mechanisms of self-renewal, differentiation and multipotency are not well understood. Pluripotency and self-renewal of embryonic stem cells are regulated by a network of transcription factors, like NANOG, OCT4 and SOX2 [7, 23]. Yu et al. [46] reported that the transcription factors NANOG, OCT4, SOX2 and LIN28 are sufficient to reprogram human somatic cells into induced pluripotent stem cells. This underlines the importance of these factors for the pluripotent state. There is growing evidence that the transcription factors NANOG, OCT4 and SOX2 are not only expressed by embryonic stem cells but also by mesenchymal stem cells [19]. These factors are supposed to regulate the processes of self-renewal, differentiation and multipotency in mesenchymal stem cells [42, 43]. The flow cytometry data of our study revealed that NANOG, OCT4 and SOX2 were expressed by a large part of our heterogeneous cell populations. Therefore, we examined how the expression of these transcription factors was changing during neurogenic and angiogenic differentiation. If the multipotent state is depending on NANOG, OCT4 and SOX2, one would assume that the expression of all these transcription factors is decreasing in the course of differentiation processes. However, the expression of NANOG was significantly up-regulated, the expression of SOX2 was significantly down-regulated (especially at the beginning of the differentiation experiments) and the expression of OCT4 did not significantly change in our study. The large error bars in Figures 4 and 6 reflect that there were distinct inter-individual differences. Interestingly, the expression of OCT4 was significantly down-regulated during both differentiation pathways in 3 donors (with expression patterns of great similarity), almost unchanged in one donor, and clearly up-regulated in one donor (data not shown). Therefore, the most frequently observed decrease in OCT4-expression failed to be statistically significant.

There are several studies investigating the expression of NANOG, OCT4 and SOX2 in mesenchymal stem cells, but only a few assessing the expression changes in the course of *in-vitro* differentiation processes. Greco et al. [19] investigated the expression of NANOG, OCT4 and SOX2 in human bone marrow mesenchymal stem cells using semi-quantitative RT-PCR. They found strong expression of all 3 transcription factors in uninduced cells, but no expression 6 and 12 d following neuronal induction. For OCT4 and SOX2, a similar tendency of decreasing expression could be observed in our study for both, the neurogenic and angiogenic differentiation. Pierantozzi et al. [35] investigated the expression of NANOG, OCT4 and SOX2 in human adult mesenchymal stem cells (bone marrow MSCs, adipose tissue MSCs and cardiac tissue MSCs) using semi-quantitative RT-PCR and immunofluorescence assays. While OCT4 and SOX2 were not detectable at any time of their experiments, NANOG was not expressed by freshly isolated mesenchymal stem cells, but by proliferating cells under *in-vitro* culture conditions. These



(Fig. 1–6; Tab. 1: K. Adam)

Figure 6a–i Expression of angiogenic (VEGFR1, VEGFR2, PECAM1, ANGPT1), osteogenic (BMP2, BMP4) and embryonic markers (NANOG, OCT4, SOX2) during angiogenic differentiation: The qRT-PCR data are presented as recalculated averages with upper and lower confidence interval (cells grown in ADM: red columns; cells grown in CCM: blue columns). One-way ANOVA with Dunnett's Multiple Comparison Test was used to detect significant differences to the reference value at day 0 (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; †: $p < 0.05$; ††: $p < 0.01$; †††: $p < 0.001$).

findings suggest that the expression of NANOG is not required *in-vivo* and only activated when mesenchymal stem cells are grown *in-vitro*. This might be a possible explanation for the continuously increasing expression of NANOG in our study. In addition, Pierantozzi et al. [35] figured out that there was not a direct correlation between the number of NANOG-positive cells and the adipogenic, osteogenic and chondrogenic differentiation potential of the investigated cell populations. Liu et al. [26] investigated the effects of ectopic NANOG and OCT4 overexpression on human bone marrow-derived mesenchymal stem cells. They could show that NANOG and OCT4 overexpression had different effects on adipogenesis. While NANOG overexpression slowed down adipogenesis, OCT4 overexpression improved adipogenesis. Moreover, NANOG and OCT4 overexpression both improved chondrogenesis. These findings suggest that NANOG and OCT4 play a functional role in the *in-vitro* differentiation of mesenchymal stem cells with different functions depending on the differentiation pathway.

To conclude, there are controversial data about the functional role of the transcription factors NANOG, OCT4 and SOX2 in mesenchymal stem cells. However, our data suggest that NANOG and SOX2 are involved in the regulation of multipotency and differentiation, at least under *in-vitro* culture conditions.

Conclusions

The inflamed granulation tissues derived from intra-bony periodontal defects contain cell populations with properties of mesenchymal stem cells. These properties comprise the expression of characteristic cell surface antigens and multilineage differentiation potential. In addition, the pluripotency markers NANOG, OCT4 and SOX2 are expressed by a wide range of the isolated cell populations. In particular NANOG and SOX2 seem to be involved in the processes of self-renewal and differentiation in adult mesenchymal stem cells. Moreover, our *in-vitro* data suggest that BMP2, but not BMP4 is required for the processes of neurogenic and angiogenic differentiation. Future research shall confirm our data on translational level.

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Conflicts of interest:

The authors declare that there is no conflict of interest within the meaning of the guidelines of the International Committee of Medical Journal Editors.

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(Photo: Hannover Medical School)

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Karl Häupl (1893–1960) – His life and works with special consideration of his role in the Third Reich

Introduction: Karl Häupl is considered one of the most famous European dentists of the 20th century. The aim of this article is to trace the life and work of the Austrian university lecturer and to evaluate his professional contributions. An additional focus is put on Häupl's role in the Third Reich.

Material and Methods: The methodological basis of the study is the evaluation of sources from various German and Austrian archives (some of which have been evaluated for the first time) and a critical re-analysis of the relevant research literature.

Results: The analysis demonstrates that Häupl was one of the most influential and effective university lecturers in dentistry and, in particular, one of the pioneers of functional orthodontics; this is fully in line with the contemporary assessment. In contrast, the classification of his role in the "Third Reich" is clearly discrepant: Although Häupl's relationship to National Socialism was not addressed for decades, the archival sources provide clear evidence of political entanglement.

Discussion and Conclusion: The analysis of the relevant sources leads to the conclusion that in the Third Reich Häupl was politically true to the line. He did not only join the National Socialist Party, but also enjoyed the backing and support of the major Nazi networks in his chair applications (German University Prague, University Berlin), honours, and further initiatives.

Keywords: National Socialism; history of dentistry; functional orthodontics; periodontology; NSDAP

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Introduction

Karl Häupl (1893–1960, Fig. 1) is, without a doubt, one of the most well-known European dentists in recent history. Considered to be a pioneer in the area of functional orthodontics, Häupl held numerous prestigious professional positions and he received many awards. He was the dean of the Medical Faculty at the University of Innsbruck, rector of the Medical Academy of Dusseldorf, he was awarded two honorary doctoral degrees, became an honorary citizen of his hometown, an honorary member of various international professional associations, and a selected member of the American College of Dentists – just to cite a few of his many achievements. In 1978, his name was posthumously ascribed to the "Karl Häupl Institute", a renowned professional dental training establishment in Dusseldorf.

The aim of the present article is to reconstruct and professionally situate the life and work of this Austrian dentist. An additional focus is on Häupl's role in the Third Reich. This investigation was carried out as part of the national project "Dentists and Dentistry under National Socialism". The three-year research, which was completed in 2019, revealed the broad political commitment of German and Austrian dentists during this period. The year 2020 also marks the sixtieth anniversary of Häupl's death.

Materials and Methods

The main sources used for this study are archival documents from the German Federal Archives in Berlin, the State Archives in Dusseldorf and the University Archives in Vienna. Additionally, a critical analysis of relevant international research findings on the life and works of Häupl was conducted, including contemporary professional debates about orthodontics and dentistry under National Socialism. A total of about 40 laudations, obituaries and other publications related to his person were identified and evaluated.

Findings

Karl Häupl – central biographical stations

Karl Häupl was born in Seewalchen am Attersee, Austria, on April 12, 1893 [9–12, 15, 39, 43–44, 47–48, 52]. His father (1865–1927), of the same name, was a local inn-keeper and the mayor of the town for a time. Häupl attended elementary school in the town of his birth and spent his secondary school years at the episcopal Petrinum Gymnasium, a private catholic school in the Linz diocese. He quickly came to receive recognition from his superiors for his industriousness and "extraordinary memory" [44]. After obtaining his degree from the humanistic secondary school (gymnasium) in the town of Kremsmünster, Häupl went on to study human medicine at the University of Innsbruck in 1912, while his brother Josef was tasked with taking over the inn from their father [14]. On account of the First World War, Häupl was forced to interrupt his medical studies in 1914, the year he was conscripted in the First Territorial Army Regiment. After being seriously injured during a battle in Poland in April 1915, Häupl was sent to serve at the division for orthodontic medicine at Clinical Reserve Hospital in Innsbruck.

In March 1919, Häupl obtained his license to practice medicine followed by an academic promotion to Doctor of Medicine in Innsbruck. He soon found a position at the Dental Institute of the University of Innsbruck under Bernhard Mayrhofer. He was promoted to First Assistant after just 6 months.

In 1920, Häupl moved to Norway, where he worked at various dental practices in Bergen and Oslo. He obtained a position as First Assistant at the Surgical Department of the Royal Dental College in Oslo in 1923, where he also became certified in the area of dental medicine. In 1924, he passed the dental medicine examination and received his license to practice medicine in Norway. A few years later, in 1927, Häupl attained a postdoctoral qualification (*habilitation*) – which was accompanied with a Norwegian M.D. title – as well as a lectureship. In 1929, he became the head of the Laboratory for Pathology at the Dental College in Oslo, and in 1931 professor for General and Specialized Dental and Maxillofacial Pathologies. At the end of 1930, Häupl married his first wife, the Norwegian Karen Hangsöen, with whom he had his first child in 1931 and his second in 1936 [2].

On October 1, 1934, Häupl became a full professor and the chair of the Clinic for Dental and Maxillofacial Diseases at the Germany University of Prague [41, 49, 55] in former Czechoslovakia. The Charles University of Prague, founded in 1348 by King Charles IV, was the oldest university in the "Holy Roman Empire of the German Nation". In 1882, the university was divided into a German and a Czech university as a result of growing nationalism in Austria-Hungary. While in this position, Häupl played a key role in expanding the clinic. Starting in 1941, he was also appointed as a medical officer and as the head of the military hospital for patients with maxillofacial and facial injuries in Prague.

In 1943, his career experienced another significant leap forward when Häupl assumed the role of full professor and head of the department for Orthodontics and Dental Prosthetics at the Dental Institute of Berlin. Upon assuming this position, he succeeded the then recently deceased Hermann Schröder and, as of 1944, he assumed the role of director of the entire institute. Schröder was considered to be one of the most important university professor for dental medicine of his time, and the institute itself was the leading institution in Germany.

After the end of the war, Häupl returned to Austria. Here his brother Josef had served as mayor of Seewalchen during the NS era. Karl Häupl was unceremoniously offered a professorship in Innsbruck; he accepted and worked to rebuild the city's dental institute [57]. During this period, he declined numerous professorships at various German universities (Hamburg, Marburg and Freiburg) and at the University of Vienna [54]. Though he did not accept the latter position in Vienna, Häupl did seek to influence the selection process by announcing his praise for candidates Hermann Wolf and Arthur Martin Schwarz while offering a negative assessment of Fritz Driak – who would ultimately assume the position: "The answer to the question of what lasting contribution

(Source: German Dentistry, Oral and Maxillofacial Surgery 1958;28:353)

Figure 1 Portrait Karl Häupl

Driak has made to dentistry cannot be anything positive" [46].

In 1951, Häupl took on a professorship for oral, jaw and dental medicine and maxillo-facial surgery at the West German Jaw Clinic of the Medical Academy of Dusseldorf [17, 37–38, 53]. As the West German Jaw Clinic was a leading institution in its area at the time, this was an extremely prestigious position [17, 38].

On June, 29 1960, Häupl passed away in Basel as a result of highly dramatic circumstances. While giving a speech to commemorate the 500th anniversary of the University of Basel in 1960, he suffered a heart attack and collapsed in front of the attendees and in front of his second wife, Katharina – an event that was subsequently mentioned in various obituaries and remembrances [39, 44, 52]. In his biography, Jüliger speculated that Häupl had suffered from the stress of a trip to the United States that he had just taken, having arrived in Basel at the last minute after the train he had been riding on derailed [39]. Häupl's second wife outlived him by 28 years, passing away in Seewalchen in 1988 (Fig. 2).

Häupl's scientific oeuvre and his impact in the area of dental medicine

Together with the Norwegian dentist, Viggo Andersen, Häupl was the founder of internationally acclaimed practice of functional orthodontics [9–12, 39, 43, 45, 47, 48, 52, 56]. Functional orthodontics is a treatment concept that uses passive tooth-born appliances placed in the oral cavity to stimulate the soft and hard tissue of the masticatory (chewing) system to alter its muscular functional patterns and thereby react to adjustments and growth. Starting in the mid-1920s, both dentists entered the public spotlight with their concepts and devices, first in Oslo and later internationally, especially with the so-called "Andersen-Häupl Activator". Häupl's book, "Functional Jaw Orthodontics" (1936), co-authored with Viggo Andersen, quickly established itself as a standard reference work, with 6 different editions published up to 1957 [1]. At the same time, Häupl emerged as a critic of the competing treatment concept based on "removable plates". He engaged in a professional dispute with his colleague Martin Schwarz in Vienna on this issue, which did not, however, disrupt the personal "esteem and friendship" the two had for one another. Additionally, he also had a scientific disagreement with the no less influential orthodontist from Bonn Gustav Korkhaus about the risks and side effects of fixed orthodontic appliances [18, 42].

Besides functional orthodontics, Häupl also did research in the areas of periodontology as well as bone histology and pathology, accompanied by work on the periodontium and dental surgery. It was not without reason that, in 1957, Reichenbach cited Häupl one of his few remaining colleagues "with a mastery of the largely expanded area of dental, oral and jaw medicine and with the ability to excite and guide numerous specialists working in this area" [48].

In his lifetime, Häupl would author 150 publications, including 10 books. Along with the textbooks about functional orthodontics, 2 highlights include the development of his post-doctoral piece about marginal periodontitis (published in 1927 with Franz Josef Lang) and his book about dental crown and bridge work (published in 1929 with Ingjald Reichborn-Kjennerud), the second edition of which was published in 1938 under the title "Dental Crown and Bridge Work". His histological studies about tissue remodeling and tooth displacement in functional orthodontic (1938), of tooth histopathology and the support brace (1940) and the two-volume textbook of dentistry (1949–1950, 2nd edition 1953) went on to become standard references in the area. One of Häupl's final books was "Kieferorthopädie" (1959, 2nd edition 1963) and he also published a handbook about dental oral and orthodontic medicine, released as 6 volumes in 7 parts (published in 1955ff with Wilhelm Meyer and Karl Schuchardt) [31–36].

During his career, Häupl held numerous offices and received many honors and awards, only a small sample of which we are able to present here [9–12, 39, 43, 44, 47, 48, 52]: In the post-war era, he held the positions of senator and dean of the Medical Faculty of the University of Innsbruck in 1949, he was named honorary citizen of Seewalchen (his town of birth) in 1952, he was elected president of the German Working Group for Periodontics Research (ARPA, today known as the DGParo), he received an honorary doctoral degree from the University of Freiburg in 1958 and from the University of Halle/Saale in 1960, and he was selected as a member of the American College of Dentists in 1959. Häupl was a member of the German National Academy of Sciences Leopoldina and an honorary member of German, Austrian, Finish, Danish, Swedish, Norwegian and Italian professional associations. After his death, Häupl was buried in a grave of honor in the town of Seewalchen. In 1978 – 18 years after passing away – the Dental Association of Nordrhein founded the "Karl-Häupl Institute" in his honor, a professional training establishment in Dusseldorf.

Häupl had left a special mark on the city: After years of reform bottlenecks, he brought about a far-reaching reconstruction and expansion of the West German Jaw Clinic in Dusseldorf. Additionally, the pinnacle of his career came in 1957 when he assumed the position of rector there. Following Oskar Römer (1928), Johannes Reinmöller (1933) and August Lindemann (1948), this made Häupl only the fourth university

professor of dental medicine that held this position at a German university.

Karl Häupl studied under influential academics, including Gustav Adolf Pommer (1851–1935), Arturo Hruska sen. (1880–1971) and Bernhard Mayrhofer (1868–1938). Häupl himself guided many of his own pupils to success, including Fritz Brosch (1903–1981), Josef Eschler (1908–1969), Heinz Raab (1909–1987), Hans Wunderer (1912–1994) and Hubert Stöger (1913–1980) [39].

Häupl's relation to National Socialism

There is no doubt that in the Third Reich (1) Häupl was looked upon as politically loyal to the line, and that (2) he enjoyed the support of his Nazi superiors. There is a wide range of formal and factual indications supporting this claim:

The first *formal* indication of this is the fact that the native-born Austrian became a member of the NSDAP after the "Anschluss" (annexation) of Austria to the German Reich which is documented in the Federal Archives [5, 7]. Though no specific date is given for his entry into the party, Häupl himself stated that he had submitted a request for membership into the NSDAP in April 1939, a statement that is also contained in the archives [2]. This coincides with information from Míšková (2007): She noted (but without mentioning the primary source) that Häupl had been a member since 1.4.1939 and had received the party number 7,187,557 [45].

A second formal indication is offered by a term that Häupl himself chose to use: During his time in Prague, he referred to himself as "gottesgläubig" (believer in God) on a questionnaire that he filled out [2]. "Gottesgläubig" was a term introduced and used by the Nazis, referring to an individual who was religious but had turned away from his church for political reasons – Häupl was originally a Protestant. The word served as "proof of ideological proximity to National Socialism" [8].

Besides, there are also a number of factual indications of Häupl's commitment to the National Socialist party. One early piece of evidence is offered by Häupl's successful bid to assume a professorship at the German University of Prague: the relationship between the adjacent German and Bohemian universities in Prague that existed since 1882 became politically very tense during this period, with nationalist radicalization occurring at both universities at the time. After the "Munich Agreement" from the fall of 1938, the German university officially renounced its loyalty to the Czechoslovakian state, just prior to the disintegration of the rest of Czechoslovakia by the Nazis in March 1939.

The German University of Prague became a (imperialistically oriented) prestige project for the Nazis following Hitler's rise to power. Thus professorships at the German University were generally reserved for instructors loyal to the regime, as Míšková has described in detail [45]. The fact that Häupl played a major role in the development of the German University for many years (1934–1943) underlines that he was seen as politically trustworthy. In his memoirs, the pathology professor Herwig Hamperl, who was working at the German University of Prague at the same time as Häupl, noted that he had been surrounded by colleagues with a National Socialist orientation [25], a circumstance he highlighted in order to justify his own NSDAP membership. Additionally, Häupl's colleague and eventual successor in Dusseldorf, Carl-Heinz Fischer, also made direct reference to Häupl's professorship in Prague. Fischer remembers the speech by the National Socialist "Reichszahnärzteführer" (Reich dentist leader) Ernst Stuck on the occasion of the DGZMK annual conference in 1938, which was "entirely under the influence of the Third Reich". In the speech in question, Stuck spoke of Häupl's role at the German University in Prague and described Häupl as a "man called up for this difficult task" [12]. The support that Häupl enjoyed from his Nazi superiors is also illustrated by the fact that he was promoted to corresponding member of the politically centralized DGZMK the same year, 1938 [24].

From other files of the Federal Archives it is clear that Häupl was in exchange with both "Reichszahnärzteführer" Ernst Stuck and "zahnärztliche Reichsdozentenführer" (Chief Lecturer Dentist) Karl Pieper and that he could rely on the support of these two influential Nazis. Häupl had asked for support for Josef Eschler, his closest academic *protégé* and later successor in Prague, and obviously succeeded: On May 13, 1942, he thanked Pieper for his "outstanding services" in promoting Josef Eschler: "[...] I would like to take this opportunity to thank them very much for their commitment to Eschler at the time. Heil Hitler!" [4]. At the beginning of 1940 Pieper had already arranged for Eschler to be appointed as a "Privatdozent" sooner than usual so that Eschler fulfilled the requirements to be appointed professor in Tokyo – this initiative was also preceded by a letter of request from Häupl (dated November 11, 1939) [4].

Another clear indication of Häupl's political propinquity to the Nazi regime was his appointment as professor at Berlin in 1943. The Dental Institute in Berlin was the most prestigious institution of its sort under the Third Reich. As with the German University of Prague, only individuals with a National Socialist orientation who towed the party line were considered for eminent positions. This is evidenced by the circle of individuals ultimately considered for the corresponding professorship. Favored were "Reichsdozentenführer" Karl Pieper – adecorated "Blood Order" bearer and a glowing National Socialist with a very modest academic body of work [24, 29] who would ultimately turn down the position in favor of negotiations to remain at Munich –, Erwin Reichenbach, a member of the NSDAP and SA since 1933 [27, 50] and the candidate who was ranked first for this position, Karl Greve, a self-confessed National Socialist and Wehrmacht soldier, and Karl Häupl himself.

The fact that Häupl had particularly important advocates in the relevant Nazi networks was revealed in the further decision-making process: According to archive sources, Hermann Göring – the "Reich's Marshal" and unquestionably one of the most important members of the National Socialist party – personally supported

(with friendly permission of Hans Rauchenzauner, Seewalchen)

Figure 2 Grave Karl Häupl

Häupl's candidacy for the professorship [3, 5]. Specifically, the files state that "by order of the Reich's Marshal" it was announced "that Professor Häupl from Prague would be appointed in place of the now deceased Professor Schroeder [...] His appointment should be carried out without debate." In fact, Göring's order was carried out, as the representative of the responsible ministry told him submissively: "Your wish and the scientific qualification of Professor Häupl were decisive for the appointment." However, the ministerial representative did not fail to point out "that the Berlin faculty had not included Professor Häupl on the list", since he "would not be considered as the successor of Professor Schröder for the subject of dental prosthetics, since his scientific research field was in a different area" [5].

In fact, even Professor Eugen Wannenmacher – official head of the dental press – had himself expressed his views on the appointment issue in letters, arguing *against* Häupl's election for purely technical reasons: "Reichenbach and Greve have proven themselves as heads of prosthetic departments for years. These comparisons explain that Häupl could not be mentioned on the same level as Reichenbach and Greve on the list of appointments" [6]. But Wannemacher's argumentation went unheard and Häupl was appointed.

The Berlin faculty was also unhappy with Göring's demand that Häupl should become full professor – in contrast to the two other representatives of the Berlin Institute, Otto Hofer and Eugen Wannenmacher, who were only associate professors. The faculty argued as follows: "As the youngest representative of the subdivision brought to Berlin, he would be the only full professor. This means a great setback for the other two representatives of the subdivision." But also in this point Göring stuck to his position [5].

One final piece of evidence indicating Häupl's allegiance to National Socialism comes from 1944. In this year, Häupl was appointed by to the "Scientific Committee of Representatives for the Health System Karl Brandt", a prestigious honor that was only granted to individuals who were loyal to the regime. Karl Brandt was one of the highest-ranking physicians in the context of the Nuremberg Doctors' Trails: During the Third Reich, he served as SS *Brigadeführer* and General Major of the Waffen-SS as well as the General Commissioner for the Sanitary and Health System. It was probably against this background that Ernst Klee integrated Häupl in his frequently cited "encyclopaedia of persons" (*Personenlexikon*) of the Third Reich published in 2003. According to Klee, the encyclopaedia listed "the social elite in the time of the Third Reich" and those individuals "who always [resurface] in studies of the Nazi era" [40].

Häupl's brother Josef, who had taken over their father's inn, also placed himself at the service of National Socialism in the "Great German Reich". As mentioned, he held the post of mayor of Seewalchen during the Nazi regime, for which he should be held accountable after the war: from 1945 to 1947 he was forced to shut down his traditional inn [13].

Discussion and Conclusions

Karl Häupl's life deserves special attention for 3 principle reasons. First, an analysis of his writings and awards underscores Häupl's very pivotal role in the area of academic dental medicine and especially orthodontics – contemporary and retrospective assessments are fully in accord on this matter. Second, Häupl led a notable life full of exceptional experiences with professional periods in 4 European countries (Norway, Czechoslovakia, Germany and Austria) – a life that ended abruptly and quite dramatically in 1960. Third, the reception of Häupl's relationship to National Socialism was subject to a notable transformation. The findings about Häupl's role in the Third Reich are clearly in strong contrast to the descriptions that were written about Häupl in post-war Germany as well as in the subsequent decades. For a long period of time, the predominant view about Häupl was largely uncritical and rather euphemistic. The question as to his relationship to National Socialism was simply ignored in his biographies – a phenomenon that also applied to the broader populace at this time, *cum grano salis*, and for the organized dental profession, which significantly contributed to delaying the entire process of coming to terms with the Nazi professional community [21, 22, 30, 51].

In particular, during the post-war years in Germany, Josef Eschler constructed a positive, almost hagiographic, depiction of his academic

mentor Häupl via numerous laudations [9–12]: "Hard with himself and benevolent with his colleagues, he always tried to resolve every dispute amicably. His incredible spirit, his generosity and his great modesty attest to his true devotion to medicine and his humaneness" [12]. The same applies for Jüliger, whose doctoral thesis was a biography of Häupl. Not one of the 135 pages of his work talks about Häupl's role during the Third Reich. He neither makes mention of Häupl's membership in the NSDAP nor does he address the issues related to his numerous appointments and professorships cited above [39]. On the contrary, in reference to Häupl's professorship in Prague, Jüliger fails to differentiate between the German and the Czech university there. According to him, Häupl's appointment as professor at the German University of Prague (orchestrated by the Nazis) was allegedly an initiative taken on the part of the Czech university officials. The "University of Prague", he writes, had "strong interest" in "winning [Häupl] for the position of clinic director." Jüliger also offers a simplistic explanation for the professorship Häupl attained in Berlin (1943). "The high renown that Häupl enjoyed was honored with a professorship at the University of Berlin in 1943." He does not even mention the fact that university professors such as Häupl, who joined the NSDAP, were removed from their positions by the Allies in 1945. Instead, Jüliger makes a veiled comment, simply stating that the "end of the Second World War in 1945 unfortunately saw the end of Häupl's position in Berlin after just two years" [39].

Despite numerous archival requests, we have been unable to locate any Austrian denazification documents about Häupl. It is quite conceivable that Häupl succeeded in avoiding this process. Indeed, the provisional Austrian government allowed for exemptions from "mandatory registration" when the individual in question had not "abused" their NSDAP membership. This clause was expanded further and further over time until, eventually, 85 to 90 percent of those who would have had to register their membership attempted to appeal for an exemption, based on the argument that they had "never abused" their membership. This also applied to Häupl's colleague in Prague Herwig Hamperl mentioned above, who, just like Häupl, went to Austria right after the war [16, 25].

The biographies about Häupl written by Eschler (1953–1960) and Jüliger (1988) likewise demonstrate that Häupl's relation to National Socialism had not been addressed for many years, leading Häupl to be considered as a politically uninvolved individual. As recent studies have acknowledged, a very similar course of events can also be identified for other professors of dental medicine from this era, including Hermann Euler, Erwin Reichenbach, Reinhold Ritter, Guido Fischer and Fritz Faber [19, 20, 23, 27, 28]. Such thematic "omissions" might explain why the professional training institute in Dusseldorf was named after Karl Häupl in 1978, posthumously elevating him to prominence: people were simply unaware of Häupl's political standing in the Third Reich; they also avoided asking any more far-reaching questions.

Conflicts of interest:

The author declares that there is no conflict of interest within the meaning of the guidelines of the International Committee of Medical Journal Editors.

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Replacement of missing teeth with tooth-implant supported fixed dental prostheses

Summary: The aim of the S3 guideline was to assess the survival and success rates of tooth-implant supported fixed dental prostheses (T-I FDPs). A literature search was conducted in MEDLINE/PubMed, Cochrane Library, and Embase in order to identify qualified studies (randomized controlled trials [RCTs] or prospective studies, observation period > 3 years, > 10 participants). In the qualitative and quantitative analyses, 8 and 7 studies were included, respectively. The survival rates for the T-I FDPs were 90.8 % (95%-CI: 86.4–93.8 %) after 5 years and 82.5 % (95%-CI: 74.7–88.0 %) after 10 years. The implant survival rates were 94.8 % (90.9–97.0 %) and 89.8 % (82.7–99.4 %) after 5 and 10 years, respectively. From 185 T-I FDPs, 21 (11.4 %) minor and 23 (12.4 %) major biological complications as well as 23 (12.4 %) minor and 3 (1.6 %) major technical complications were reported. Based on current data, rigidly fixed 3- and 4-unit T-I FDPs show acceptable survival rates after 5 and 10 years.

Keywords: fixed dental prosthesis; implant prosthetics; tooth-implant supported; S3 guideline

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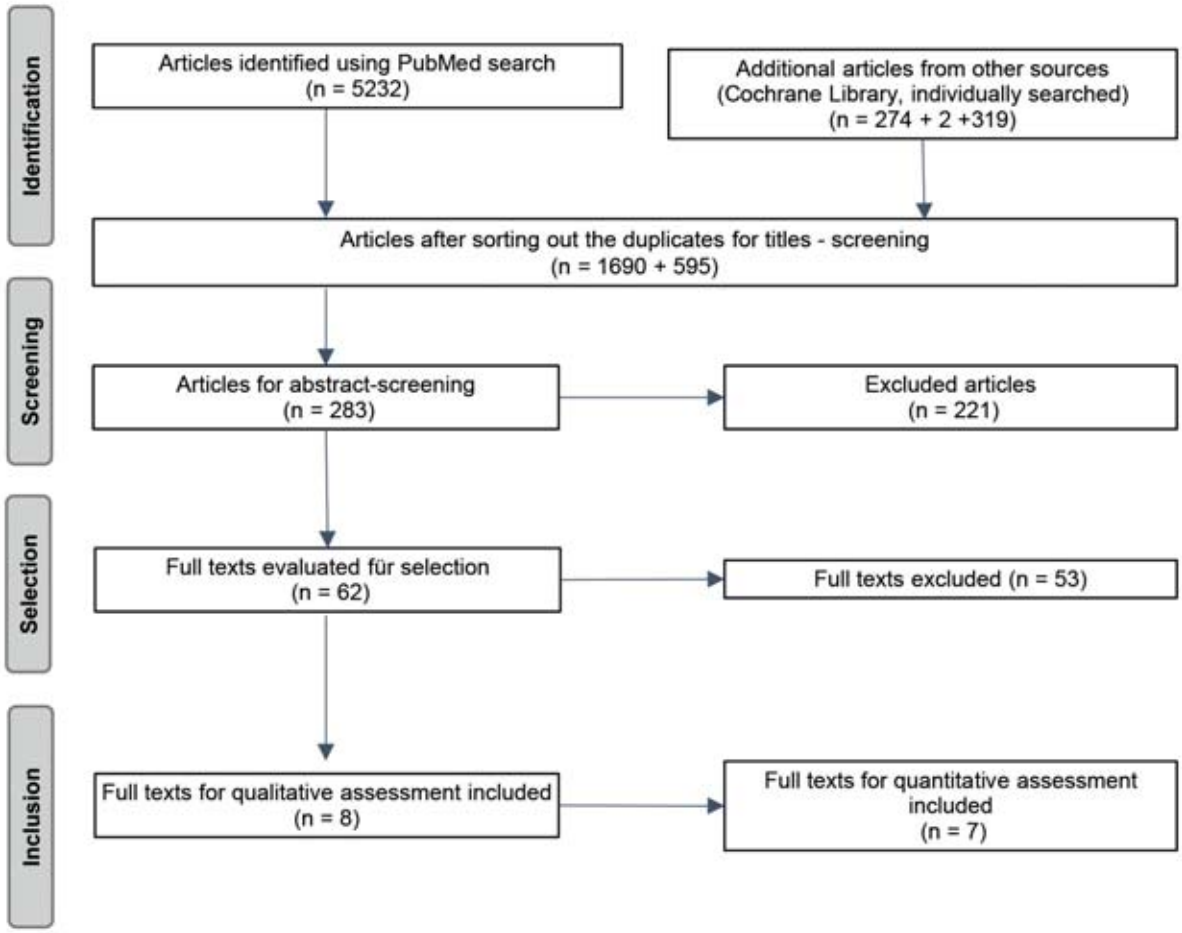

Figure 1 Overview of the screened and included articles in the systematic review.

Introduction

Tooth-implant supported fixed dental prostheses (T-I FDPs) represent a therapy option for the rehabilitation of the partially edentulous dental arch after partial tooth loss. This treatment approach aims to rehabilitate the functions of the stomatognathic by using a fixed restoration concept together with the simultaneous preservation of occlusal support zones when rehabilitating both partially edentulous jaws. T-I FDPs offer the possibility of treating patients using fixed restorations with less surgical effort, especially when there are general anamnestic and/or local constraints, financial motives, or the patient wishes to keep surgical interventions to a minimum.

Systematic review and meta-analysis

At the beginning of the search, the key question was formulated using the PICO scheme to define inclusion and exclusion criteria and search terms: "How is the replacement of missing teeth with T-I FDPs to be assessed in terms of their survival probability and complication rates?"

The databases PubMed, Cochrane Library and the databases of the German Institute for Medical Documentation and Information (DIMIDI) were used for the search. The following inclusion criteria were defined for the selection of literature in relation to the key question:

- randomized controlled trial
- prospective clinical trial
- Meta-analyses based on randomized controlled, prospective studies
- fixed FDP restorations
- observation period of at least 3 years and longer
- clinical follow-up examinations
- languages German and English
- data on the number of patients, FDPs, teeth, implants, and implant system used.

The following criteria were explicitly excluded:

- retrospective studies
- case reports
- in vitro studies
- observation period less than 3 years
- studies including less than 10 patients
- studies with removable implant-supported dental prostheses.

The results of the search are shown schematically in Figure 1. The assessment of the results was carried out using the checklists from "SIGN 50-A A guideline developer's handbook" using the levels of evidence 1++ to 3 [1].

Therapeutic requirements and indications

Generally, the same indications and contraindications apply for implant-prosthetic rehabilitation with FDPs as for dental implants. Likewise, the natural abutment teeth for T-I FDPs

Figure 2 Clinical photo of 2 zirconia abutments on implants in area 35 and 45.

Figure 3 Clinical photo of 2 T-I FDP zirconia frameworks during try-in.

Figure 4 Clinical photo after cementation of 2 T-I FDPs.

(Fig. 1–4: F. Beuer)

must fulfill the same requirements as abutment teeth for fixed, purely tooth-supported restorations. Natural teeth which necessitate crowns can also be used as abutments for T-I FDPs. Rehabilitation with T-I FDPs should be considered as a treatment option when additional implants are to be avoided, bone augmentation is not possible or desired, a removable denture is not an option and the condition of the partially edentulous dental arch is favorable. Endodontically treated teeth can also be used for T-I FDPs provided that the root fillings are satisfactory, a definite 2 mm high dentin margin is present, and the periapical conditions are inflammation-free.

T-I FDP restorations

T-I FDPs should always be designed without cantilever, whereby the dental implant can represent either the mesial or distal abutment. The data is best for three-unit T-I FDPs, thus offering the most predictable prognosis. For more than 4-unit T-I FDPs, the available data is insufficient. In literature, studies on T-I FDPs in the posterior region are preponderant, but this type of therapy can also be applied for the anterior region given that the treatment recommendations are followed.

The rigid connection between the tooth and implant plays a decisive role for the success of the T-I FDP [2, 3, 5–7]. According to one study, if the T-I FDPs were not rigidly constructed, they would have shown significantly more complications [9]. The rigid connection can be either a continuous, definitely cemented bridge framework or a screw-retained attachment [7]. The semi-permanent cementation of rigid frameworks on permanently cemented primary copings on natural abutment teeth has been reported in spite of the fact that intrusions of the abutment teeth have occurred in some cases [9]. Thus, the current recommendation is to permanently cement 1-piece T-I FDP restorations on both abutments [2, 5]. If a separate T-I FDP restoration with a screw-retained attachment is chosen, it should be permanently cemented in the area of the tooth, while it should be screw-retained or provisionally cemented in the area of the implant. Presently, sufficient data is only available for T-I FDPs with metal frameworks. One study reports promising results for ceramic veneered zirconia frameworks after a 3-year observation period [2]. No data is available for modern monolithic zirconia systems. Therefore, metal frameworks are recommended for T-I FDP restorations.

Survival rates and complications

For the rehabilitation of shortened dental arches in posterior regions, T-I FDPs made of veneered zirconia frameworks show a survival probability of 93.9 % after 3 years (Figures 2–4). Various studies have reported survival rates of T-I FDPs with metal frameworks ranging between 91.6 % and 97.6 % [7, 9, 11] after 5 years and 81.7 % [8] and 87.8 % [10] after 10 years. Retrospective studies, which were explicitly excluded from the data analysis based on the guideline used, reported survival rates of up to 100 % after 6 years [13].

The meta-analysis showed survival rates of T-I FDPs of 90.8 % after 5 years and 82.5 % after 10 years [4].

One of the major biological complications associated with the abutment teeth were fractures of endodontically treated teeth. In comparison, implant loss (4.5 % after 10 years) [3, 9] or marginal bone loss of more than 2 mm occurred relatively rare [9].

Among the reported technical complications were loss of retention on the natural abutment teeth, which in some cases led to secondary caries. Occasionally, the loosening and loss of screws occurred for screw-retained attachments which were used to create rigid connections. Abutment fractures of the implants occurred more frequently when the abutment teeth and implants were not rigidly connected [7].

The comparatively low percentage of technical complications of T-I FDPs relative to purely implant-supported bridges could potentially be explained by the preserved tactile sensitivity [12]. However, to date, this apparent advantage has not been sufficiently proven in the clinical setting.

Future prospects

In conclusion, clinical data with respect to T-I FDPs is rather limited. There is a great need for research on all-ceramic T-I FDPs, as well as the analysis of complications with regard to existing tactile sensitivity. Lastly, future studies should also consider patient-related outcomes, especially in comparison to alternative treatment options.

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