K Ø B E N H A V N S U N I V E R S I T E T - T A N D L Æ G E S K O L E N

Forsøgsprotokol
Jf. GCP-enhedens protokolvejledning

(*The main research protocol is developed based on the guidelines for Good Clinical Practice (GCP)*)

1. Title:
DIMOH: New **Di**gital **M**ethods for **M**onitoring **O**ral **H**ealth. An i*n vivo* assessment.

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2. Objectives

The objectives of this study are *i*) to monitor the oral health of young people over a period of 12 months and *ii)* to assess the ability of a new intraoral scanner combining fluorescence (from emitted blue light) with 3D imaging to detect and monitor changes in the dental hard tissues *in vivo*.

a. Hypotheses

The working hypotheses of this study are:

1. The monitoring of oral health will benefit from using a new intraoral scanner combining fluorescence with 3D imaging.
2. The new intraoral scanner combining fluorescence with 3D imaging will aid dentists to identify changes in the dental hard tissues at earlier stages than the traditional diagnostic methods (*i.e.* visual-radiographic methods).

b. Background

Literature Review and Research Question

Currently, monitoring oral health relies mainly on the visual examination of the oral tissues by the dental professional, aided electively by radiographic or photographic images (1, 2). In the context of oral health, monitoring involves detecting changes, sometimes rather subtle, in the soft or hard oral tissues; such changes are associated with the development of oral diseases or ageing (3, 2). Through the course of their lives, people will experience changes in the level of gingiva, increments on the teeth surface due to calcification of biofilm, loss of mineral tissues due to caries or tooth wear, wear of restorative materials, or modification in the in the position or color of the teeth. The slow rate of change involved in some of these situations makes it extremely difficult for the human eye alone to identify them. It is even more challenging to accurately register and recall the original situation on the patient's follow-up visits. Clinical photographs are therefore used to aid the monitoring (4, 2); however, it is difficult to obtain comparable photographs from different points in time and the subjectivity involved in the process cannot be avoided.

Different criteria are used in clinical practice to register and monitor changes in the oral tissues, according to the specific condition under investigation. While identifying significant changes is an easy task, the challenge lies particularly in identifying early, incremental changes. Regarding the detection of caries lesions, a number of initial lesions typically remain unnoticed when visual examination alone is used (5); or even when radiographs are employed, as the latter are not sensitive to early demineralization in enamel (6). Concerning tooth wear (*i.e.* erosion, abrasion, attrition), as the gradual mineral loss occurs progressively and irreversibly, it is usually only noticed when a significant amount of hard dental tissue is already lost (2). Additionally, minor changes on the gingival level, *e.g.* resulting from improper oral hygiene habits or yet an early inflammation of the periodontal tissues, may pass unnoticed to the dental personnel.

A promising clinical solution to overcome the challenges involved in the detection of early changes and monitoring of oral tissues is the use of 3D intraoral scans (7, 8). 3D scans obtained from gypsum models (*ex vivo*) have previously been used to identify changes of tooth position (9, 10), gingiva volume (11, 12), loss of mineral tissues (13) or wear of restorative materials (14). Although gypsum models offer information about volumetric changes (*e.g.* tooth

substance loss, movement of teeth, gingival level, stagnation of biofilm), the color information is lost. However, color is a valuable parameter for the previously mentioned clinical criteria as it is one of the parameters used to identify diseases (*e.g.* caries, gingivitis) or other oral conditions (*e.g.* tooth discoloration due to ageing, tooth whitening or discoloration of dental materials) (15, 2). Hence, obtaining 3D scans directly from the patients (*in vivo*) using intraoral scanners is desired, as these scans contain color information of the natural tissues. Additionally, by comparing 3D scans obtained from the same patients at different points in time, a less subjective and more reliable comparison of data is expected: the 3D scans can be overlapped and analyzed using specific software (9, 7, 16). Therefore, it is hypothesized that 3D intraoral scans can be used for more consistent monitoring of oral health in relation to clinical photographs or clinical records.

The current 3D intraoral scanners capture the color of the oral tissues by emitting visible white light. A recently developed 3D intraoral scanner manufactured and CE marked by 3Shape A/S, Denmark, is also able to emit visible blue light (405 nm wavelength) (17) that allows capturing fluorescence from the oral tissues. Fluorescence is one of the most promising technologies for accurate detection of the early stages of enamel demineralization (18, 19, 20), but is currently available only in 1D or 2D devices. The main limitation of the existing devices featuring fluorescence, as already mentioned, is the challenge in comparing single images obtained at different points in time, which is at large influenced by imaging artifacts and noise. Imprecision in the comparison of these images compromises the ability to accurately monitor progressive demineralization of the dental hard tissues. To the best of our knowledge, there is no intraoral scanner reported in the scientific literature that combines fluorescence with 3D imaging. Thus, we hypothesize that this new intraoral scanner will benefit the monitoring of dental hard tissues and will aid dentists to identify early changes in tissue mineralization. With this method it is only possible to examine the tooth surfaces that are visible and directly exposed into the mouth (*i.e.* the smooth free surfaces and the occlusal fissures); the areas between the teeth (*i.e.* the approximal surfaces) cannot be visualized and therefore cannot be examined using the scanner.

3. Methods

Study execution

The participants will be monitored for a period of 1 year. The study will last approximately 2 years in total, with the baseline examination taking place in the beginning of 2019 and the last examination in the Spring – Winter 2020. Detailed plan of the study is shown in Table 1.

Information about the project

Potential participants will find contact information of the responsible researcher on diverse project announcements. By contacting the responsible researcher, the potential participants accompanied by their parents/guardians (in case of underage candidates) will be able to book time for an information meeting regarding the clinical oral examination and will receive detailed written information material about the study. Appropriate language will be used to make sure that the information is clearly understood by all potential participants. The potential participants and their parents/guardians will be asked to read the written information before the in-person information meeting.

The in-person information meeting will take place in a room where no disturbances can occur. All underage candidates should be accompanied by their parents/guardians. The responsible

researcher will inform the potential participants about the study and the clinical procedures. The responsible researcher is a dentist with experience in communicating with young patients and has finalized pedagogical training. Therefore, she fulfills the prerequisites to be the responsible person to inform the young participants.

After attending the information meeting and they (for adults) or the parents/guardians (for underage) receiving a copy of the inform/parental consent, 24 - 48 hours will be allowed to decide about participation. Furthermore, they will all be informed about the voluntary nature of participation in the study and the freedom to withdraw – at any time – their participation. All potential participants will receive the documents "Før du beslutter dig" which includes the "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt" , which they are encouraged to read thoroughly. Copies in Danish and English will be provided for the Danish and Greek participants respectively.

Participants who decide to join the study will be asked to fill out a 4-day diet history, from Friday through Monday (Appendix 1). There the participants should register everything that they eat and drink, excluding water. Furthermore, they will be asked to fill out a questionnaire regarding their oral hygiene habits (Appendix 2). Both forms will be provided at the in-person information meeting, together with the copy of the inform/parental consent. All forms should be delivered on the second appointment (baseline examination).

Clinical and radiographic examination

A second appointment will be scheduled to conduct the oral health examination, including intraoral scanning and 2 bitewing radiographs (BW). The responsible researcher will request the participants to provide any recently available BW, in case these are not older than 6 months. No study-related examination will be conducted before the signed parental consent form has been obtained by the responsible researcher. The participants will not be offered any treatment other than routine professional tooth cleaning, which is important for a thorough visual examination and scanning of the teeth. In case any oral disease is detected, the participants will be referred to their dentist for treatment.

If no radiographs are available from the past six months, BW of the upper and lower posterior teeth on both sides will be taken. Since radiographs are part of the participants' annual dental check-up, these will be made available to the participants' dentist. Additionally, an oral examination will be conducted, and the condition of teeth, gums and fillings will be registered. The approximal plaque accumulation will be registered by employing the approximal plaque index (21). Thereafter, the teeth will be professionally cleaned, and the presence of caries lesions will be registered based on the visual and radiographic assessments. Caries lesions will be characterized as active or inactive and classified according to the ICDAS criteria into 7 stages (22). Furthermore, the presence of other visible defects on the oral hard tissues (*i.e.* erosive – abrasive lesions) will be registered using appropriate criteria (*i.e.* BEWE index for erosive tooth wear) (2, 23).

Subsequently, both the upper and lower jaw of the participant will be scanned using the intraoral scanner (Trios 4, 3Shape Trios A/S, Denmark). Scans will be obtained using visible white and blue light (wavelength 415 nm).

At the end of the session, the participants will be classified into different risk groups (low, moderate, high) according to the clinical findings and the information collected from the diet

history and the oral hygiene habits questionnaire (Appendix 1, 2). According to this classification, the responsible researcher will set the follow-up intervals for each participant (3-12 months). All patients will be monitored for 1 year.

The same clinical procedures will be followed on the follow-up examinations (3 or 6 months) as well as on the final examination (1-year follow-up). The diet history, the oral hygiene habits questionnaire and the BW radiographs will be repeated only on the final examination (Table. 1).

4. Statistics

Paired T-test will be conducted to identify differences between the clinical scores at the baseline and the subsequent follow-ups for the different conditions investigated (*i.e.* caries score, erosion score) (24).

Exploratory analysis of the data extracted from the 3D scans will be conducted and compared to the clinical scores. Pearson correlation coefficients between the clinical scores and scores obtained from the 3D scans will be calculated. Paired t-test will be conducted to compare the number of lesions per patient (*i.e.* caries, tooth wear) that will be detected with the 2 different methods (scanning and clinical-radiographic examination).

All statistical analysis will be conducted using a 95% level of confidence.

Information regarding the sample size calculation using power analysis is provided on the following paragraph (§5. Research subjects - Sample size calculation)

5. Research subjects

The participants in this research project will be adolescents (12-16 years old) and young adults (18-19 years old) in Denmark and in Greece respectively.

As previously mentioned, this project will assess the ability of the intraoral scanner combining fluorescence to detect and monitor initial changes in the dental hard tissues, with special focus on caries: the most prevalent oral disease. The most important benefit expected by using the fluorescence method is the detection of initial lesions on dental surfaces directly exposed to the mouth. Fissure lesions in permanent posterior teeth usually appear in the long-lasting period of tooth eruption, *i.e.* from when the tooth first appears in the mouth until it contacts with the opposite dentition (28). Eruption of the first permanent molar starts around the ages of 6-8 years, the second molar at 12-14 years (28) and the third molar at 17-18 years. During the eruption period, the posterior teeth are at a higher risk for developing fissure caries. For the second permanent molars, this period can last up to 27 months form the first appearance in the mouth (~12 years old) (29) though for the third molars this period is usually longer.

The initial state of the caries lesion is short-lived before progression of the disease. In older patients, caries lesions in fissures are either found at more advanced stages or they have already been treated by the dentist (*i.e.* sealed, filled or extracted as in the case of third molars) (28). Although initial caries lesions can be found in older patients, such initial lesions are located on the surfaces between the teeth, which are not visible to the intraoral scanner and therefore cannot be detected using this method.

For these reasons, the age group is set from 12 to 19 years. It is necessary to conduct the study on this group of young people, as the study is expected to benefit them directly. The same benefits are not expected if the study is conducted in older adults.

The early diagnosis of initial lesions in the young participants is more beneficial as it will allow the implementation of preventive measures to stop the progression of the disease. This will decrease the complexity of the treatments needed in the target group, as the initial lesions can be treated with minimal or non-invasive approaches. Thus, the economic burden for the state regarding treatment expenses of the adolescents and the individual costs related to future dental treatment will be reduced.

Inclusion criteria:

- Young people (12-19 years old) without chronic diseases.

Exclusion criteria:

- Participants in need of complex dental treatment (*e.g.* extensive restorative work, extractions, prosthetic treatment).
- Participants using partial/complete removable dentures or other appliances (*i.e.* orthodontic devices).

Sample size calculation

Caries data was used in order to calculate the desirable sample size for the current study, as that is the most prevalent oral disease in young patients and is widely investigated in epidemiological studies (1). Therefore, data regarding initial caries lesions was used for the sample size calculation, assuming that the new method will aid dentists to detect significantly more initial caries lesions compared to traditional methods.

For the sample size calculation, data collected by the Central Odontology Register of the Danish National Board of Health (Sundhedsstyrelsens Centrale Odontologiske Register - SCOR) during the year 2017 from municipal dental clinics at 98 different municipalities in Denmark was used. According to the data, an average of 3.08 initial lesions, with a standard deviation of 1.23 were identified on 15-year old patients at the different municipalities. In this study, the desirable power was set on 90%, the level of significance on 5% and the effect size on 30% (1 lesion). By applying these parameters, the sample size was calculated to be 64 adolescents. Nevertheless, as a 10% drop-out is expected for this type of study, the final number of participants to be included in the study should be 70.

6. Risks, side effects and shortcomings in short and long term

Risks

This study will be conducted on healthy persons, on whom the procedures followed in this study are assumed to have a negligible risk.

No risk is related to the clinical visual examination.

Regarding the 3D intraoral scanning procedure, if the scan quality is poor and thus the scan is not useful for the research objectives, the scanning procedure should be repeated. This is of no risk for the patient but represents the inconvenience of a delay of the dental visit.

For the scanning using blue light (wavelength 415nm) possible risks exist. For the participant, light irritation of the mucosa and lips may result from a local, acute overexposure to the strong blue light. This irritation, though, is mild and temporary. For the operator, possible harm to the eyes, especially on the lenses and the retinal tissues, may be caused by long-term cumulative exposure to blue light. These risks are not particular for this specific intraoral device but are

common to any dental equipment that uses blue light. Having these risks in mind, the equipment will be used properly and with care: the exposure time will be limited to 15 seconds per tooth and direct exposure to mucous membranes will be avoided. The equipment will be started only after it has been inserted into the patient's mouth. The operator will avoid looking directly into the mouth and instead will look on the computer screen during the scanning procedure. Eye-protection goggles filtering light under 500 nm are suggested to be used by the operator.

According to the Classification for Medical Devices in Europe, the mentioned 3D scanner is a Class 1 device and therefore is considered of low risk. All in all, minimal risks are at stake for the participants and the operator under proper use of the equipment. Any safety issues will be reported to the manufacturers, the VEK and the Patient Safety Board.

Side-effects

There is no side effect from the clinical examination or the scanning.

The radiation dose used for the acquisition of the dental radiographs varies between 1-10 μSv, depending on the technique used, and is equivalent to the average background radiation dose for 2-20 hours (the natural background radiation in Denmark is 3 mSv per year) (25). This project is classified as Category 1 according to the guidelines from the International Commission of Radiation Protection (ICRP) and the European Commission (26, 27). The overall stochastic effect from the exposure of the participants to ionizing radiation is estimated to be 1 in 1 million or smaller and the risk is thus considered insignificant.

Shortcomings:

All the procedures followed in the study (scheduling, radiographs, dental check-up, scanning) are time consuming and may inconvenience the participants.

7. Biological material

No biological material will be obtained from the participants or from another existing biobank.

8. Information from the participants' medical journal

No information will be retrieved from the participants' medical journal. The required information for the present study will be extracted from the participants during the clinical examination and scanning. All information will be registered on the digital dental journal used internally at the Dental Schools of the University of Copenhagen and the National and Kapodistrian University of Athens (for the Danish and Greek participants respectively. External, unauthorized people do not have access to this database.

Recent BW radiographs (no older than 6 months) will be retrieved from the participants' dental journal only after the participants' consent.

9. Data handling

The data will include the condition of oral health (plaque, caries, tooth wear etc.) gathered from the visual and radiographic assessments, as well as from the 3D scans. All data and sensitive personal information obtained from the participants will be treated and stored in compliance with the EU General Data Protection Regulation (GDPR) and following good research ethics.

10. Participant Recruitment

The study will be advertised at local schools and at the Dental Schools of the University of Copenhagen and the National and Kapodistrian University of Athens (on announcement boards and/or on the schools' webpages) and eventually giving presentations about the study by the responsible researcher. Further information regarding the informed consent and the in-person information meetings with the participants are provided on paragraph §3. Methods – Information about the project.

11. Research Ethics

The physical and mental integrity of the participants, as well as their privacy, will be respected. The good clinical practice (GCP) guidelines and EU General Data Protection Regulation (GDPR) will be followed.

Benefits of the Study

The risks, shortcomings and side effects (see above) are surpassed by the benefit of early diagnosis of oral diseases. The early diagnosis benefits the participants because oral problems can be treated more easily before they develop into more severe problems. The early detection of oral diseases is crucial, as often the problems can be treated non-invasively and different preventive strategies can be implemented to stop disease progression.

Additionally, the 3D intraoral scanner has the potential to aid dentists identifying changes in the oral tissues at earlier stages than with the visual – radiographic examinations. If this concretizes, the use of this equipment may potentially reduce the need for ionizing radiation for detecting oral problems and monitoring oral health, something that would be of significant benefit to all patients.

12. Participant compensation

This study is carried out on healthy persons under the direct responsibility of the dental school – University of Copenhagen. Thus, possible injuries to participants will be covered by the Danish "Patienterstatningen".

Table 1. Study Plan

Information meeting (~20 min)	**Baseline examination** January – September 2019 (~60 min)	**3-month / 6-month follow-up examination** *(only for moderate/high risk groups)* July 2019-March 2020 (~45 min)	**1-year follow-up Final examination** April – September 2020 (~60 min)	**Study Termination** September – December 2020
• Oral information about the clinical examination • Distribution: - Inform consent agreement - Diet history registration form - Questionnaire about oral hygiene habits	• Registration of diet history and oral hygiene habits • Clinical examination (registration of plaque, caries and other findings) • Teeth cleaning • Radiographic examination • Scanning • Participant risk assessment – Set follow-up intervals • Data selection and management	• Clinical examination (registration of plaque, caries and other findings) • Teeth cleaning • Scanning • Data selection and management	• Registration of diet history and oral hygiene habits • Clinical examination (registration of plaque, caries and other findings) • Teeth cleaning • Radiographic examination • Scanning • Data selection and management	• Data management • Statistical analysis • Publication

References

1) Pitts NB, Zero DT, Marsh PD, Ekstrand K, Weintraub JA, Ramos-Gomez F, Tagami J, Twetman S, Tsakos G, Ismail A. Dental caries. Primer 2017:3:17030.
2) Ganss C, Lussi A. Diagnosis of erosive tooth wear. Monogr Oral Sci. 2014; 25:22-31.
3) Hassel A, Johanning M, Grill S, Schröder J, Wahl H, Corcodel N, Zenthöfer A. (2017). Changes of tooth color in middle and old age: A longitudinal study over a decade. Journal of Esthetic and Restorative Dentistry, 29(6), 459-463.
4) Wilder-Smith C, Materna A, Martig L, Lussi A. (2017). Longitudinal study of gastroesophageal reflux and erosive tooth wear. BMC Gastroenterology, 17(1), 113.
5) Ridell K, Olsson H, Mejàre I. Unrestored dentin caries and deep dentin restorations in Swedish adolescents. Caries Res 2008;42(3):164-170.
6) Mejàre I, Axelsson S, Dahlén G, Espelid I, Norlund A, Svensson Å, Tranæus S, Twetman S. The Swedish Council on Technology Assessment in Health Care. Karies – diagnostik, riskbedömning och icke-invasiv behandling. En systematisk litteraturöversikt. 2007; 403p.
7) Bertl K, Gotfredsen K, Jensen S, Bruckmann C, Stavropoulos A. (2017). Can hyaluronan injections augment deficient papillae at implant-supported crowns in the anterior maxilla? A randomized controlled clinical trial with 6 months follow-up. Clinical Oral Implants Research, 2*8*(9), 1054-1061.
8) Marro F, De Lat L, Martens L, Jacquet W, Bottenberg P. (2018). Monitoring the progression of erosive tooth wear (ETW) using BEWE index in casts and their 3D images: A retrospective longitudinal study. Journal of Dentistry, 73, 70-75.
9) Cho M, Choi J, Lee S, Baek S. (2010). Three-dimensional analysis of the tooth movement and arch dimension changes in Class I malocclusions treated with first premolar extractions: A guideline for virtual treatment planning. American Journal of Orthodontics and Dentofacial Orthopedics: *Official Publication of the American Association of Orthodontists, Its Constituent Societies, and the American Board of Orthodontics, 138*(6), 747-57.
10) Rossini G, Parrini S, Castroflorio T, Deregibus A, Debernardi C. (2016). Diagnostic accuracy and measurement sensitivity of digital models for orthodontic purposes: A systematic review. American Journal of Orthodontics And Dentofacial Orthopedics, 149(2), 161-170.
11) Schmitt C, Matta R, Moest T, Humann J, Gammel L, Neukam F, Schlegel K. (2016). Soft tissue volume alterations after connective tissue grafting at teeth: The subepithelial autologous connective tissue graft versus a porcine collagen matrix – a pre-clinical volumetric analysis. Journal of Clinical Periodontology*, 43*(7), 609-617.
12) Zuhr O, Rebele S, Schneider D, Jung R, Hürzeler M. (2014). Tunnel technique with connective tissue graft versus coronally advanced flap with enamel matrix derivative for root coverage: A RCT using 3D digital measuring methods. Part I. Clinical and patient-centered outcomes. Journal of Clinical Periodontology*, 41*(6), 582-592.
13) Alaraudanjoki V, Saarela H, Pesonen R, Laitala ML, Kiviahde H, Tjäderhane L, Lussi A, Pesonen P, Anttonen V. Is a Basic Erosive Wear Examination (BEWE) reliable for recording erosive tooth wear on 3D models? (2017). Journal of Dentistry, 59, 26-32.
14) Mehl A, Gloger W, Kunzelmann K, Hickel R. (1997). A New Optical 3-D Device for the Detection of Wear. Journal of Dental Research,76(11), 1799-1807.
15) Papapanou P, Lindhe J, (2015) 'Epidemiology of Periodontal Diseases'. In Lindhe J, & Lang NP, *Clinical periodontology and implant dentistry (Sixth ed.).* Chichester, West Sussex Ames, Iowa: John Wiley and Sons.

16) Michou S, Vannahme C, Benetti AR, Ekstrand K, 3D Assessment of Erosive Tooth Wear Using Intraoral Scanner. An In Vitro Examination, 65th ORCA Congress, July 4–7, 2018, Copenhagen, Denmark, Caries Res 2018;52:468–547, Abstract nr 3.
17) Van der Poel M, Hollenbeck K. 3D intraoral scanner measuring fluorescence. US, EP, CN patent application 2012.
18) Pretty IA. Caries detection and diagnosis: novel technologies. J Dent 2006;34(10):727-739.
19) Pretty IA, Ellwood RP. The caries continuum: opportunities to detect, treat and monitor the re-mineralization of early caries lesions. J Dent 2013;41(Suppl 2):S12-21.
20) Gomez J, Zakian C, Salsone S, Pinto SC, Taylor A, Pretty IA, Ellwood R. *In vitro* performance of different methods in detecting occlusal caries lesions. J Dent 2013;41(2):180-186.
21) Paris S, Haak R, Meyer-Lueckel M. Diagnostics, treatment decision, and documentation. Meyer-Lueckel M, Paris S, Ekstrand KR, eds Caries Management, Sciences and Clinical practice Thieme, Stutgard pp293-299.
22) Pitts NB, Ekstrand KR; ICDAS Foundation,
International Caries Detection and Assessment System (ICDAS) and its International Caries Classification and ManagementSystem (ICCMS) -methods for staging of
the caries process and enabling dentists to manage caries. Community Dent Oral Epidemiol. 2013 Feb;41(1):e41-52.
23) Bartlett D, Ganss C, Lussi A. (2008). Basic Erosive Wear Examination (BEWE): A new scoring system for scientific and clinical needs. Clinical Oral Investigations, 12(Supplement 1), 65-68.
24) Armitage P, Berry G: Statistical Methods in Medical Research. Oxford, Blackwell Scientific Publications, 1994
25) Wenzel A, Wiese M, Sewerin I. Stråledoser ved røntgenundersøgelser. Stråledoser. stråleskader. Strålebeskyttelse. En orientering for tandlægestuderende og personale i tandlægepraksis. 3 edn. 2011.
26) Radiological protection in Biomedical Research. ICRP Publication 62, Annals of the ICRP, Oxford Pergamon Press, 1992. 4.
27) Guidance on medical exposures in medical and biomedical reseach, Radiation protection 99, European Commision.
28) Nørrisgaard, P., Qvist, V., & Ekstrand, K. (2016). Prevalence, risk surfaces and inter-municipality variations in caries experience in Danish children and adolescents in 2012. Acta Odontologica Scandinavica, 74(4), 291-297.
29) Koch, Göran, & Poulsen, Sven. (2009). Pediatric dentistry, a clinical approach (2.nd ed.). Oxford: Wiley-Blackwell.