STUDY PROTOCOL

# Cross-sectional examination for the certainty of success of oral implants

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## 1. Aim of the study

The aim of the present multi-centre, cross-sectional study is to determine the prevalence and incidence of mucositis and peri-implantitis. Furthermore, with the help of a cytokine analysis of peri-implant swab samples and of blood lymphocytes or monocytes on titanium platelets and particles in vitro, the tolerance of titanium in relation to the clinical conditions will be examined. In total, a maximum of 200 patients will be examined at 10 centers over a period of 6 months using clinical, genetic and microbiological parameters.

## 2. Material and methods

200 patients will be enrolled in the study at a maximum of 10 centers (20 patients per center) that have been presented for a routine check-up. The centers are 3 university clinics, a hospital and 6 private practices:

- Clinic for Periodontology at the University of Bern
- Polyclinic for Dental Surgery and admission to Heinrich Heine University Düsseldorf
- Clinic for Maxillofacial Surgery at the Georg-August University in Göttingen
- Clinic for maxillofacial surgery at the Red Cross Hospital Kassel
- Private dental practice Dr. Karl-Ludwig Ackermann / Filderstadt
- Private dental practice Dr. Gerhard Iglhaut / Memmingen
- Private dental practice Prof. Dr. Werner Lill / Vienna, Austria
- Private dental practice Dr. Ralf Rössler / Wetzlar
- Private dental practice Dr. Michael Stimmelmayr / Cham
- Private dental practice PD Dr. Ata Anil / Bitburg

Titanium implants had been placed in all of the test subjects in the individual centers within the last 10 years. After the implantation, they were included in a regular recall system. All test subjects are informed in detail about the course of the study both verbally and in writing and give their written consent. At any point in time, the patient has the option of leaving the examination. The study protocol is checked by the ethics committees of the medical faculties of Heinrich Heine University in Düsseldorf, Georg-August University in Göttingen, Ludwig Maximilian University in Munich and the University of Bern.

## 3. Inclusion criteria for patients

- Presence of at least one helical dental implant made of cp-Ti with an insertion date after April 1st, 2001
- No other titanium implants in the body

• Regular participation in a recall

4. Course of studies

4.1 General medical history
As part of the survey of the general anamnesis, the underlying internal diseases of all patients are recorded. In particular, questions are asked whether the patient has diabetes mellitus, whether bisphosphonates or acetylsalicylic acid are regularly taken and whether there are allergies. In addition, the patients' smoking habits are asked about.

4.2 Clinical investigation parameters
For patients with multiple implants, a maximum of two implants are examined, the most clinically noticeable and one normal implant. All measurements are carried out by a previously calibrated person using a PCP 12 periodontal probe (Hu-Friedy kal, Germany).
The following clinical parameters are determined:

Plaque Index (according to O'Leary):
Determination in each case on the gingival margin to record the cleaning success in 6 places around the implant (mesio-facial, mid-facial, disto-facial, mesio-oral, mid-oral, disto-oral). There is no staining test.

Bleeding on probing (BOP):
Determination 30 seconds after probing at 6 points around the implant (mesio-facial, mid-facial, disto-facial, mesio-oral, mid-oral, disto-oral) to determine the peri-implant inflammation status.

Probing depths (ST):
measured at 6 places around the implant as a distance: marginal mucosal edge - pocket floor (mesio-facial, mid-facial, disto-facial, mesio-oral, mid-oral, disto-oral).

4.3 X-ray diagnostics

An x-ray image, preferably a dental film, is made for all patients as part of a routine diagnosis. In individual cases, an orthopantomogram can also be made. These are compared with the X-ray images already available at the time the prosthetic superstructure was incorporated and an assessment of the peri-implant bone is carried out.

4.4 blood test
A blood sample (fresh heparinized blood) is taken from each patient, with which a lymphocyte activation test is carried out in vitro. For this purpose, the samples are sent overnight to the Prof. Thomas Center / LMU Munich. There, lymphocytes and monocytes are isolated from the samples and incubated in vitro with titanium particles and on titanium plates from Astra, Camlog, Dentsply, Nobel Biocare and Straumann. After several days of culture, the release of inflammatory cytokines is measured (IL-1, IL-6, IL-8, interferon $\gamma$, TNF$\alpha$, TNF$\beta$, MMPs, etc.). Furthermore, a DNA bank for further polymorphism studies is created from a small additional sample and the CRP, beta crosslaps and HbA1c values are measured from the serum sample obtained.

4.5 IL-1 polymorphism analysis
With the help of a brush (GenoType® PST® plus, Hain Lifescience GmbH, Nehren), a smear is also taken in the peri-implant area. The brushes are then placed in a test tube and examined in the laboratory for an IL-1 polymorphism (Bioscientia GmbH, Ingelheim).

4.6 Microbiological test parameters
A microbiological examination is carried out on all patients. For this purpose, the qualitative and quantitative presence of Aggregatibacter actenomycetemcomitans (Aa), Porphyromonas gingivalis (Pg), Prevotella intermedia (Pi), Tannerella forsythia (Tf), Treponema denticola is determined with a marker germ analysis (micro-IDent® plus, Hain Lifescience GmbH, Nehren) (Td), Peptostreptococcus micros (Pm), Fusobacterium nucleatum (Fn), Campylobacter rectus (Cr), Eubacterium nodatum (En), Eikenella corrodens (Ec) and Capnocytophaga sp. (C.sp.) examined. For this purpose, after the examination area has dried, a sterile paper tip is inserted to the bottom of the respective peri-implant pocket and left there for about 20 seconds. These are then placed in a test tube and examined in a laboratory (Bioscientia GmbH, Ingelheim).

4.7. Quantitative determination of the protein aMMP-8
Furthermore, a quantitative determination of the tissue-degrading protein aMMP-8 is carried out in all patients (Bioscientia GmbH, Ingelheim).

5. Evaluation
Based on the clinical and radiological findings, the prevalence of mucositis and peri-implantitis in all patients is statistically recorded with the software program ImpDat (Kea GmbH, Pöcking). In addition, it is checked whether there is a correlation between the occurrence of peri-implant inflammation and the genetic, immunological and microbial factors also recorded.