Changes in the biomechanical properties of the bone during implant placement

Ph.D. Thesis

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I. PUBLICATIONS

1. Publications related to the subject of the thesis

I. **Nagy ÁL**, Tóth Z, Tarjányi T, Práger NT, Baráth ZL: Biomechanical properties of the bone during implant placement. *BMC Oral Health* 2021; 21(1): e86.
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II. Szabó ÁL, **Nagy ÁL**, Lászlófy C, Gajdács M, Bencsik P, Kárpáti K, Baráth ZL: Distally Tilted Implants According to the All-on-Four® Treatment Concept for the Rehabilitation of Complete Edentulism: A 3.5-Year Retrospective Radiographic Study of Clinical Outcomes and Marginal Bone Level Changes. *Dent J* 2022; 10(5): e82.
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2. Publications not related to the subject of the thesis

I. Donadu MG, Mazzarello V, Cappuccinelli P, Zanetti S, Madléna M, **Nagy ÁL**, Stájer A, Burián K, Gajdács M: Relationship between the Biofilm-Forming Capacity and Antimicrobial Resistance in Clinical *Acinetobacter baumannii* Isolates: Results from a Laboratory-Based *In Vitro* Study. *Microorganisms* 2021; 9(11): e2384.
IF_{2021}: 4.926, SJR ranking: Q2, Citations: 12 (Independent citations: 12)

II. Gajdács M, Kárpáti K, **Nagy ÁL**, Gugolya M, Stájer A, Burián K: Association between biofilm-production and antibiotic resistance in *Escherichia coli* isolates: A laboratory-based case study and a literature review. *Acta Microbiol Immunol Hung* 2021; 68(4): 217-226.
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III. Donadu MG, Zanetti S, **Nagy ÁL,** Barrak I, Gajdács M: Insights on carbapenem-resistant *Acinetobacter baumannii*: phenotypic characterization of relevant isolates. *Acta Biol Szeged* 2021; 65(1): 85–92.
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II. INTRODUCTION

The loss of teeth is considered as an end-point of a life-long history of oral diseases. Once the extraction of teeth occur, the jaw undergoes degenerative changes in size and shape that are continuous for the duration of the individual's life. Edentulism has a considerable negative impact for esthetic and functional aspects for patients, thus, it should be managed through prosthetic rehabilitation with fixed or removable prostheses. Implants are used as a framework to transfer functional and parafunctional stresses generated during mastication onto peri-implant tissues, and to allow for the introduction of a restoration, which may be according to an an immediate-loading or delayed-loading concept. Implant placement requires clinicians to utilize the remaining bone in the most efficient way possible in view of the severity of the involution. Implant placement in heavily atrophied jaws is usually impossible without guided regeneration surgery, a sinus elevation procedure, nerve transposition and soft tissue management, especially in case of elderly people, who typically have severely atrophic alveolar process with D1 quality bone and a high degree of cortical bone volume. The All-on-Four^{TM} (Ao4) concept – introduced by Maló and colleagues – requires four implants are applied in the anterior part of completely edentulous jaws to support provisional, fixed, and immediately loaded prosthesis, which allows the avoidance of complicated surgical procedures. After implant placement, primary implant stability is fundamental to avoid micro-movements (micromotions) at the bone-implant interface during osseointegration. Thus, to ensure complete successful osseointegration, micromotion values should be below 50-150 μm, according to several pre-clinical and clinical studies. Transmission of loads at the bone-implant interface is mediated by a variety of factors, including occlusal loads, the number, the geometric and material properties of the implants and/or prosthesis, and the quality and quantity of the alveolar ridge (AR). Dentists must be aware of the tensile, compressive and shear stresses arising in the bone from the chewing forces and the implants during treatment planning. Exceeding the load-bearing capacity of the alveolar bone during implant placement may result in decreased primary stability, marginal bone resorption and even implant failure. There is limited evidence on whether pre-drilling or implant placement detrimentally affects the mechanical properties of the jaw bone, which could have deleterious effects for the restorative procedure (decreasing primary stability), in addition to having severe consequences patients with limited bone supply.

III. AIMS OF THE STUDY

The immediate loading concept has become a mainstay of implant-based restorations, due to reliable clinical outcomes and patient preferences. However, there is limited evidence available whether pre-drilling (implant nest preparation) or implant placement detrimentally affects the mechanical properties of the jaw bone, which could have deleterious effects for the restorative procedure (decreasing primary stability). In addition, in patients with limited bone supply, whom are affected by other underlying conditions and/or other parafunctional habits, marginal bone loss (MBL) over time may have severe consequences for secondary implant stability and threaten long-term implant survival. Thus, the aims of our present study were to: *i)* simulate implant placement according to the Ao4 protocol and immediate loading, to assess whether drilling and implant placement had harmful effects on the bone (and to investigate the risk of pathological fractures) in an *in vitro* study using a porcine rib model; *ii)* assess the influence of various clinico-epidemiological correlates on the rate of MBL in a retrospective single-center experience, following the implantation of distally tilted implants according to the Ao4 concept, evaluated by radiographic findings.

The specific goals of the study were the following:

1. Determination of **bone mechanical properties** of porcine bone after different treatments (bones with no intervention, bones with implant nests drilled, bones with implants placed) using **a static mechanical testing protocol, based on a 3-point bending test**
2. Determination of **bone mechanical properties** of porcine bone after different treatments (bones with no intervention, bones with implant nests drilled, bones with implants placed) using **a dynamic mechanical fatigue protocol, based on a 3-point bending test (at the 100th, 2000th an 9000th cycle)**
3. Determination of the **most likely point of fracture in the bone** after different treatments (bones with no intervention, bones with implant nests drilled, bones with implants placed) **during the static and mechanical testing protocols**
4. Determination of the **effects of clinico-epidemiological correlates** (e.g., oral hygiene, parafunctional habits, and smoking habits) on **MBL around distally tilted Ao4 implants** in a retrospective fashion, after **18 months** (T1; 1.5 years post-restoration), **30 months** (T2; 2.5 years post-restoration), and **42 months** (T3; 3.5 years post-restoration) **of follow-up**

IV. MATERIALS AND METHODS

1. Bone material

Fresh, non-frozen, young (~ 180 days) domestic porcine ribs with soft parts (i.e. periosteum, attached muscles, fascia, fat) were obtained from an abattoir (Szeged, Hungary). The preparation of the samples was carried out in the following fashion: excess soft parts were removed with a sharp scalpel (15C; Swann-Morton, Sheffield, UK), with care being taken to ensure that the periosteum was left intact. The rationale for the selection of porcine ribs was due to the excellent homogeneity and thickness of cortical bone, which is similar to the composition of a human mandible. The dimensions of the ribs were measured with an analog dial caliper (0.01 mm spacing, Hoffmann Gruppe AK600203, Hoffmann Gruppe AG, Winterthur, Switzerland).

2. Measurement groups, drilling and implant placement protocol

Following measurement, the porcine ribs were randomly divided into three groups (Groups 1, 2 and 3 in the subsequent text). In Group 1 (*n* = 17), implants were placed according to the Ao4 implant placement protocol: implant nests were drilled with a well-known and accepted physiodispenser (Implantmed Classic SI-923 physiodispenser, W&H, Bürmoos, Austria) and with its recommended surgical hand piece for implant placement (WS-75L surgical contra-angle handpiece, W&H, Bürmoos, Austria). Two implants (cylindro-conical; ICX TEMPLANT 4.1 mm x 10 mm, Medentis Medical GmbH, Bad Neuenahr/Ahrweiler, Germany) were placed parallel 5 and 5 milimeters (mm) laterally from the geometrical mean of the length and in geometrical mean of the width of the samples, while the two tilted implants (cylindro-conical; 45°; ICX TEMPLANT 4.1 mm x 15 mm, Medentis Medical GmbH, Bad Neuenahr/Ahrweiler, Germany) were inserted 20 mm laterally from the adjacent, previously inserted implants. During pre-drilling and implant placement, manufacturer recommendations and accepted professional rules/guidelines were kept in mind, the surgical set and drills of the implants' manufacturer were used (ICX Premium surgical set, Medentis Medical GmbH, Bad Neuenahr/Ahrweiler, Germany). During the use of the physiodispenser (drilling), constantly controlled irrigation was used with isotonic (0.9% NaCl) saline solution (B. Braun Hungary, Budapest, Hungary). In Group 2 (*n* = 16), the implant nests were drilled with the same instrument described previously, for the same type and size of implant, but the implant nest was left empty without implant placement. In Group 3 (or the control group; *n* = 18), no intervention was carried out on the bones. Following the necessary preparations, the samples were stored in a refrigerator (at 5°C) until further measurements.

3. Static and dynamic mechanical testing protocol

Each group was randomly divided into two parts to carry out the mechanical testing (static and dynamic fatigue) protocols. The first half of the samples were tested with a static tensile and compression materials testing machine (Tinnius Olsen H5KT Benchtop Materials Testing, Atec, Horsham, PA, USA), while the other half were involved in a fatigue test by an All-Electric Dynamic Test Instrument (Instron ElectroPuls^{TM} E3000, Norwood, MA, USA). For the mechanical testing, a 3-point bending test was performed, which is a widely accepted method for fracture testing. Special mechanical components were designed and manufactured for the purposes of the study, which could be applied in both the static and dynamic equipments.

During the **static load** measurements, the bending deformation was increasing steadily on the bones, with the force being measured and digitized. The testing equipment recorded the position of the crosshead and the measured force. The maximum deformation was 10 mm, which was reached in 5 seconds. During the measurements, an automatic halt was actuated, when the device observed a sudden decrease in force. From the static load diagrams resulting from our experiment, a quantity (**S**) could be calculated according to the formula (1) below (corresponding to the area under the curves [AUC]), which correlates with the toughness of the ribs.

$$S=\int_{0}^{x1} F(x)\cdot dx \qquad (1)$$

Similarly to the static load test, the **dynamic fatigue tests** followed the arrangement of 3-point measurements. Prior to these tests, the stiffness of each rib was determined by measuring the force-deflection curve between 0.2 and 0.8 mm deflection. After this process, the fatigue test was performed on the samples in deflection control mode, where the initial deflection was set to 2 mm, which was reached in 5 seconds. The fatigue signal was a sinus function with 20 Hz frequency at 0.5 mm deflection amplitude over 10.000 cycles. At the end of the fatigue process, the load was decreased to 0 N in 5 seconds.

4. Retrospective clinical study

This retrospective, single-center study aimed to evaluate the clinico-epidemiological and radiographic data (peri-implant bone-level changes) from patients undergoing an implant surgical procedure with an immediately-loaded, four-implant-supported fixed prosthetic concept, following the Ao4 protocol, between 2017.01.01. and 2022.01.01. The study was based on purposive sampling at the study center, according to previously set inclusion and exclusion criteria. Prior to the surgical intervention, the medical and dental history, relevant lifestyle habits (e.g., smoking), and potential drug allergies of the patients were reviewed, which was carried out by a prosthodontist and a periodontist. Following the discussion of the treatment plan and obtaining consent, surgical treatment was scheduled. Cone-beam computed tomography (CBCT) scans (i-CAT cone beam CT-scanner, Imaging Science) were carried out for preoperative assessment. All relevant operative interventions were performed by the same surgeon with more than twenty years of experience associated with immediate loading procedures. Quantitative and qualitative assessment of the jaw bone was performed by means of preoperative radiographs, visual inspection, and tactile evaluation during drilling; appraisal of bone quality was carried out using CBCT scans. Each patient received two distally tilted implants in the posterior region and two anterior implants in the maxilla or the mandible. Implant placement was carried out according to the Ao4 concept, using the Ao4 surgical guide (Nobel Biocare; Kloten, Switzerland). Localized bone grafting was performed to cover exposed threads and/or other osseous defects associated with extraction sockets, as needed with demineralized allografts. Peri-implant bone-level changes were measured by matched and calibrated OPT images taken at the 3-month appointment (i.e., baseline, T_0) and follow-ups after 18 months (T_1; 1.5 years post-restoration), 30 months (T_2; 2.5 years post-restoration), and 42 months (T_3; 3.5 years post-restoration); marginal bone level (the most coronal bone-to-implant contact) was assessed on the mesio- (MA) and disto-approximal (DA) aspects. The change in marginal bone levels (ΔBL (mm)) from the baseline (T_0) to the values recorded at the follow-ups T_1, T_2, and T_3 were calculated. Marginal bone level changes were studied in the context of patients presenting with underlying conditions/parafunctional habits.

5. Ethical considerations and consent to participate

The animals were not sacrificed for the purpose of the experiment; therefore, the present study was not subject to review by a biomedical research ethics committee. Informed consent is not applicable.

The clinical study was conducted in accordance with the Declaration of Helsinki and national and institutional ethical standards. Ethical approval for the study protocol was obtained from the Human Institutional and Regional Biomedical Research Ethics Committee, University of Szeged (registration number: 158/2021-SZTE [5035]). All participants were informed of the nature and aims of the study and the data collected; all participants of the study signed an informed consent form.

6. Statistical analysis

6. 1. Bone drilling experiments *in vitro*

Descriptive statistical analysis (including means ± SEM (standard error of the mean), ranges and percentages) was performed using Microsoft Excel 365 (Microsoft Corp., Redmond, WA, USA). Based on the sample size in the study, the Shapiro-Wilk test was performed to validate the normality of distribution of the measured data; based on the results ($p<0.05$, the data was not normally distributed), nonparametric tests were used. Kruskal-Wallis test was performed to compare the measured force values between the different groups (Groups 1, 2, and 3); in case of significant differences overall, the Mann-Whitney U was used as a post-hoc test to identify individual (between the groups) differences. Inferential statistical analyses were carried out using the SPSS (Statistical Package for the Social Sciences) software version 22.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 365 (Microsoft Corp., Redmond, WA, USA), respectively. p values < 0.05 (5%) were considered statistically significant.

6. 2. Retrospective clinical study

Descriptive statistics (including means ± SEM (standard error of the mean), ranges and percentages) was performed using Microsoft Excel 365 (Microsoft Corp., Redmond, WA, USA). Statistical analyses were carried out the SPSS (Statistical Package for the Social Sciences) software version 22.0 (IBM Corp., Armonk, NY, USA): the normality of variables was tested using the Shapiro–Wilk test; inferential statistics were performed using independent-sample t-test and one-way ANOVA with Tukey’s post hoc test. p values < 0.05 were considered statistically significant.

V. RESULTS

1. Bone drilling experiments *in vitro*

1. A. Initial measurements of the porcine ribs, results of the static load tests

The mean length, width and height of the bones were 117.1 mm, 13.4 mm and 9.8 mm, respectively. The mean±SEM value of the cortical bone thickness was 2.13 mm ± 0.08 mm. The first stage of the load-deflection curve could be described as almost linear (resembling a straight increasing line), which represents the flexible range of the rib. After the maximum force was exerted, even a small force was sufficient for further deflection. The measured mean ± SEM force values were highest among Group 3 (control group) samples (298.9 ± 30.95 N), followed by Group 1 (implanted group) (280.29 ± 27.51 N) and Group 2 (pre-drilled group) (287.1±25.93 N) samples; no significant differences were found among the groups ($p = 0.979$).

In intact bone samples (Group 3), the sudden reduction in force associated with fractures was observed only after a large deformation of around 6.6 mm. The maximum forces observed for Group 3 were in the range of 200-800 N; typically, the maximum force values were achieved with 1.5-3 mm deflection. In drilled bone samples (Group 2), the maximum force values (170-390 N) decreased compared to Group 1, with most measurements showing single or gradual fractures in the 2.4-5 mm deflection range. In line with this, in the implanted bone samples (Group 3), the maximum force values (175-380 N) decreased compared to Group 1 and Group 2, the deflection values corresponding to the first partial fracture were in the range of 1.6-4.5 mm. Initally, partial cracks were observed between the two middle implants during the load. Fracture lines were always at the sites where the pre-drilling or the implant placement happened previously. Small breaks on the force-deflection curves indicated the appearance of new cracks; during loading, the appearance of a crack was often accompanied by a sound effect. Based on the AUC values corresponding to the curves, the toughness of the bone (S) was expressed in Nmm, registered during the test. Mean ± SEM S values (in decreasing order) were 1701.37 ± 166.335 Nmm among Group 3 members, 1235.56 ± 248.392 Nmm in Group 1 samples, while 1175.77 ± 128.832 Nmm in Group 2 samples; no significant differences were found in toughness among the groups ($p = 0.16$).

1. B. Results of the dynamic fatigue tests

During the analysis of the dynamic fatigue test results, force values for maximum deflection (2.5 mm) were measured at specified times (namely, at the 100th, 2000th and 9000th cycles, respectively). The measured mean ± SEM force values at the 100th cycle (in decreasing order) were 0.5766 ± 0.033 kN for Group 3 (control group) samples, 0.4991 ± 0.073 kN for Group 1 (implanted group) samples and 0.4030 ± 0.081 kN for Group 2 (pre-drilled group) samples, respectively; according to the Kruskal-Wallis test, significant differences were shown between the groups ($p = 0.014$). The measured mean ± SEM force values at the 2000th cycle (in decreasing order) were 0.3896 ± 0.027 kN for Group 3 samples, 0.3530 ± 0.049 kN for Group 1 samples and 0.2800 ± 0.056 kN for Group 2 samples, respectively; significant differences were shown between the groups ($p = 0.015$). Furthermore, the measured mean ± SEM force values at the 9000th cycle (in decreasing order) were 0.2999 ± 0.015 kN for Group 3 samples, 0.2840 ± 0.042 kN for Group 1 samples and 0.2227 ± 0.042 kN for Group 2 samples, respectively; significant differences were shown between the groups ($p = 0.026$).

Statistically significant differences were tested between groups with the Mann-Whitney U-test: relevant differences were shown between the measured force values between Group 3 (control group) and Group 2 (pre-drilled group) ribs at the 100th cycle ($p = 0.001$), which remained consistant at the 2000th cycle ($p = 0.002$) and 9000th cycle ($p = 0.005$). Measured force values did not show significant differences in any of the cycles examined among the Group 3 (control group) and Group 1 (implanted group) samples (100th cycle: $p = 0.243$; 2000th cycle $p = 0.447$; 9000th cycle $p = 0.72$). Similary, no significant differences were noted between Group 2 (pre-drilled group) ribs and Group 1 (implanted group) samples any of the cycles examined (100th cycle: $p = 0.33$; 2000th cycle $p = 0.136$; 9000th cycle $p = 0.094$).

2. Retrospective clinical study

Thirty-six ($n = 36$; males: $n = 24$, females: $n = 12$) patients underwent implant placement using the Ao4 concept, with complete records of periapical radiographs; $n = 144$ and $n = 144$ implants placed in the maxilla and mandibles of patients, respectively, therefore the analysis of $n = 288$ individual implant data was carried out. The mean age of patients at the time of fixture installation was 58.75 ± 13.71 years (range: 19–90 years). Out of the enrolled patient population, $n = 6$ patients receiving implants in the mandible (controlled DM $n = 1$, mild bruxism $n = 1$, impacted oral hygiene (i.e., full-mouth plaque score and full mouth bleeding score 0–20%) $n = 1$, smoking $n = 3$, smoking and impacted oral hygiene $n = 1$) and $n = 5$ patients receiving implants in the maxilla (controlled DM $n = 1$, impacted oral hygiene $n = 1$, mild bruxism $n = 1$ and smoking $n = 1$, smoking and impacted oral hygiene $n = 1$) had underlying conditions/habits relevant to the outcome of the study (i.e. MBL); these patients were grouped together for our comparative analyses. In patients presenting with underlying conditions/habits described previously, a tendency was shown for higher bone loss rates in the maxilla (T_1: −0.633 ± 0.056 mm, T_2: −0.780 ± 0.056 mm, and T_3: −0.830 ± 0.053 mm) and the mandible (T_1: −0.535 ± 0.048 mm, T_2: −0.700 ± 0.054 mm, and T_3: −0.763 ± 0.051 mm), however none of these differences were statistically significant ($p > 0.05$). Significantly higher ($p < 0.05$) bone resorption levels were observed for 14MA, 24DA and 44D, while only numerical tendencies were shown for the other teeth.

VI. DISCUSSION

Successful implant placement is dependent on – among other things – the availability of adequate bone quality, while the longevity of the implants may be ensured by keeping the stresses on the bone within physiological range. The primary aim of our study was to establish whether pre-drilling (to prepare implant nests) and implant placement could have detrimental effects, i.e. to affect primary stability of the implant in the short term, while threatening therapeutic success in the long term; in addition, the risk and relevance of pathological fractures associated with immediately-loaded implants were also investigated. If this process affects bone biomechanical properties, the possibility of three-dimensional (3D) torsion deformation of the jaw has to be considered as a harmful effect, as the decreased mechanical properties the jawbone will render it less resistant against even everyday physiological impacts. Our initial hypothesis was that implant placement and augmentations preceding it should negatively impact the mechanical properties of the bone. To this end, an *in vitro* study was carried out using porcine ribs (to simulate an atrophic jaw), where mechanical properties of the bone were tested for static and dynamic load-bearing capacity (to simulate masticatory forces) – based on a 3-point bending test – following a pre-drilling procedure and/or implant placement as based on the Ao4 protocol, in comparison to the properties of untreated bone. As a secondary aim of this research, the bone loss levels in patients presenting with underlying conditions and lifestyle factors were assessed as a sub-group of patients receiving Ao4 implants in a retrospective radiographic study. It is well-known that inadequate oral hygiene (and a lack of motivation to practice good oral care), chronic conditions affecting the physiology of the oral cavity, smoking, and bruxism have a considerable influence on implant survival and clinical outcome, so much so that severe cases of the above mentioned are considered contraindications for the use of dental implants.

We have found that Group 2 (pre-drilled group) and Group 1 (implanted group) bone samples consistently had lower static load-bearing capacity, toughness and dynamic fatigue-bearing capacity, compared to the Group 3 (untreated, control group) samples; pre-drilled bone samples consistently showed the lowest values, followed by implanted bones and the untreated bones. While in the static load tests, the differences in force values and toughness were only numerical (not statistically significant), in the dynamic fatigue tests, significant differences were shown between the three bone groups; upon more careful analysis, it was observed that pre-drilled bone had considerably worse mechanical properties compared to Group 1 and 3, on the other hand the control and implanted bone samples presented with very similar mechanical properties by the 9000th cycle (as demonstrated by the similar course of the force curves). Subsequent bone breakage (shown by the appearance of partial cracks and subsequent fracture lines) were always shown at the sites where the pre-drilling or the implant placement occurred previously. Overall, the results of our mechanical examinations highlighted that placement of the holes via pre-drilling considerably reduced the stiffness and mechanical strength of the bone, which has led to macroscopic fractures from loading even at smaller deformations. The reduction of the damage limit clearly indicates the weakening of the bone’s resistance to force, which may partly be due to the decrease in the effective bone thickness in the drilled region. According to our static load tests, filling the pre-drilled nest with implants did not considerably improve the mechanical resistance of the bones. The reason for the appearance of cracks may be to be due to the fact, that the holes are filled with harder material than the spongy bone, thus, consequently local stresses at the implant-bone interface are exerted during loading. While implant placement has partially restored the load-bearing capacity and mechanical strength in the dynamic tests, implanted bone still did not reach the mechanical strength of intact bone. With regard to the risk of pathological fractures, the chance for breakage was always highest at the sites where the pre-drilling or the implant placement had occurred, which is presumed as a consequence of the reduced mechanical resistance of the treated bone samples compared to the untreated ones. Among the thirty-six patients, eleven were impacted by relevant clinic-epidemiological factors (controlled DM, mild bruxism, impacted oral hygiene and smoking) where MBL levels were comparatively assessed: while a tendency for higher bone loss values were shown around the implants in these individuals, significant differences were not shown.

The use of implant-supported prostheses for the rehabilitation of edentulous patients has become a widely used and effective method in prosthodontics; as a form of tertiary prevention in dental care, prosthetics allow individuals to regain both functionality and psychological well-being, which has wide-ranging consequences for the general and oral health-related quality of life (QoL) experienced by these patients. In these procedures, effective prosthetic restorations are carried out using 6-8 implants, with a posterior cantilever extension added where possible. Nevertheless, dentists are required to find solutions for patients with diverse jaw anatomy, bone quality, and functional, esthetic and economic expectations. The Ao4 treatment concept is an attractive treatment option for the rehabilitation of patients with severely atrophic AP and advanced involution, without the need of carrying out risky surgical augmentations with high rate of morbidity. Additional advantages of the Ao4 technique include the smaller number of implants needed, greater distance between the implants, and the use of tilted implants (30-45°), resulting in a shorter cantilever. However, as the Ao4 concept is based on immediate loading implants (which is associated with higher levels of stress in the surrounding bone), therefore achieving appropriate levels of primary (mechanical) implant stability – which has a considerable influence on the immediate outcome of the surgery – is essential. Implant failure, if insufficient primary stability is reached, may be as high as 30-40%. Transmission of masticatory loads on osseointegrated implants (which are directly fixed into the cortical and cancellous bone) is dissimilar to the mechanisms occurring with natural teeth; as periodontal ligaments are unable provide stress reduction, this leads to the direct transmission of occlusal forces into surrounding tissues. Reduced load-bearing capacity increases the risk of micro-crack formation, bone resorption and peri-implant bone defects. Similarly, if first and third principal stress values exceed characteristic physiological limits (i.e., the ultimate strength) of the bone, bone resorption would occur. Implant health may be influenced by numerous factors, which may be classified as: *patient-related local attributes* (e.g., oral hygiene status, adherence, gingivitis, periodontal disease, quality and quantity of the jaw bone, configuration of adjacent natural teeth, viability of the soft tissue), *patient-related systemic attributes* (e.g., advanced age, smoking, alcohol use, bruxism, diabetes or other chronic conditions, steroid therapy, head-neck radiotherapy, anticancer or immunosuppresive drugs, hypersensitivity reactions), *mechanical factors* (loading, occlusion), *attributes of the surgical technique* (e.g., extensive trauma, overheating of bone, bacterial contamination) and *implant characteristics* (e.g., previous implant failure in the anamnestic data, implant length and diameter, surface roughness, purity and sterility, implant fintess and load-bearing capacity). During surgery, clinicians may rely on classic qualification systems (e.g., Lekholm-Zarb) to assess the quality of the available bone at the edentulous bone sites, as these are based on the cortical-medullar bone ratio – therefore the density of the bone – and the crestal cortical bone thickness has a good predictive power for implant primary stability, which is protective against micromovements during load transmission to the implants, e.g., in case of an immediately loaded Ao4 restoration.

If the biomechanical barriers of the freshly inserted implants and the surrounding bone structures, are not respected enough, immediate loading is performed and temporary restorations are made before osseointegration occurs, we can easily induce excessive micromotions and localized stress at the bone-implant interface, which may lead to premature implant loss. Additionally, our experimental results have shown that local mechanical stresses appear at the bone-implant interface, which reduces the force required to cause fractures; this means that – especially in patients with a severely atrophic AP and relatively low bone quality – even the loss of a single implant after the surgery may eliminate the stabilizing effect of the implants on the mechanical properties of the bone structure, rendering it more susceptible to cracks and pathological fractures. Many studies have demonstrated showed that the use of tilted implants in Ao4 increases tension around them, however, splinting of the prosthetic parts together is a viable method to decrease the amount of stress on the implants.

In addition to working with non-osseointegrated samples, several limitations our study need to be acknowledged: firstly, the bending forces applied in our tests would occur only in extreme cases in clinical circumstances, and the direction of the loads were dissimilar to those of the masticatory forces; however, the cyclicity and the magnitudes of forces involved were in accordance with physiologically observable movements in mastication. As there was no abutment attached, the role and influence of implant–abutment connection in influencing bone mechanical properties and stress tolerance could not be assessed, the bone model was loaded directly. A further limitation of our research is that the applied protocol does not allow the implant-bone interface to be investigated in a direct way, unlike in 3D FEA studies.

Within its limitations, our study aimed to fill a gap in the literature, whether pre-drilling for implant nest preparation and/or implant placement has a negative effect on the mechanical properties of the jaw bone, which could have consequences in immediate outcomes (implant failure) or as long-term sequelae (pathological fractures). Our results showed that bone drilling has considerably impacted bone mechanical properties, which were in many cases, improved by implant placement, but never to the extent of the strength of the untreated bone. In addition, we have shown that inadequate oral hygiene, chronic conditions affecting the physiology of the oral cavity, smoking, and bruxism have a considerable aggravating role in enhancing marginal bone loss over time, increasing the risk for complications and implant failure. The data presented in this study may serve as a basis for additional experimental studies, in addition, it may also inform clinical decision-making in prosthodontics (especially in the case of restorations based on immediate loading) for debilitated patients with severely atrophic jaw bones.

VII. NEW FINDINGS

a. Pre-drilling and implant-placement had detrimental effects on the mechanical strength of the bone against static load: numerical, but not statistically significant differences were seen in load-bearing capacity and toughness in pre-drilled and implanted bone, compared to untreated bone. Pre-drilled bones had the worse mechanical properties, while the placement of implants considerably increased mechanical strength.

b. Pre-drilling and implant-placement had detrimental effects on the mechanical strength of the bone against dynamic fatigue: significant differences were seen in load-bearing capacity in pre-drilled and implanted bone, compared to untreated bone. Pre-drilled bones had the worse mechanical properties, while implanted bone showed similar load-bearing capacity to untreated bone by the 9000th cycle.

c. Pre-drilling and implant-placement had increased the risk of fracture during loading: partial cracks were situated between the two middle implants, while fractures always occurred next to pre-drilled nests and the inserted implants.

d. The effect of patients' clinico-epidemiological correlates (controlled diabetes mellitus, mild bruxism, impacted oral hygiene and smoking) on marginal bone loss after Ao4 implant treatment: in patients presenting with underlying conditions/habits, numerical, but not statistically significant differences were seen for higher bone loss rates in the maxilla and mandibular bone after 18 months, 30 months and 42 months of follow-up

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