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

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2. Publications not related to the subject of the thesis

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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. LIST OF ABBREVIATIONS

3D: three-dimensional
Ao4: All-on-Four
Ao6: All-on-Six
AP: alveolar process
AUC: area under the curve
BOP: bleeding on probing
CBCT: cone-beam computed tomography
CT: computed tomography
DA: disto-approximal aspect
DM: diabetes mellitus
E: Young's modulus/elastic modulus
FEA: finite element analysis
MA: mesio-approximal aspect
MBL: marginal bone loss
MRONJ: medication-related osteonecrosis of the jaws
OPT: panoramic X-ray
QoL: quality of life
RCT: randomized controlled trial
S: toughness
SEM: standard error of the mean
SPSS: Statistical Package for the Social Sciences
Ti: titanium
v: Poisson's ratio
WHO: World Health Organization

III. INTRODUCTION

A. Edentulism

Oral health has a multidimensional (physiological, functional, psychological) role in the general health and well-being of individuals; however, oral diseases are some of the most common non-communicable illnesses globally, affecting around 3.5 billion people [1]. With considerable demographic changes and an ageing population, the long-term consequence of these oral conditions is expected to be more pronounced in the coming decades. The loss of teeth is considered as an end-point of a life-long history of oral diseases. According to the World Health Organization (WHO), severe tooth loss (or partial edentulism) is a state of having ≤9 permanent teeth, while edentulism is a state of complete toothlessness [1,2]. Edentulism may result from teeth not developing in the first place (i.e., true or total adontia), however, this condition is fortunately extremely rare. In the overwhelming majority, edentulism is a result of the extraction of permanent teeth in adulthood, which may be due to long-term consequences of caries and its complications, periodontal disease, orofacial trauma or other orofacial pathologies (e.g., cysts, tumours) [3]. Edentulism is a definite condition, which has emerged as a global public health issue: according to the WHO Global Oral Health Status Report (2021), the estimated prevalence of edentulousness globally is 6.82%, with an increase of over 80% between 1990 and 2019 [4,5]. Among high-income regions, the WHO European Region has the highest prevalence (12.42%), but lowest proportional change (+30%) worldwide [4,5].

Once the extraction of the teeth occurs, the jaw undergoes degenerative changes in size and shape that are continuous for the duration of the individual's life. The alveolar process (AP) is a thick rigde of bone, which is part of the maxilla and the mandible [6]. The AP supports the teeth as a functional part of the jawbones (containing the tooth sockets), and is a tooth dependent structure: the volume, shape, height and width of the AP are determined by the shape of teeth [7]. Once the teeth are lost to the body, degenerative processes are initiated, as well as the alteration of the width (horizontal dimension) and height (vertical dimension) of the AP. It is established knowledge that post-extraction resorption affects the buccal bone plate in both jawbones more extensively than the oral bone walls [8]. These degenerative changes are the most prominent in the first three months after tooth loss [9], i.e., two-thirds of the horizontal reduction of the bone occur within the first three months of healing after tooth extraction, if unaltered by prosthetic procedures [10].

After the physiological forces associated with mastication are no longer present on the cancellous alveoral bone (applied via the roots of the teeth), the loss of mechanical stimulation invariably leads to reduction in bone mass [11]. These changes – based on physical laws, such as the Mechanostat Model and Wolff's Law – were first described for long bones of the limbs; however, they are relevant for the AP and other regions of the skull, with some differences in etiopathology, specific for the jaws (e.g., site-specific behavior or osteoblasts/osteoclasts, matrix composition) [12-14]. Following the extraction of teeth, the first step in remodeling occurs with the resorption of the bundle bone (initiates after ~ 2 weeks), which has no further functionality without the corresponding periodontal ligaments; the bundle bone will then transform into woven bone [15]. This phenomenon correlates with and may explain the height decrease of the buccal side of the edentulous site in the first four weeks of healing. In response to the balance of osteobast and osteoclast activity, dimensional reduction of the AP and formation of new bone happens in parallel in the 3 months following extraction [10]. In the second phase (4-8 weeks following extraction), the woven bone will transform into lamellar bone and bone marrow to a large degree; the resorption continues, and the height of the buccal side of the edentulous site continues to decrease, as well as the width from the buccal and lingual outer walls [16,17]. This width reduction will reach ~50% of its original volume in the first year after extraction; this irreversible process is a well-known pathophysicological occurrence, which is termed residual ridge resorption or remodeling [18]. Over time, bone resorption progresses on the edentulous ridge of the mandible [19], with not just horizontal and vertical dimensions affected by the remodeling, but significant changes in the quality of the bone as well. The atrophy of the AP may greatly vary between individuals, affected by the anatomic characteristics of the jaws, age, sex, inflammatory and immune status, hormone levels, among others [20]. The reduction of the AP is an irreversible, life-long process; however, it may be slowed down using a treatment plan involving the use of prostheses to transfer the loads to the underlying bone in the most physiologic way (usually by using implant-supported overdentures or endosseous implants) [21].

Several classification systems have been devised to describe the quality of the edentulous jaw bone prior to implant placement [22]; the most commonly used classification is by Lekholm and Zarb (1985), which serves as a recognized prognostic indicator for future implant performance. This classification is based on the ratio of the cortical and medullar bone in the residual alveolar bone: *type I* corresponds to large quantities of homogenous cortical bone, *type II* corresponds to the case when a dense medullar bone is surrounded by a thick cortical layer, in case of *type III*, a thin cortical layer surrounding a dense medullar bone, while for *type IV*, only a thin cortical layer is available, surrounding a soft, low-density medullar bone (**Figure 1.**) [23,24]. Overall, types II and III are generally noted to ensure favourable implant stabilization and good healing conditions. The other frequently used method to assess bone quality is associated with Misch [25]; this classification system is based on the density of the remaining alveolar bone, with different bone types being characteristic in different regions of the edentulous jawbones. Therefore, *D1* bone type is the densest in structure, mostly found in the interforaminal region of the mandible, *D2* is less dense, and typically found in the rest of the mandible, *D3* is frequent in the anterior maxilla, while *D4* may be identified in the posterior part of the maxilla, and is the least dense.

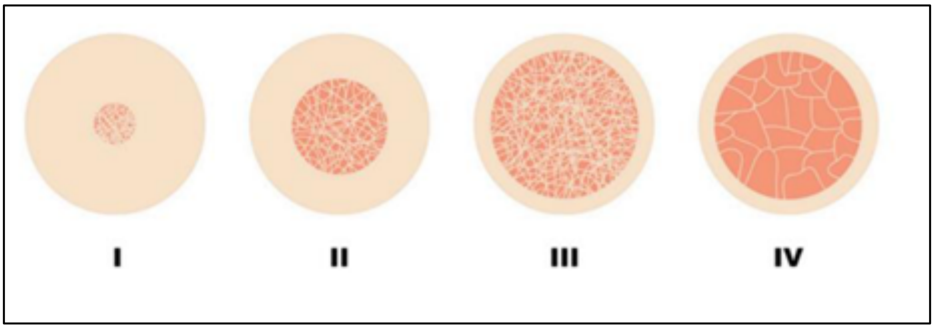

Figure 1. Lekholm-Zarb classification for the bone quality of the edentulous jaw (type I-IV) Types II and III provide favourable outcomes after implant placement [23,24]

As edentulism has a considerable negative impact for esthetic and functional aspects for patients, it should be managed through prosthetic rehabilitation, which can be either be implant or tissue-supported, with fixed or removable prostheses, that are not only suitable for providing the functional rehabilitation of the masticatory system and proper phonation, but also restores the lost facial aesthetics of the patients [26]. The rehabilitation of edentulous mandibles is especially difficult, as the residual ridge has smaller surface than the maxilla, where we can also gain considerable extrension on palatal surfaces to establish a peripheral seal and to retain a complete denture. In addition, the retention of mandibular dentures is hindered by the presence of the moving tongue and orofacial muscles, which tend to dislodge the denture during function [27]. The possible complaints and adverse events associated with wearing removable prostheses include the occurrence of mucosal irritation, under-extension of the denture bases, incorrect jaw relationships, incorrect occlusal vertical dimensions, and an inadequate posterior palatal seal [28].

B. Implant placement, osseointegration

Clinical decision-making in modern dentistry should always be based on the most reliable scientific evidence, with the clinico-epidemiological correlates of the patients in mind [29]. Nevertheless, the costs of the treatment, long-term durability and the expectations of the patient should also be considered, in line with shared decision making for the treatment plan. With the development of dentistry, the esthetic and functional expectations of patients have also increased considerably; therefore, patients anticipate fixed dentures even in a total edentulous state. These expectations may be challenging for the dentist, especially in particularly complicated cases with severe atrophy of the AP (e.g., if tooth extractions happened a long time ago, or the teeth were extracted with resective surgical procedures) [30]. Implant surgery is characterized by placing a dental implant made from alloplastic material – in most cases titanium (Ti) – in a previously prepared nest in the jawbone. The biocompatibility, mechanical properties and corrosion resistance of Ti is excellent, and it is a relatively strong and durable metal, which is able to withstand the mechanical stresses and strains arising during the everyday chewing and biting [31]. Ti is also a relatively light metal (with a density [ρ] of 4500 kg/m^3, a Young's modulus [E] of 102 GPa, and a Poisson's ratio [ν] of 0.36), which reduces the total implant weight, and also reduces the occurring strains in the nearby tissue. Ti dental implants also have a unique ability to osseointegrate with the living tissue, which leads to a direct bond with the jaw bone. Based on the special characteristics, we can agree that the Ti-anchored dental implants provide a stable foundation for dental prostheses [32].

Implant placement protocols allow us to deliver fixed implant-supported dental prostheses to patients, to achieve a high degree of satisfaction, and to avoid lack of stability and retention failure [33]. Implant placement requires clinicians to utilize the remaining bone in the most efficient way possible in view of the severity of the involution. Unfortunately, limiting factors may occur in case of dental implant surgery, especially in case of edentulous patients; these factors include decreased bone volume, poor bone quality in the posterior parts of the jaws, and expanse of the laterobasal wall of the maxillary sinus [34]. 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 [35-37]. Although guided bone regeneration procedures, alveolar crest augmentation and other surgical procedures have predictable success rate, they are also associated with a high-risk of patient morbidity, adverse events (e.g., graft failure, loss of soft tissue contours, infections, hemorrhage, neurosensory disturbances), and improper implant placement [38-40].

Following implant placement, implant survival is dependent upon the fixation of alloplastic material to the biological surface. Per-Ingwar Branemark (1965) described the phenomenon of osseointegration to explain the bond between the Ti implant surface and the bone, establishing the scientific basis for modern implantology [41,42]. Osseointegration is a successful outcome, a direct functional and structural connection between the bone and the implant surface [43]. In the healing process, the rigid fixation of an alloplastic material is realized, and functional ankylosis may be seen during histologic examination with no fibrous or connective tissue, between the bone and implant surface [44]. According to Branemark the requirements for succesful osseointegration are the following:

1. Implant material with biocompatibility
2. Implant design – perfect fit and maximum contact between the implant and the bone
3. Implant finish – a larger surface is more beneficial for the cell attachments
4. Status of the bone – proper bone quality and quantity
5. Surgical technique – minimal surgical trauma and cooling
6. Implant loading – undisturbed healing period for osseintegration

The process of bone healing after implant placement is similar to primary bone healing. Blot clots form between the bone-implant interface, which is later transformed by immune cells, and first a procallus, then a dense connective tissue forms. Osteoblasts and osteoclasts differentiate from mesenchymal cells, forming a callus that later will be become the new bone [45]. After the loading of the implant, bone remodelling occurs by the stimulation of masticatory forces, and the newly formed immature bone becomes denser and more homogenous with the calcifation of the Haversian canals. Nevertheless, many failures and complications may arise during the use of implants to support restorations; while many of these failures may be prevented by appropriate patient selection and a careful treatment planning, their risk should always be considered [46]. Implant failures may be classified as primary (or early), resulting from failure of osseointegration, and secondary (late), where usually soft-tissue and/or biomechanical factors are implicated (**Figure 2.**) [47]. Both early and late implant failure may be affected by patient characteristics (i.e., non-modifiable risk factors such as age, sex, immune status, chronic conditions or diseases, oral status and inadequate oral hygiene, periodontal disease, bruxism, medication intake, smoking) and adherence to treatment guidelines [48].

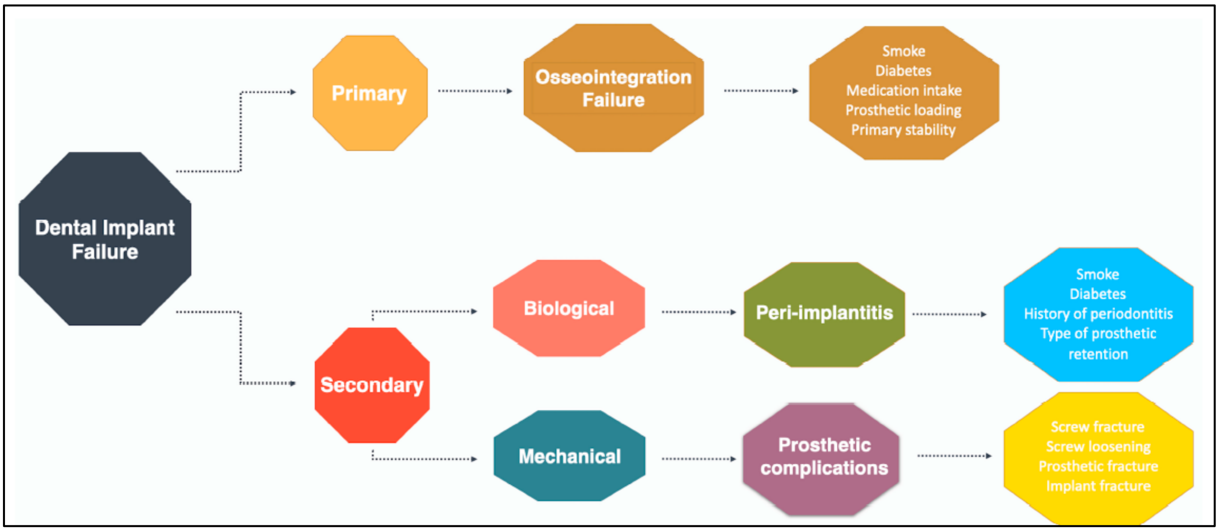

Figure 2. Classification and causes of dental implant failure [47]

Pre-surgical implant planning and bone preparation are some of the critical aspects to ensure a successful intervention and a pleasing outcome of implant-supported prostheses. Before implant placement, preparation of the implant bed (implant nest) needs to take place. Implant bed preparation should be performed as effectively and gently as possible, to ensure the primary healing and the long-term success of the implants [48]. The conventional drilling is a commoly used technique to prepare implant nests [49]; first, a gradual drilling of the osteotomy site occurs, which is later enlarged to the desired diameter. To ensure reliable implant-to-bone connection, mechanical and thermal trauma of the bone should be limited. It has been described that intraosseous temperature should not exceed 47 °C (otherwise it will lead to bone tissue necrosis, and a disruption in the architecture of collagen fibers), as it may interfere with osseointegration [50]. It is plausible to suggest that the mechanical properties of the mandible may be affected by the procedure of pre-drilling, and the subsequent substitution of space with a different characteristic material.

C. Fracture of the atrophic mandible related to dental implants

A bone fracture is a medical condition in which there is a partial or complete break in the continuity of any bone in the body. Pathological fractures are special kind of disruption of bone continuity, that occur in those regions where the volume or the quality of the bone has been decreased by any ongoing pathological condition [51]. Pathological fractures in the jaw bones may be a result of ostemyelitis [52], osteoradionecrosis [53], medication-related osteonecrosis of the jaws (MRONJ) [54], or are facilitated by cystic lesions [55], benign, malignant or metastatic tumors [56,57], or caused by surgical procedures, e.g., removal of an impacted third molar [58], or implant placement. Pathological fractures as complications of oral surgery occur at a rate of 0.2% [40]. Pathological fractures of the mandible after enosseus implant placement have rarely been reported in the literature [59]. To establish the quality and availability of the mandibular bone is critial to ascertain the possible adverse effects and the risk of pathological fractures. This phenomenon may take place at the time of the surgical procedure of implant placement, but more frequently, when the implant fails and additional osteomyelitis occurs, especially in severly resorbed mandibles [60]. In the event of short implants placed in the edentulous ridge with severe atrophy for anchoring fixed dental prosthetic devices, the ratio between the length of the implant and the length of the suprastructure (e.g., crown, bar attachment, bridge) is compromised, resulting an extented arm of force; the resuling extended toque leads to unfavorable biomechanics. In these cases, even performing routine oral functions could cause a fracture without any direct trauma to the mandible [61]. The use of wide diameter implants and bicortical penetration may also endanger the integrity of a severly atrophic mandible [51].

The management of pathological fractures may be challenging, and it is different case-by-case, according to the etiology of the pathological condition that has led to the fracture. In most cases the treatment is open reduction and internal fixation, via an extraoral or intraoral approach [62]; however, in some cases when the fractures are linear, non-displaced and located at an inter implant location, stabilization with closed reduction techniques (e.g., using splints on the remaining implants) may also present as a good solution. In most cases, conservative techniques are not going to be efficient in case of a severly athrophized mandible, therefore osteosynthesis plates are used for rigid fixation and after the surgery, soft diet is recommended [63]. Elderly patients are predominantly affected by severely resorbed mandibles, and such a surgical intervention may be quite burdensome in this age group, especially when considering the prolonged recovery period and the possible surgical complications [64].

D. Immediate loading, the All-on-Four^{TM} treatment concept

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 [65]. Immediate loading (or immediate function) concept refers to the insertion of dental implants, abutments and restoration within the same day (or within 48 hours of implant placement) [66]. In practice, a preliminary acrylic immediate prosthesis is delivered within 2 hours after the surgery, after 4-6 months the final prostheses are made. The concept is a response to patients' increasing demand for quick, esthetic treatment and reduced time-to-teeth [67]; this has been verified by the study of Hof et al., where patients preferred immediate implant placement, instead of four other treatment protocols [68]. In addition to reduced treatment duration, the advantages of immediate rehabilitation – in patients where it is applicable – include lower morbidity rates and higher esthetic value. The clinical success of immediately-loaded implants is influenced by numerous factors (see **Figure 3**), such as the oral hygiene of the patient [69], bone quality and ratio of cortical/trabecular bone [31,70], the surgical technique used [71], type and nature of the occlusion [72], implant design and macrogeometry (threaded vs. cylindrical, length, diameter) [73-75], and the abutment fit and conical angle connection [76] among others. However, one of the most critical aspects of the success of immediate loading implants is primary stability, influencing the early phase of osseointegration, regulated by the quality and quantity of bone tissue surrounding the implant [77]. After implant placement, primary implant stability is fundamental to avoid micro-movements (micromotions) at the bone-implant interface during osseointegration. If micromotions values are exceedingly high, a non-mineralized, fibrous, fluid-filled capsule forms around the implants instead of skeletal attachment and osseointegration [78]. Thus, to ensure complete successful osseointegration, micromotion values should be below 50-150 μm, according to several pre-clinical and clinical studies [79,80]. Maximum micromotion values are considerably influenced by the density of cancellous bone, while crestal cortical bone density only had a major role, it if was found together with low cancellous bone density [81].

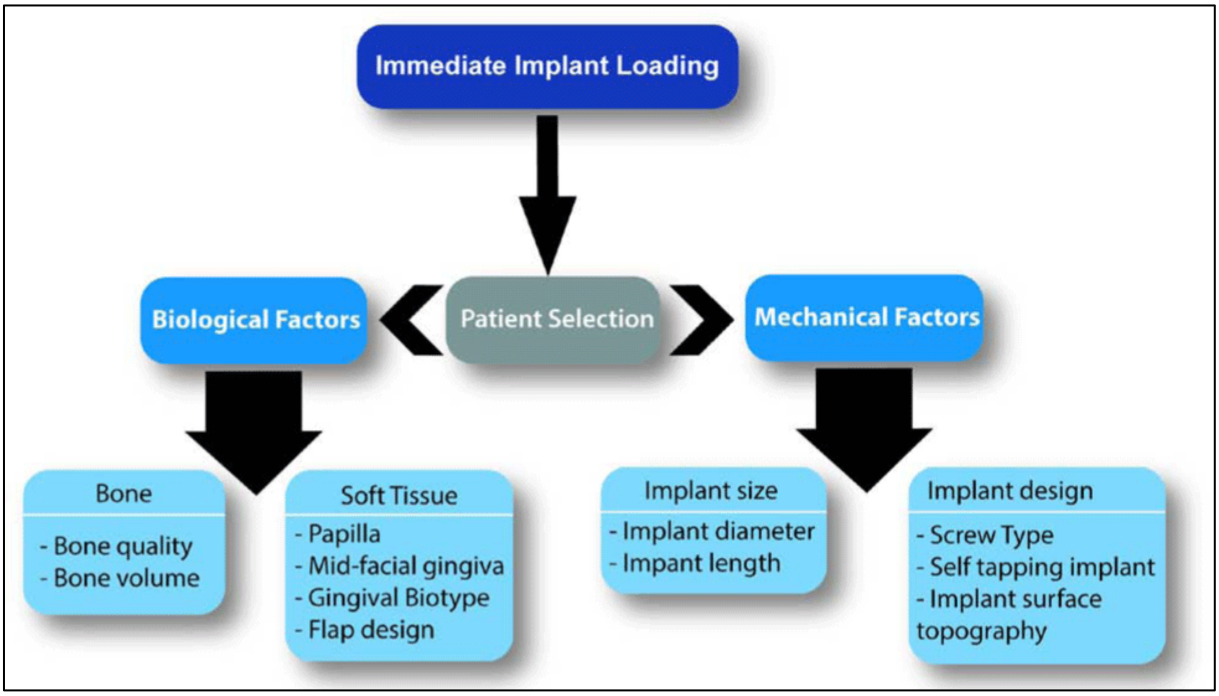

Figure 3. Main factors influencing the success of the immediate loading concept [82]

As previously described, in patients with severely atrophic AP and advanced involution, complex bone augmentation procedures may be necessary prior to implant placement. However, bone grafting may be avoided by the use of tilted implants – associated with an extension of the distal cantilever – in the maxilla or the mandible, which has shown to be a viable alternative with no significant difference in clinical success rates [83,84]. Based on this strategy, numerous novel treatment concepts have emerged in the the recent years, including the "All-on-Four^{TM}" (Ao4) and "All-on-Six^{TM}" (Ao6) concepts. The Ao4 concept was introduced by Maló et al. (Nobel Biocare AB, Göteborg, Sweden), where four implants are applied in the anterior part of completely edentulous jaws to support provisional, fixed, and immediately loaded prosthesis [85,86]. In Ao4 treatment, all implants are placed in the interforaminal area of the maxilla/mandible, with two anterior implants placed axially and parallel to each other, while the two posterior implants are distally tilted (30°-45°) to achieve the most favourable implant distribution in the edentulous jaws [87,88]. The role of the tilted implants is to provide anchorage for the first molar occlusion with a short cantilevered segment, in addition, violation of the surrounding nerves is also avoided [89,90]. Ao4 are many times done with the use of computer-assisted procedures and implant guides, further enhance the reliability and safety of the procedure [91]. After the surgery implants are immediately loaded, which therefore highly relies on achieving adequate primary stability, affected by the preparation of the implant bed, implant geometry and bone quality [92]. Adequate cortical bone volume favours implants achieving high primary stability, however, in many cases, if this is not available (e.g., implant anchorage in the total edentulous maxilla is often restricted), then immediate loading may be a greater challenge [93].

As the Ao4 concepts is based on the use of reduced number of tilted implants, individual implant properties (e.g., length, diameter, macrogeometry, surface) have considerably higher relevance [94]. For example, it has been demonstrated that the use of longer implants – corresponding to a longer bone-to-implant contact area – leads to greater primary stability, but only up to a cut-off point of about 12-15 mm [95]; on the other hand, implants with greater diameter are associated with better secondary stability [96]. Many studies have shown that making immediate rehabilitations on fully edentulous jaws using tilted implants is a safe and effective approach, with marginal bone loss levels not greater as compared to axially placed implants [97]; based on retrospective studies, marginal bone loss levels were around 0.5-1.5 mm in 3-5 years, both in the maxilla and the mandible [98]. Ao4 procedures have a predictable and positive prognosis, and high patient satisfaction rates [99,100]. While long-term analyses are not available, short-term success rates (92-100%) are impressive, and a decade-long study by Maló et al. reported a mandibular implant survival rate of 98.2% [101,102]. Additionally, finite element analysis (FEA) studies have also verified Ao4 as a good alternative with regards to stress and strain distribution, which can safely support the fixed dentures [103,104].

E. Basic physical concepts, stresses

Dental biomaterials – such as implants – and the surrounding alveolar bone are continously being subjected to various mechanical forces (or loads) during functional (biting, chewing) and parafunctional (e.g., bruxism) activities of the mouth, which may affect their primary stability during immediate loading [105]. Nonetheless, the distribution of mechanical forces and the load transfer at the bone-implant interface is also critical from the standpoint of secondary implant stability, which includes the long-term tissue response to the implant, and subsequent bone remodeling processes (i.e., mechanotransduction) [106]. 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 AR [107]. The denser the cancellous bone, the more stress it bears, and less stress is expected to be seen in other structures. Assessing how bone and implant components behave demands the understanding of the underlying mechanical and biological processes, in the context of each patients’ unique jaw anatomy, bone quality and occlusal load exerted on the prosthesis and on any type of suprastructure material.

In response to external forces, bodies and/or materials will also respond by the awakening of internal forces (*stresses*), that are of the same magnitude, but with the opposite direction. The explanation of complex stresses may be divided into basic stress types, i.e., tensile, compressive and shear stresses. For every body or material, there is a limit to the amount of applied force that can be whitstanded, which is termed fracture stress or ultimate tensile strenght. In addition to stress, strain is also an important term, which refers to dimensional changes occurring in a body or material, when external forces apply. Stress and strain are not independent or unrelated properties of materials: i.e., the application of an external force, producing a stress within a material, results in a change in dimension or strain within the body. The relationship between stress and strain is often used to characterise the mechanical properties of materials; such data may be generated using mechanical testing machines. In addition to ultimate tensile strenght, density, Young's modulus (elastic modulus; tensile elasticity along a line when opposing forces are applied), Poission’s ratio (informing the ratio of expansion along one axis to contraction along the opposite axis when a material is subjected to tensile or compressive stresses) and yield limit number (defined as the mechanical stress where the material enters into its plastic behavior) are also important material properties to be considered for dental biomaterials (**Figure 4**); these properties considerably affect the load-bearing capacity of implants [108,109] Dental materials (implants, prostheses) are subjected to intermittent stresses over a long period of time; although these stresses encountered may be far too small to cause fracture in the material when measured in a direct tensile, compressive or transverse tests, it may be possible that, over a period of time, failure may occur by a fatigue process. This involves the formation of micro cracks – caused by a stress concentration at a surface fault or due to the shape of the restoration or prosthesis – which may slowly propagate, until a fracture occurs [110]. The masticatory is also a kind of dynamic load in case of dental implants. During the dynamic loads, the forces appear repeatedly (cyclically) due to the chewing, which may cause micro-cracks, leading to implant failure or a fatigue fracture of the material. Dentists all have to be aware of the tensile, compressive and shear stresses arising in the bone from the chewing forces and the implants during treatment planning.

When assessing the biomechanical properties of the peri-implant bone, maximum principal stress (1st principal stress; corresponding to strongest tensile stress values), minimum principal stress (3rd principal stress; corresponding to strongest compressive stress values) and equivalent stress (von Mises stress; representing stress around the implant and implant-to-bone load transfer) are often used [111]. Compression is one of the main types of mechanical force, which acts along the vertical axis; these forces are typically generated during the biting and chewing. Compressive stress might cause micro-movements in the bone-implant connection although they range in an elastic boundary. Compressive forces during chewing are usually in the 400-500 N range, however, considering the cross-sectional area of an implant, this may lead to several hundreds of MPa mechanical stress on the implant-bone interface [112]. Tensile stress values occur for dental implants as shear forces that appear perpendicular to the vertical axis; these forces also occur during mastication, and may lead to changes in implant volume (i.e., expansion and contraction), leading to mechanical stress within the implant. Tensile stress values are usually highest at the implant neck, while compressive stresses peak at at the tip of the implant or at implant-bone contact surfaces. The mentioned mechanical stress values should not exceed the plasticity of the dental implants. 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 [113].

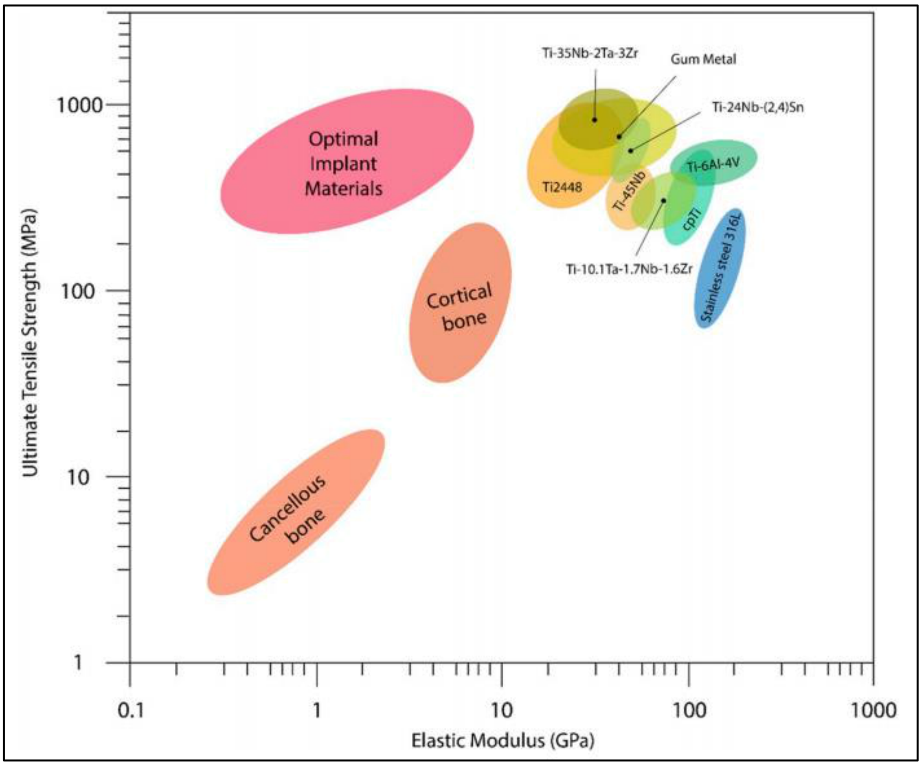

Figure 4. Association between Young's modulus (elastic modulus) and ultimate tensile strength values in cortical/cancellous bone and commonly used implant materials [108,109]

IV. 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.

<u>**The specific goals of the study were the following:**</u>

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**

V. MATERIALS AND METHODS

1. Bone drilling experiments *in vitro*

1. A. 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 [114], which is similar to the composition of a human mandible [115,116]. The dimensions of the ribs were measured with an analog dial caliper (0.01 mm spacing, Hoffmann Gruppe AK600203, Hoffmann Gruppe AG, Winterthur, Switzerland).

1. B. 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 refridgerator (at 5°C) until further measurements.

1. C. 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) [117]. For the mechanical testing, a 3-point bending test was performed, which is a widely accepted method for fracture testing [118,119]. Special mechanical components were designed and manufactured for the purposes of the study, which could be applied in both the static and dynamic equipments; the setup of the bone and mechanical components in measurements is presented in **Figure 5**.

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 [120,121]. 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.

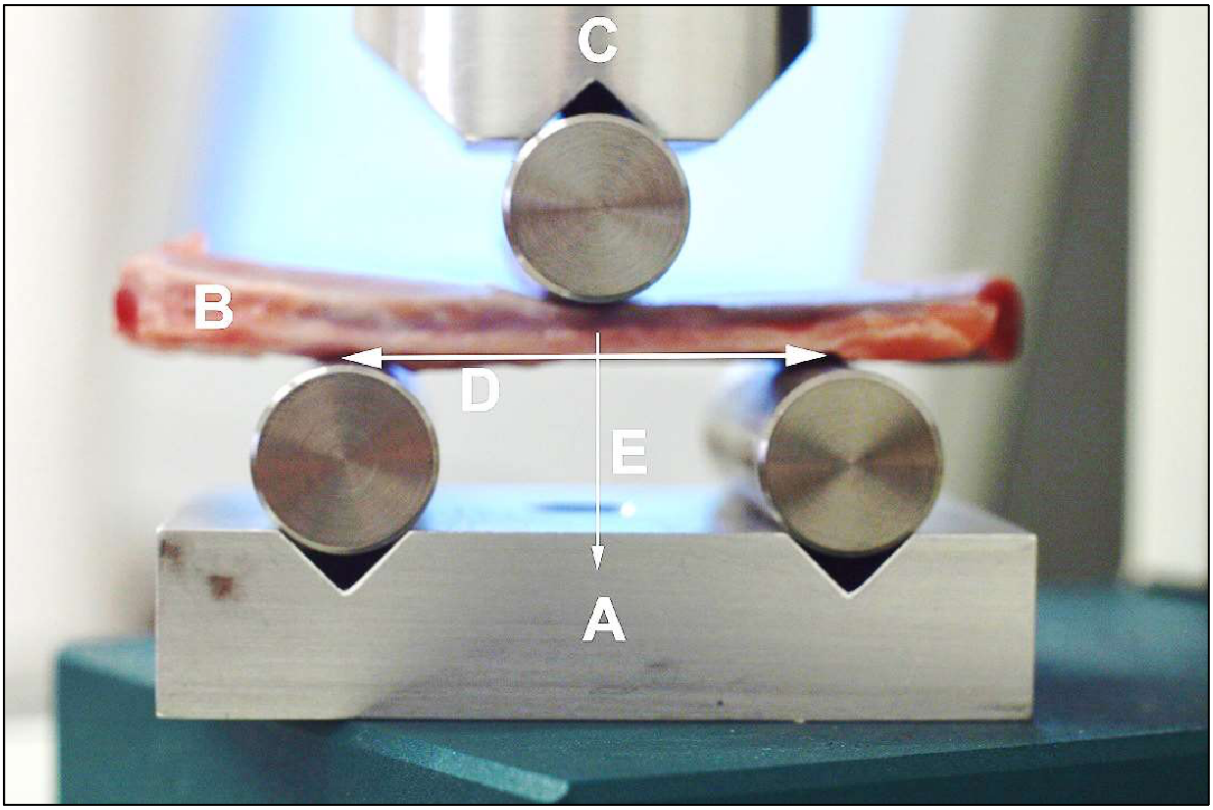

Figure 5. Experimental layout with special mechanical components designed and manufactured for the purposes of the study

A: supporting platform with point support rollers; **B:** pork rib segment; **C:** pressure head of the mechanical tear/break device with the roller used for point loading; **D:** distance between support points (standard 40 mm). **E:** vector of the force acting on the bone segment.

1. D. 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.

2. Retrospective clinical study

2. A. Study design, inclusion and exclusion criteria

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 01.01.2017. and 01.01.2022. The study was based on purposive sampling at the study center, according to the following criteria:

- *inclusion criteria:* age ≥18 years, overall good health condition, able to undergo surgical intervention, in need for a complete rehabilitation of the edentulous maxilla or mandible, and the possibility of placing a minimum of 4 implants (at least 10 mm long), with sufficient bone height in the sites intended for implants (evaluated by preoperative CT scans).
- *exclusion criteria:* presence of an acute infection at the planned implant sites, known coagulopathies or other hematologic diseases, recent occurrence of severe cardiovascular or cerebrovascular event, immune disorders, uncontrolled diabetes mellitus (DM), pregnancy or lactation, metabolic illnesses affecting the bones, bisphosphonate therapy, heavy smoking (>10 packs/day), systemic chemotherapy or irradiation of the head and neck region within the last 12 months, presence of severe bruxism or clenching (assessed and identified by the clinicians, based on clinical signs and symptoms), and inadequate oral hygiene level (full-mouth plaque and bleeding scores over 20%), poor perceived motivation on the part of the patients to maintain good oral hygiene.

2. B. Preoperative treatment and implant placement protocol

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. Individuals followed an antibiotic regimen per os (clindamycin 300 mg q.i.d.) three days prior to the surgical procedures in cases where teeth had to be extracted simultaneously. Preceding surgery, local anesthesia was administered. 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. For the fabrication of the master cast to create the patients' provisional restoration, open-tray multi-unit impression copings were placed on the multi-unit abutments to make an impression using precision impression material (Flexitime, Heraeus Kulzer, Hanau, Germany). Following the operative procedure, patients were instructed to abstain from brushing in the first 7 days post-op, and to rinse using warm water. For 24 h post-io, instructions and recommendations were given for a soft diet (cold or at room temperature), to be followed by a semisolid diet for the following three months. Patients were supplied with antibiotics and analgesics to control post-operative pain and inflammation as per standard guidelines and protocols in oral surgery. To confirm implant positions, and the positions of the prosthetic components, a CBCT scan was taken immediately postoperatively.

2. C. Restorative protocol

Preceding surgery, a heat-cured acrylic resin (Ivocap High Impact acrylic, Ivoclar Vivadent, Amherst, NY, USA) was prefabricated, which was amended to the master model directly after the surgery. Fabrication was carried out using cold curing material (Probase, Ivoclar Vivadent, Amherst, NY, USA). Following 3–4 weeks after the completion of the operation, the provisional all-acrylic prosthesis was seated. Routine follow-ups were scheduled for the patients after surgery at 7, 14, and 28 days and 3 months after surgery, and on a yearly basis thereafter. Following the 3-month appointment, fabrication of the definitive prosthesis was initiated, consisting of a milled titanium frame with a wrap-around heat-cured acrylic resin (Nobel Procera Implant Bridge titanium framework veneered with composite). The antagonist denture was a fixed denture/implant supported restoration in all cases. A long-cone paralleling method was applied to obtain matched and calibrated orthopantomogram (OPT; panoramic X-ray) images at the 3-month appointment and at the subsequent appointments continuously. The 3-month radiographs after the time of placement of the definitive prosthesis were utilized as a baseline (T_0) to assess the bone levels longitudinally. At the respective follow-ups, the implants were assessed for signs of peri-implantitis, plaque, and bleeding on probing (BOP), based on routine clinical guidelines.

2. D. Calculation of marginal bone loss, outcome variables assessed

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. An independent researcher—not affiliated with the primary center and investigators—evaluated the OPT images. Radiographs were digitized in a 640 (H) × 480 (V) pixel matrix image with an 8-bit depth. The density and contrast were then adjusted for optimal visualization of the marginal bone, and the digital images were saved as a TIF extension image. The 2D images were then exported and analyzed using the CLINIVIEW image analysis software (MI Dental, Knowsley, Prescot, UK). Calibration for image analysis was performed on an individual implant-level to achieve the most accurate results possible, where the known size and specifications of the individual documented implants were used as the basis for calibration to allow for the calculation of marginal bone level changes in the area. 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.

2. E. Ethical considerations and consent to participate

The 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.

3. Statistical analysis

3. 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.

3. 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.

VI. 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 measurement results of the static load tests are summarized in **Figures 6-8 (Group 3: Figure 6, Group 2: Figure 7, Group 1: Figure 8)**; 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. **Figure 9** shows the occurred maximum static load force values: 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 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 (**Figure 10**). In line with this, in the implanted bone samples (Group 3), the maximum force values 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 (**Figure 11**). 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 of **Figures 6-8**, the toughness of the bone (S) was expressed in Nmm, registered during the test; the results of these measurements are shown on **Figure 12.** 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 anaylsis 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); results of these experiments are summarized in **Figure 13**. 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 $p = 0.72$); in addition, **Figure 13.** showed that these two groups exhibited very similar force values from the 9000th cycle onward. 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 $p = 0.094$).

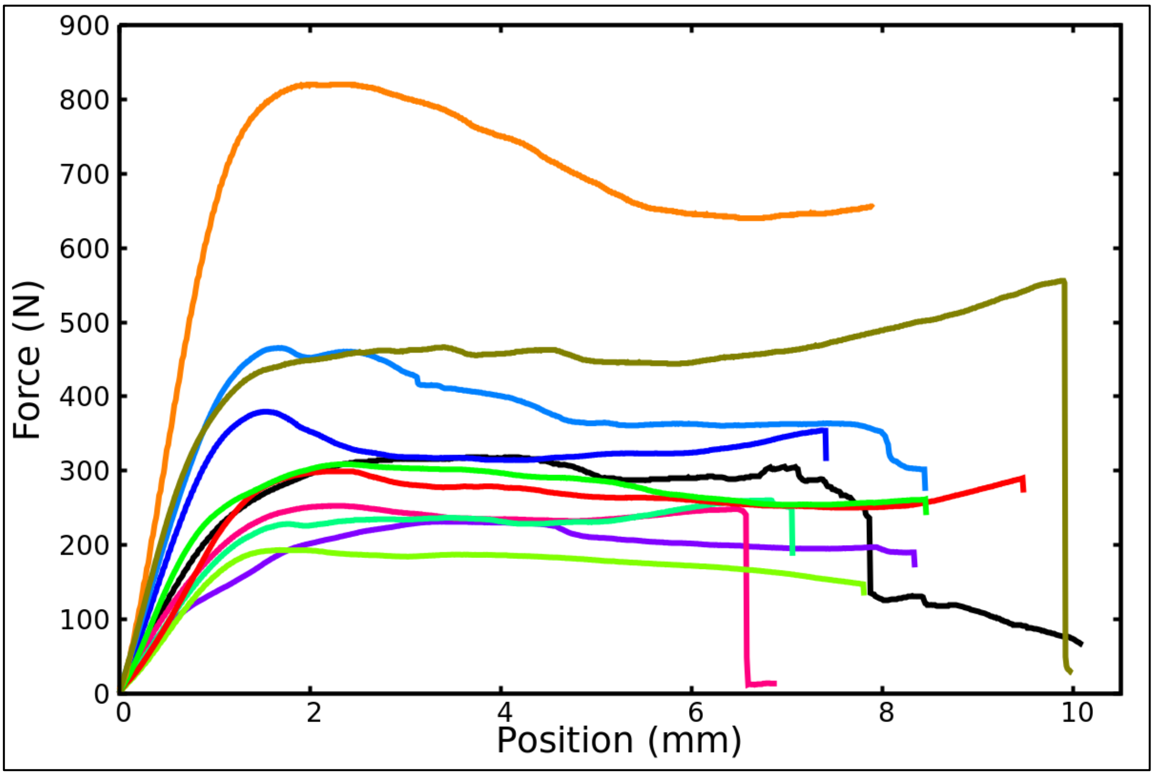

Figure 6. Static load diagram of Group 3 (control group)

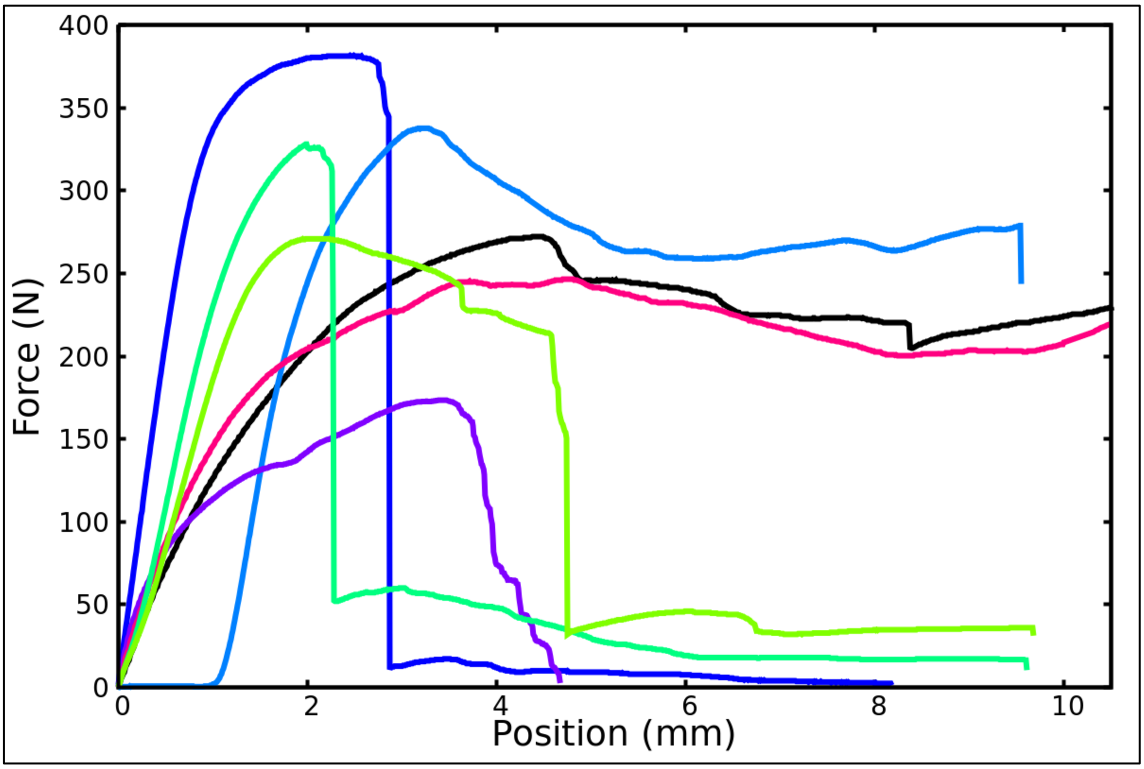

Figure 7. Static load diagram of Group 2 (pre-drilled group)

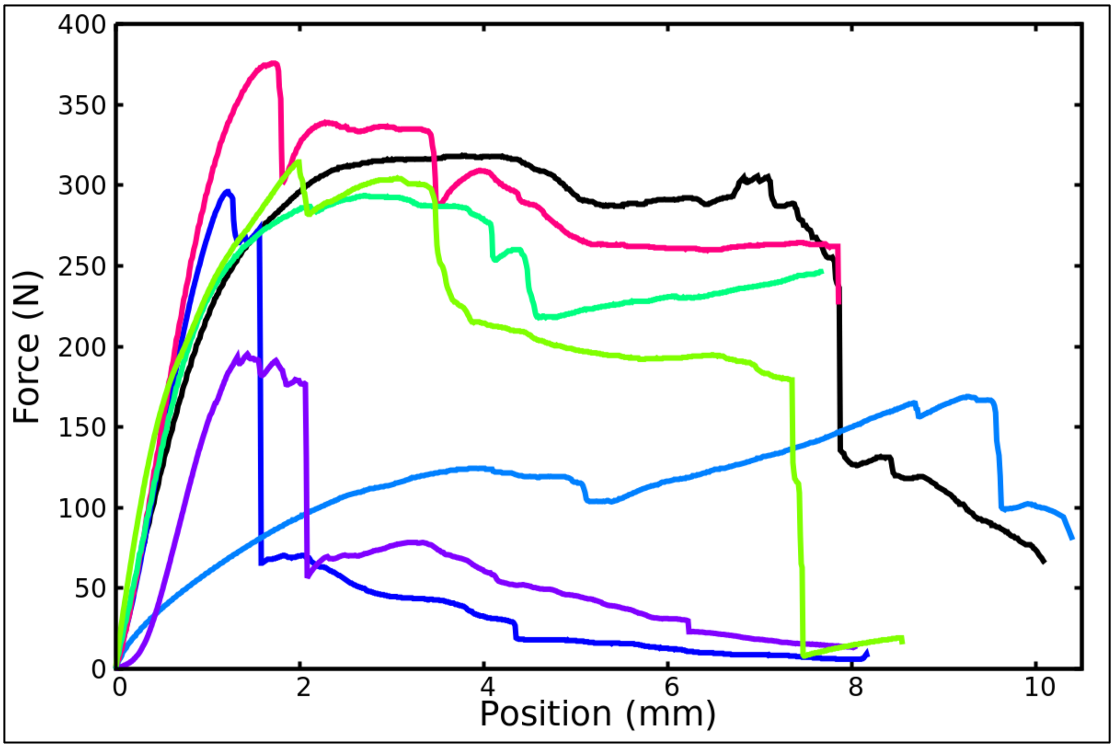

Figure 8. Static load diagram of Group 1 (implanted group)

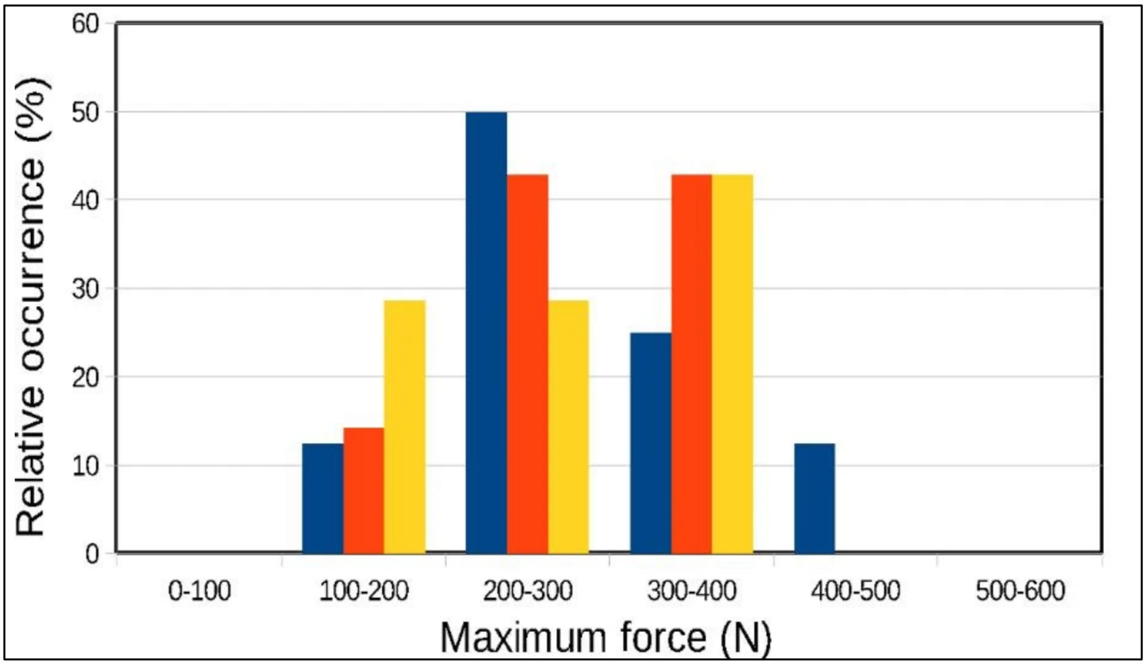

Figure 9. Occurrence of the maximum static force values

Blue: Group 3 (control group) samples, Orange: Group 2 (pre-drilled group), Yellow: Group 1 (implanted group)

Figure 10. Localization of the fracture line in case of pre-drilled samples during static tests

Figure 11. Localization of the fracture line in case of implanted samples during static test

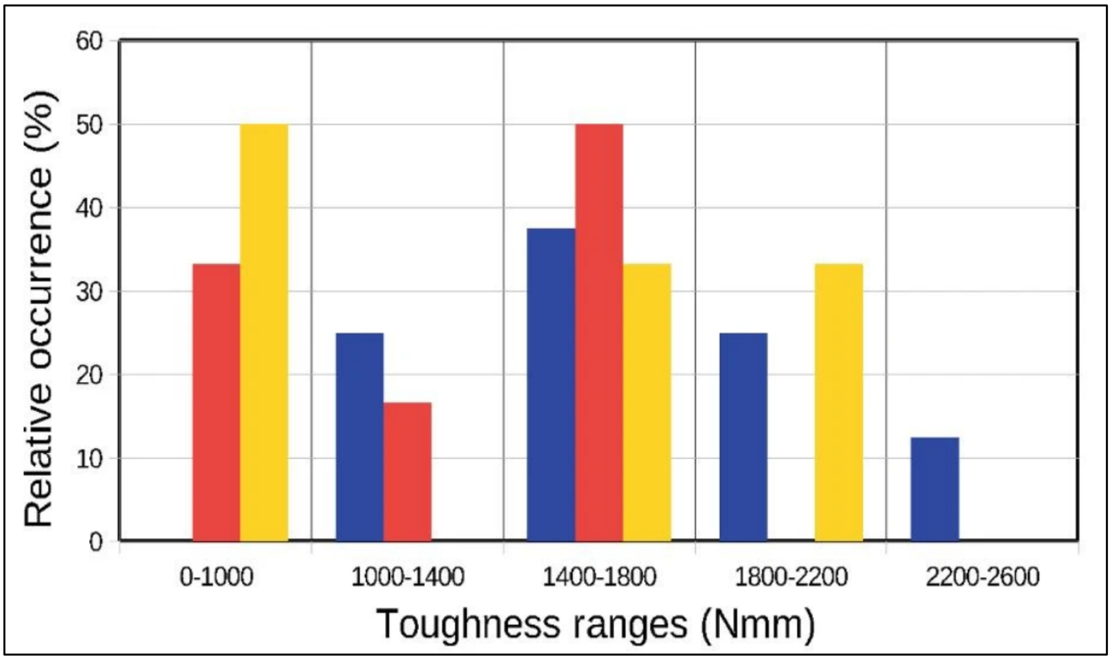

Figure 12. Occurrence of toughness values among the studied groups

Blue: Group 3 (control group) samples, Orange: Group 2 (pre-drilled group), Yellow: Group 1 (implanted group)

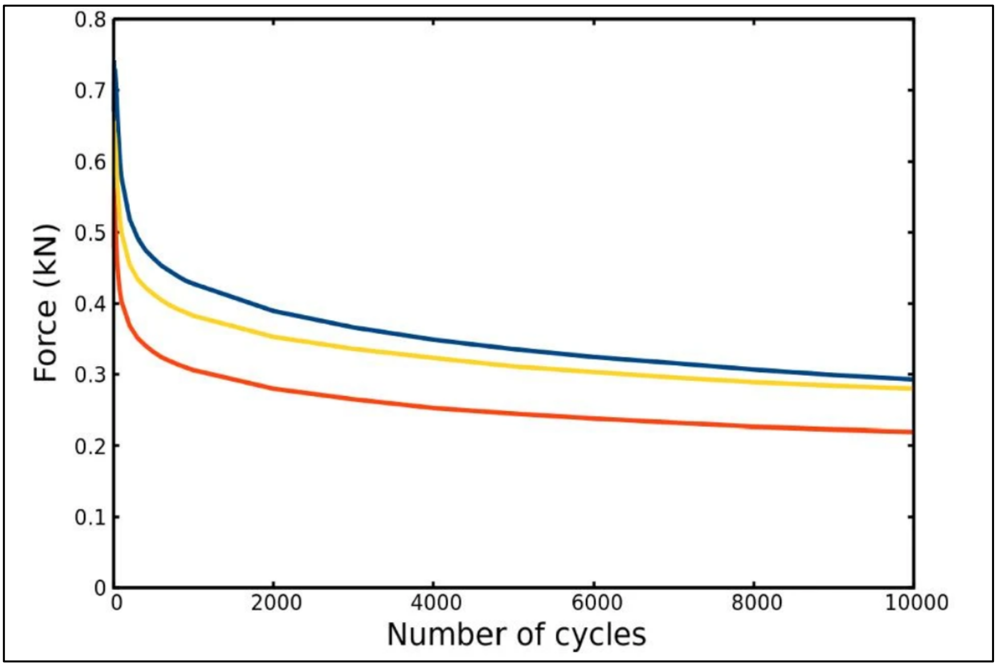

Figure 13. The force values measured for maximum deformation (2.5 mm) depending on the number of cycles among the studied groups in the dynamic fatigue tests

Blue: Group 3 (control group) samples, Orange: Group 2 (pre-drilled group), Yellow: Group 1 (implanted group)

2. Retrospective clinical study

In the 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.

Mean MBL after the 1.5-year follow-up was −0.558 ± 0.029 mm and −0.484 ± 0.024 mm, after the 2.5-year follow-up was −0.747 ± 0.030 mm and −0.678 ± 0.036 mm, while by the 3.5-year mark, bone loss was −0.770 ± 0.029 mm and −0.713 ± 0.026 mm regarding the implants placed in the maxilla and mandibular bone, respectively. 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 ($p > 0.05$). The degree of bone resorption was also assessed on an individual implant-level, separately in the maxilla and mandible; although we had a limited number of patients to pool from for aggregated data, significantly higher ($p < 0.05$) bone resorption levels were observed for 14MA (T_1: −0.760 ± 0.137, T_2: −0.900 ± 0.129, and T_3: −0.940 ± 0.117), 24DA (T_1: −1.100 ± 0.231, T_2: −1.240 ± 0.211, and T_3: −1.260 ± 0.219) and 44DA (T_1: −0.700 ± 0.143, T_2: −1.050 ± 0.183, and T_3: −1.117 ± 0.168), while only numerical tendencies were shown for the other teeth.

VII. 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 [122,123]. Our initial hypothesis was that implant placement and regenerative procedures 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 [122]. 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 [123]. 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 [124]. 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 [125]. Implant failure, if insufficient primary stability is reached, may be as high as 30-40% [126]. 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 [127]. 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, 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, DM or other chronic conditions, streroid 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 failue in the anamnestic data, implant length and diameter, surface roughness, purity and sterility, implant fintess and load-bearing capacity) [128]. 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 [129]. Relationship between primary implant stability and bone density is due to the the stabilizing effect of the massive cortical layer, which gives a strong mechanical support immediately after implant placement [130]. In case of reaching 30 to 40 Ncm or higher implant insertion torque values, as one the most easily measureable parameter during surgery, immediate loading may be performed, and if we respect all the strict rules of immediate loading, there are no evidence of clinical outcome differences, implant failure rate or bone loss around implants in case of different loading protocols [131,132].

The effects of underlying patient characteristics on implant survival were highlighted by the recent publication of Mohanty et al., where higher failure rates were shown in patients with bruxism (13%), periodontitis (15%), DM (29%) and in smokers (27%) [130]. Additionally, a meta-analysis of cohort studies by also verified that in patients with bruxism (vs. in non-bruxers), dental implant technical/biological complications and implant failure rate was significantly higher in all studies involved [133]. The implant-abutment connection also has a significant role in mediating the distribution of forces, stabilizing the unit [134]. In those cases when more implants are inserted in the interforaminal region, the risk increases that the structure of the atrophic madible will be compromised further. Based on our results, the surgical site of the implants placed and osseointegration did represent an area of stress concentration and weakness [135]. The lower number of tilted implants used during Ao4 procedures, may lead to overloading (i.e., exceeding the load bearing capacity of the jawbone). The jawbone adapts to its loading and responds to stresses by bone formation or resorption, which is why neither unloaded nor overloaded areas are desirable; appropriate treatment planning is imperative to avoid these long-term consequences. The resistance of bone is best under compressive stresses, while for tensile stress and shear loads, maximum resistance is less, by around 30-40% and 60-70%, respectively [136]. Implant design and geometry, therefore, has important effects on implant-to-bone load transfer: it has been described that the use of cylindrical implants may be disadvantageous, as they transfer undesirable shearing effects at the bone-implant interface; on the other hand, the presently available literature on whether to recommend cylindrical or tapered implants – based on *in vitro* or *in vivo* experimental data, finite element analysis or clinical studies – is controversal at best [137-139]. On the other hand, surface functionalization and the introduction of implant threads (increasing the surface areas) has been described to transform occlusal stresses into more desirable and tolerable compressive forces at the implant-bone interface [140]. The length of the implants is also an important attribute to consider, when assessing the distribution of stresses, bone resorption and implant survival rates, as many clinical reports have shown that extra-short and short implants have lower success rates and higher bone resorption [141]; this was confirmed by the meta-analysis of Fernandes et al., which included randomized controlled trials (RCTs), and assessed data at one-year-, three-year-, five-year- and eight-year follow-ups [142]. Therefore, in the context of our study, it would be worthwhile to assess whether a difference exists in the modulating effect on bone mechanical properties after implant placement, involving implants of different length, diameter and surface properties.

Laboratory experiments on bone ribbon samples (from animals and/or cadavers) were traditionally used for the determination of mechanical stability and stress levels in implants and bones [143]. Nevertheless, these methods are often cost and labor-intensive, thus alternative techniques to study mechanical stress distributions for dental implant research have received considerable attention. One the promising methods is the use of 3D FEA, to model stress distributions in implants, around peri-implant tissues and on prostheses; the clear advantage of 3D FEA is the ability of this digital method to mimic complex biological objects (e.g., an edentulous jaw), and the wide-range settings and parameters that may be adjusted for the analysis of specific models and clinical situations [144]. Dental implant FEA may be used for a variety of purposes, such as optimizing implant design, predicting implant failure, and determining the optimal loading conditions for dental implants. Since its introduction, Ao4 models have undergone considerable scrutiny using 3D FEA models, to the biomechanical features of the immediately loaded implants [145]; however, in most of the the immediate loading models with FEA, a non-osseointegrated contact interface was simulated between the bone and the implant [146] It is important to note that our measurements were also performed on non-osseointegrated samples. In the event that osseointegration occurs, mechanical properties are expected to improve further, although the extent of micromotions must be taken into consideration during Ao4 (and more broadly immediate loading), as these threaten primary stability. Liu et al. has demonstrated, that micromotions in their immediate-loading models were significantly higher than in delayed-loading cases, and the highest micromotions were at the alveolar around the neck of the tilted implants [147].

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 and 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 [148]: the publication of Sannino et al. reported that implants placed at 15°, 30°, and 45°, with a greater angle at the implant-bone interface, exert the greatest stress, however, all stress values were under the mechanical stress values that would be dangerous for the implant or the bone [149]. Similarly, the FEA study of Almeida et al. concluded that tilting of distal implants by 45° has lead to a >30% and a ~50% increase in first principal stress values to the peri-implant bones of an atrophic maxilla under axial and oblique load, and >70% increase of von Mises stress values respectively, compared to vertical (0°) implants [150].

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.

VIII. 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 considerby 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.

IX. SUMMARY

Edentulism has a considerable negative impact for esthetic and functional aspects for patients; thus, it should be managed through prosthetic rehabilitation using 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. 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. Implant placement requires clinicians to utilize the remaining bone in the most efficient way possible in view of the severity of the involution. 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. Porcine bone samples were randomly divided into three groups (Groups 1: implanted group; Group 2: pre-drilled group; Group 3: control group). Each group was randomly divided into two parts to carry out the mechanical testing (static and dynamic fatigue) protocols. 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). Our results 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 even at smaller deformations. 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. 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 for debilitated patients with severely atrophic jaw bones. 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.

X. ÖSSZEFOGLALÓ

A fogatlanság esztétikai és funkcionális szempontból is jelentős negatív hatást gyakorol a paciensek életminőségére, protetikai rehabilitációja rögzített vagy kivehető fogpótlásokkal történhet. Az implantátumok vázként szolgálnak a rágás során keletkező funkcionális és parafunkcionális stressz periimplantáris szövetekre történő átvitelében, illetve lehetővé teszik a restaurátum viselését, amely lehet azonnali, vagy késleltetett terhelésű. Az All-on-Four^{TM} (Ao4) koncepció – amely megalkotása Maló és munkatársai nevéhez fűződik - négy implantátum beültetését kívánja meg a teljesen fogatlan állcsontok elülső részén ideiglenes, rögzített és azonnal terhelt protézisek elhorgonyzására, mely révén elkerülhetők a bonyolult regeneratív sebészeti eljárások. Az implantátum beültetése a klinikusoktól megköveteli, hogy a megmaradt csontot a lehető leghatékonyabban használják fel, szem előtt tartva az involúció súlyosságát. Ezenkívül a korlátozott csontellátottságú, más alapbetegségek és/vagy egyéb parafunkciós szokások által érintett betegek esetében a marginális csontvesztés (MBL) idővel súlyos következményekkel járhat a másodlagos implantátum stabilitására nézve, és veszélyeztetheti az implantátum hosszú távú túlélését. Jelen vizsgálatunk céljai ezért a következők voltak: i) az Ao4 protokoll szerinti implantátum beültetés és azonnali terhelés szimulálása, annak felmérése, hogy az előfúrás és az implantátum beültetése káros hatással van-e a csontra (patológiás törések kockázatának vizsgálata) in vitro vizsgálatban, sertés borda modell segítségével; ii) a különböző klinikai-epidemiológiai összefüggések hatásának értékelése az MBL arányára egy retrospektív egyközpontú kísérletben, az Ao4 koncepció szerinti distalisan döntött implantátumok beültetését követően, radiológiai módszerekkel értékelve. A sertés csontmintákat véletlenszerűen három csoportra osztottuk (1. csoport: implantált csoport; 2. csoport: előfúrt csoport; 3. csoport: kontrollcsoport). Minden csoportot véletlenszerűen két részre osztottunk a mechanikai vizsgálati (statikus és dinamikus fárasztási) protokollok elvégzéséhez. Míg a statikus terheléses vizsgálatok során az erőértékek és a szívósság között csak tendenciózus különbségeket véltünk felfedezni (statisztikailag nem szignifikánsak), addig a dinamikus fárasztási vizsgálatok során jelentős különbségek mutatkoztak a három mintacsoport között; alaposabb elemzés után megfigyelhető volt, hogy az előfúrt csontok az 1. és 3. csoporthoz képest jelentősen rosszabb mechanikai tulajdonságokkal rendelkeztek, másrészt a kontroll és a implantált csontminták a 9000. ciklusra nagyon hasonló mechanikai tulajdonságokat mutattak (amit az erőgörbék hasonló lefutása is bizonyít). Eredményeink rávilágítottak arra, hogy az előfúrás során készített fészkek jelentősen csökkentették a csont merevségét és mechanikai szilárdságát, ami már kisebb deformációk esetén is makroszkópos törésekhez vezetett. A csontok előfúrása jelentősen befolyásolta azok mechanikai tulajdonságait, amelyek sok esetben javultak az implantátumok behelyezésével, de soha nem érték el a kezeletlen csont szilárdságának mértékét. A tanulmányban bemutatott adatok további kísérletes vizsgálatok alapjául szolgálhatnak, továbbá a súlyos atrófia miatt meggyengült állcsontú páciensek esetében a megfelelő protetikai terv felállítását is elősegíthetik. Mindezek mellett kimutattuk, hogy a nem megfelelő szájhigiénia, a szájüreg fiziológiáját befolyásoló krónikus állapotok, a dohányzás és a bruxizmus jelentős mértékben növeli a marginális csontvesztést, ami idővel növeli a szövődmények és az implantátum vesztés kockázatát.

XI. REFERENCES

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Co-author certification

I, Zoltán Lajos Baráth. Ph.D. Habil. Prof. as a corresponding author of the following publications declare that the authors have no conflict of interest, and Ádám László Nagy, D.M.D. Ph.D. candidate had significant contribution to the jointly published researches. The results discussed in his thesis were not used and not intended to be used in any other qualification process for obtaining a Ph.D. degree.

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RESEARCH ARTICLE

Open Access

Biomechanical properties of the bone during implant placement

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Abstract

Background: In this research the biomechanical properties of a bone model was examined. Porcine ribs are used as experimental model. The objective of this research was to investigate and compare the biomechanical properties of the bone model before and after implant placement.

Methods: The bone samples were divided in three groups, Group 1 where ALL-ON-FOUR protocol was used during pre-drilling and placing the implants, Group 2 where ALL-ON-FOUR protocol was used during pre-drilling, and implants were not placed, and Group 3 consisting of intact bones served as a control group. Static and dynamic loading was applied for examining the model samples. Kruskal–Wallis statistical test and as a post-hoc test Mann–Whitney U test was performed to analyze experimental results.

Results: According to the results of the static loading, there was no significant difference between the implanted and original ribs, however, the toughness values of the bones decreased largely on account of predrilling the bones. The analysis of dynamic fatigue measurements by Kruskal–Wallis test showed significant differences between the intact and predrilled bones.

Conclusion: The pre-drilled bone was much weaker in both static and dynamic tests than the natural or implanted specimens. According to the results of the dynamic tests and after a certain loading cycle the implanted samples behaved the same way as the control samples, which suggests that implantation have stabilized the skeletal bone structure.

Keywords: Biomechanics, Dental implant(s), Fixed and removable prosthodontics, Implant dentistry/implantology, Jaw biomechanics, Oral and maxillofacial surgery

Background

With the development of dentistry, the aesthetic and functional expectations of patients are also increasing. They anticipate fixed dentures even in total edentulous state. These expectations are challenging for the dentist, especially in cases with severe atrophy of the alveolar ridge, which is particularly complicated, when the teeth have been extracted long time ago. The possible treatment options which allow us to deliver fixed implant-supported dental prosthesis and to achieve a high degree of patient satisfaction, requires to utilize the remaining bone in the most efficient way possible in view of the severity of the involution. The implant placement is usually impossible without guided regeneration surgery [1] in case of elderly people, who typically have D1 quality bone with *high degree of* cortical bone volume [2]. The guided bone regeneration procedure [3] carries high risk of patient morbidity and complications. To avoid the extensive bone augmentation procedure [4, 5] due to the advanced involution, the ALL-ON-FOUR protocol was introduced by Maló [5, 6]. According to this concept, the fixed and immediately loaded prosthesis is supported by four implants in the anterior part of the complete

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edentulous jaw. The two posterior implants are placed in the interforaminal region, angled, to minimize the cantilever length; the two anterior placed axially, parallel to each other [7]. Both finite analysis and retrospective studies [5] suggest that implants placed this way could be a good alternative, which can safely support the fixed dentures. No clinically significant differences in success rates were found between these methods [8].

An idea presents itself that the mechanical properties of the mandible could be affected by the procedure of pre-drilling and then, substituting the space with a different characteristic material. In this study the possibility that drilling and implant placement could weaken the jawbone against masticatory forces was examined. If this process affects the biomechanical properties, the possibility of three-dimensional torsion deformation of the mandible has to be considered [9, 10]. It was also investigated whether it represents a risk of pathological fractures for the patient, considering the fact that the implants placed with ALL-ON-FOUR protocol are being immediately loaded with the provisional or definitive full-arch prosthesis in 48 h after surgery [5, 11]. The possibility of these deformations and micromovements can be recognized as a deleterious phenomenon during osseointegration [12], however, according to the experimental models of several authors, these micromovements were not proven to be harmful [13].

The basic hypothesis is that the implant placement weakens the biomechanical properties of the bone structure. Our objective is to investigate and compare the mechanical properties of the ribs, before and after implant placement.

Methods

Fresh, non-frozen, young domestic porcine ribs with soft parts (periosteum, attached muscles, fascia, fat) were obtained from an abattoir. The excess soft parts were removed with a sharp scalpel, however care was taken to ensure that the periosteum was left intact. The main reason for the selection of porcine ribs was the excellent homogeneity and thickness of cortical bone [14] which is similar to a human mandible [15, 16]. The animals were not sacrificed for the purpose of the experiment. The dimensions of the ribs were measured with an analog dial caliper (0.01 mm, Hoffmann Gruppe AK600203). The average length, width and height of the bones were 117.1 mm, 13.4 mm and 9.8 mm, respectively. The average value and standard error of the cortical bone thickness was 2.13 mm ± 0.08 mm. The porcine ribs were randomly divided into three groups. In the first group (Group 1, n = 17) the implants were placed according to the ALL-ON-FOUR protocol: two implants were placed parallel medially (ICX TEMPLANT 4.1 mm × 10 mm, WS-75L surgical contra-angle handpiece, Implantmed Classic SI-923 physiodispenser, W&H, Bürmoos, Austria), and two tilted implants were inserted laterally (ICX TEMPLANT 4.1 mm × 15 mm). In the second group (Group 2, n = 16) the nests of the implants were pre-drilled (WS-75L surgical contra-angle handpiece, Implantmed Classic SI-923 physiodispenser, W&H, Bürmoos, Austria) for the same type and size of implant, but left empty without implant placement. During pre-drilling and placing the implants, the manufacturer's recommendations and the rules of the profession were kept in mind. No intervention was taken on the ribs in the control group (Group 3 n = 18).

For the mechanical testing, each group was randomly divided into two parts. Half of the samples were tested with a static tensile and compression materials testing machine /Tinnius Olsen H5KT Atec, USA/, while the other half were placed under fatigue test by an All-*Electric* Dynamic Test Instrument (Instron ElectroPuls™ E3000, USA) [17].

For the mechanical testing 3-point bending tests were performed, which are most widely accepted for fracture testing [18–21]. Mechanical components were manufactured individually that could be applied for both the static and dynamic equipment. The devices thus became suitable for performing 3-point bending tests (Fig. 1).

During the static load measurements, the bending deformation was increasing steadily on the bones. The according force was measured, digitized. The equipment recorded the position of the crosshead and the measured force. The maximum deformation was

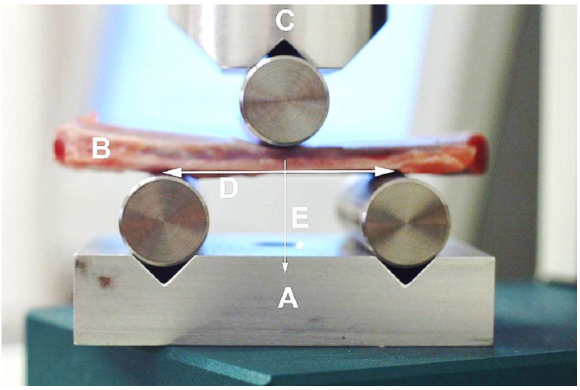


Fig. 1 Experimental layout. **a** Supporting platform with point support rollers; **b** pork rib segment; **c** pressure head of the mechanical tear / break device with the roller used for point loading. **d** distance between support points (standard 40 mm). **e** vector of the force acting on the bone segment

10 mm, which was reached in 5 s. During the measurement an automatic halt was actuated, when the device observed a sudden decrease in the force.

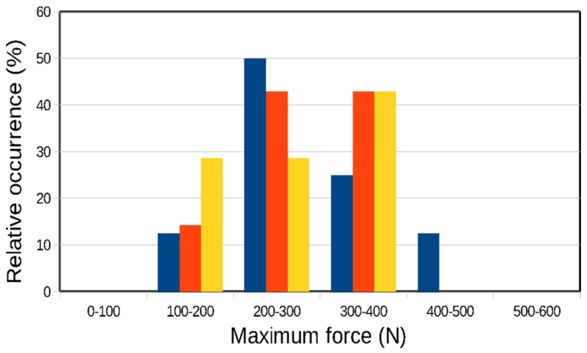
The other part of the samples was examined by a dynamic fatigue test. The dynamic test followed the arrangement of three point bending fatigue measurements. [22, 23]. Prior to the dynamic tests, the stiffness of each rib was determined by measuring the force–deflection curve between 0.2 and 0.8 mm deflection. After this process the fatigue test was performed on the samples, where the initial deflection was set to 2 mm, which was reached in 5 s. The fatigue test was performed in deflection control mode. The fatigue signal was a sinus function with 20 Hz frequency at 0.5 mm deflection amplitude over 10.000 cycle. At the end of the fatigue process the load was decreased to 0 N in 5 s.

Shapiro–Wilk test was performed to validate the normality of distribution of the measured data. Kruskal–Wallis non-parametric test was used to compare the different groups' measured force values and as post-hoc tests the Mann–Whitney U non-parametric statistical tests were used. The significance level in these tests were set to 5% ($p < 0.05$). SPSS statistical software (version 25; IBM Co., Armonk, NY, USA) was used for statistical analysis.

Results

Results of the static load test

The graph in Fig. 2 shows the measurement results of the static load tests: the first stage of the load–deflection curve can be described as an almost straight increasing line, which represents the flexible range of the rib. After the maximum force exerted, even a smaller force was sufficient for further deflection. Figure 3 shows the occurrence of the measured maximum force ranges: during the load the measured average forces values were higher on the control samples than on the drilled bones The mean of the maximum force (and standard error) for the control samples was 298.9 ± 30.95 N, for the pre-drilled was 287.1 ± 25.93 N and 280.29 ± 27.51 N for the implanted group. We found no statistically significant difference between the groups ($p = 0.979$).



Blue: control, Orange: Pre-drilled, Yellow: implanted

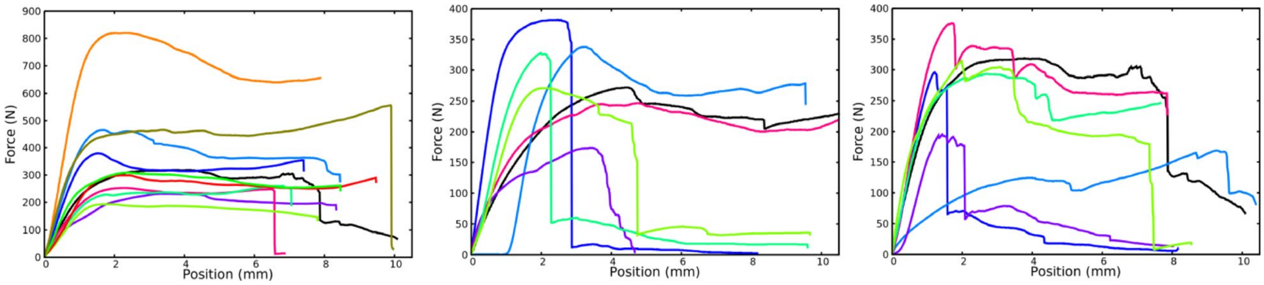
Fig. 3 The occurrence of the maximum static load force values: Blue: control, Orange: Pre-drilled, Yellow: implanted

The area under the curves on the diagrams of Fig. 2 (S) describes a quantity, which correlates with the toughness of the ribs, and can be calculated with the following formula:

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

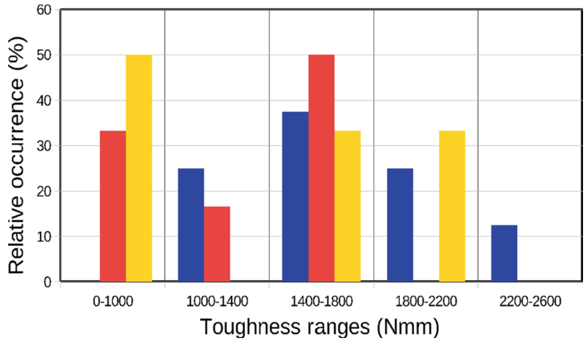
Figure 4 shows the S values in Nmm registered during the test.

Mean S value was 1701.37 ± 166.335 Nmm in the control, 1175.77 ± 128.832 Nmm in the pre-drilled and 1235.56 ± 248.392 Nmm in the implanted group. There are no significant differences between the groups in the calculated S toughness related values ($p = 0.16$, Kruskal–Wallis test).



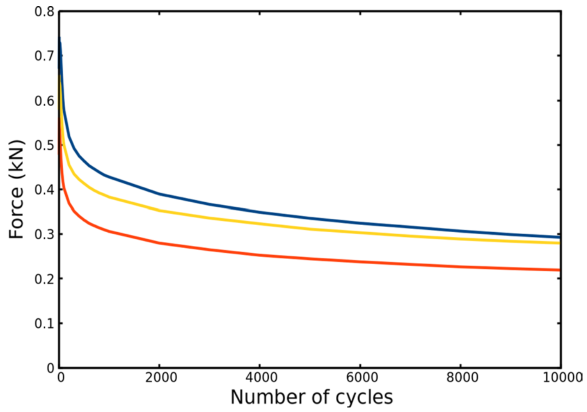
a *Static load diagram of the control group* **b** *Static load diagram of the pre-drilled ribs* **c** *Static load diagram of the implanted ribs*

Fig. 2 Measurement results of the static load tests. **a** Static load diagram of the control group. **b** Static load diagram of the pre-drilled ribs. **c** Static load diagram of the implanted ribs



Blue: control, Orange: Pre-drilled, Yellow: implanted

Fig. 4 Occurrence of various toughness ranges in the study groups. Blue: control, Orange: Pre-drilled, Yellow: implanted



Blue: control, Orange: Pre-drilled, Yellow: implanted

Fig. 5 The force values measured for maximum deformation (2,5 mm) depending on the number of cycles Blue: control, Orange: Pre-drilled, Yellow: implanted

Results of the dynamic fatigue test

To analyze the results of the dynamic fatigue tests the Kruskal–Wallis statistic test (control vs. 1, 2) was performed on the measured force values measured for maximum deflection (2.5 mm) at specified times (100th, 2000th, 9000th cycles). The results are shown in Fig. 5.

At the 100th cycle the average measured force values were: 0.5766 ± 0.033 kN in the control, 0.4030 ± 0.081 kN, in the pre-drilled, 0.4991 ± 0.073 kN in the implanted group. The statistical test showed significant differences for the measured values between the groups (p = 0.014, Kruskal–Wallis test).

At the 2000th cycle the average measured force values were: 0.3896 ± 0.027 kN in the control, 0.2800 ± 0.056 kN, in the pre-drilled, 0.3530 ± 0.049 kN in the implanted group. The statistical test showed a significant difference for the measured values between the groups (p = 0.015, Kruskal–Wallis test).

At the 9000th cycle the average values were: 0.2999 ± 0.015 kN in the control, 0.2227 ± 0.042 kN, in the pre-drilled, 0.2840 ± 0.042 kN in the implanted group. The statistical test showed a significant difference for the measured values between the groups (p = 0.026, Kruskal–Wallis test).

The difference between the groups was tested with Mann–Whitney test. This showed a significant difference in the measured force values between the control and drilled ribs 100th cycle (p = 0.001, Mann–Whitney U test), which difference remains consistent at the 2000th cycle (p = 0.002, Mann–Whitney U test) and 9000th cycle (p = 0.005, Mann–Whitney U test).

The measured force values in any of the cycles examined showed no statistical significant difference between the control and the implanted group (100th cycle p = 0.243, 2000th cycle p = 0.447, 9000th cycle p = 0.72, Mann–Whitney U test), furthermore, the summary graph (Fig. 5) shows that they exhibit very similar force values from cycle 9000.

No significant difference was found between the drilled and implanted ribs in the post-hoc test at 100th cycle (p = 0.33, Mann–Whitney U test) 2000th cycles (p = 0.136, Mann–Whitney U test), at 9000th cycles (p = 0.094, Mann–Whitney U test).

Discussion

The purpose of this study was to examine and discuss the deterioration of bone mechanical properties as a function of bending forces before and after implant placement in order to seek an answer to the question, whether implant placement can weaken the bone structure.

The three-point bending tests, reported in the literature, were performed only with intact bones [21, 28, 29] and not pre-drilled and implanted ones, as in this work.

Static load tests showed significant differences between the groups tested. In the case of intact bone samples, the load curves shown in Fig. 2 are continuous, and the sudden reduction in force associated with fractures is observed only over a large deformation of ~ 6.6 mm. The maximum force observed for the intact bones is in the range of 200–800 N with an average maximum force of 299 ± 31 N. Typically, the maximum force values were achieved with 1.5 to 3 mm deflection.

For the drilled samples, the resistance force maximum (170–390 N) decreased relative to the control samples, which is well observed in Fig. 2. Most measurements show single or gradual fractures in the 2.4–5 mm deflection range, well below the damage limit of the intact bones. The maximum force observed was 287 ± 26 N. The reduction of the damage limit clearly indicates the weakening of the bone's resistance to force, which is partly 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 improve the mechanical resistance of the bones. For the implanted samples the maximum force measured was in the range 175–380 N, the mean maximum force decreased to 280 ± 28 N. The deflection values corresponding to the first partial fracture are in the range of 1.6–4.5 mm, which is smaller compared to the intact and drilled bone values. Partial cracks were observed between the two middle implants during the load. The appearance of a crack was often accompanied by a sound effect. The earlier cracks appear to be due to the fact that the holes are filled with harder material than the spongy bone, consequently local stresses at the implant-bone interface are exerted during loading.

If the local stress value is greater than the strength of the cortical bone, a crack appears [24], but the macroscopic fracture of the bone does not occur [25]. As the deflection increases, the force–deflection curve shows small breaks, indicating the appearance of new cracks. The local fractures provide stress relaxation, resulting in a higher deflection values for appearance of macroscopic fracture at 7.3–9.5 mm compared to the drilled bone. Due to this phenomenon, the toughness of the implanted specimens will be higher than that of the drilled specimens.

For fatigue tests, the same temporal function of deflection was applied throughout the experiments. To achieve the same deflection at a higher cycle number, a lower force was required for each sample, as shown in Fig. 5. Initially, the decrease in the force values is greater, and with higher cycle numbers, the reduction of the force slows down. This phenomenon shows the weakening of the mechanical structure due to bending cycles. Each cycle causes reduction of bone stiffness [26]. However, macroscopic fractures did not occur at the set deflection values and cycle numbers.

For all fatigue tests, the force required for a pre-set deflection was the highest for intact bone and the lowest for drilled bone. This significant weakening is due to the reduction of local bone volume.

In the case of implanted bones, the maximum force values for a given deflection are between the values of the intact and the drilled bone. Initially, the difference compared to intact bone is greater, but with a higher number of cycles this difference disappears.

Overall, the results of our mechanical examinations showed that the placement of the holes in the bone significantly reduces the stiffness and mechanical strength of the bone, which leads to the appearance of macroscopic fractures even at smaller deformations. The implants partially restore the integrity of the bone and increase the load-bearing capacity against the macroscopic fracture compared to the drilled samples. However, the implanted bone does not reach the mechanical strength of intact bone.

This topic was explored by finite element analysis, and many studies have been conducted on the relationship between the bone and implants under the All-on-four protocol. According to Sannino, distal implants placed at 15, 30, and 45 degrees, with a greater angle at the implant-bone interface, exert the greatest stress, but this mechanical stress value is still lower than what the implant and bone can withstand [27].

Our static load result shows that the toughness is less in the case of drilled bones but not statistically significant. The measured maximum force values also showed no statistically significant difference during the static load. However, during the fatigue load the drilled bones showed significant difference compared to the control samples. The control and the ALL-ON-FOUR implanted samples showed very similar measured force values after the 9000th cycle.

It is important to note that these measurements were performed on non-osseointegrated samples. In the event when osseointegration occurs, mechanical properties are expected to improve further. However, our experiment shows that local mechanical stresses appear at the bone-implant interface, which reduces the force required to cause fractures. A limitation of our study is that the bending forces applied in the tests occur only in extreme cases in clinical circumstances. However, the cyclicity and the magnitudes were in accordance with physiologically observable chewing movements. 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 with the finite element analysis tests.

Conclusion

With the limitations of this in vitro ALL-ON-FOUR study, the pre-drilled bone was much weaker in both static and dynamic tests than the natural or implanted specimens. According to the results of the dynamic tests and after a certain loading cycle the implanted samples behaved the same way as the control samples, which suggests that implantation have stabilized the skeletal bone structure.

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All authors gave their final approval and agree to be accountable for all aspects of the work.

Authors' contributions

ÁLN: Contributed to conception, acquisition, and interpretation, drafted the manuscript, gave final approval. Agrees to be accountable for all aspects of work ensuring integrity and accuracy. ZsT: Contributed to conception, drafted the manuscript, critically revised the manuscript, gave final approval. Agrees to be accountable for all aspects of work ensuring integrity and accuracy. TT: Contributed to analysis, critically revised the manuscript, gave final approval. Agrees to be accountable for all aspects of work ensuring integrity and accuracy. NTP: Contributed to conception, drafted the manuscript, critically revised the manuscript, gave final approval. Agrees to be accountable for all aspects of work ensuring integrity and accuracy. ZLB: Contributed to conception, interpretation, drafted the manuscript, critically revised the manuscript, gave final approval. Agrees to be accountable for all aspects of work ensuring integrity and accuracy. All authors have read and approved the manuscript.

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Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

II.

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Article

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

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Abstract: Bone grafting procedures during the use of dental implants may be avoided by the use of tilted implants in the maxilla and the mandible; advantages of angled implants are associated with the extension of the distal cantilever, leading to better implant survival rates. However, the bending effect on the single tilting implants may increase the marginal bone stress. The purpose of the present study was to retrospectively assess the clinical success and proximal bone loss rate following the implantation of distally tilted implants according to the All-on-Four™ prosthetic concept—based on radiographic findings—in a single-center experience, in addition to the assessment of the outcomes in the context of various clinico-epidemiological correlates. During the study period, $n = 36$ patients (24 males and 12 females) with complete records of periapical radiographs, received a full-arch fixed bridge supported by two axial and two distal tilted implants; overall $n = 144$ and $n = 144$ implants (Nobel B) were place in the maxilla and mandibles of patients, respectively. Mean age of patients at the time of fixture installation was 58.75 ± 13.71 years; $n = 11$ patients presented with relevant underlying conditions/habits. To assess peri-implant bone-level changes, matched and calibrated orthopantomogram (OPT) images were taken at follow-ups after 1.5 years, 2.5 years, and 3.5 years post-restoration, and marginal bone levels were assessed on the mesio- (MA) and disto-approximal (DA) aspects. All implants were successful, resulting in a 100% overall survival rate. The radiographic mean bone loss levels at baseline (mean ± SEM) were 0.181 ± 0.011 mm and 0.178 ± 0.017 mm in the maxilla and mandible, respectively, while by the 3.5-year mark, bone loss was 0.770 ± 0.029 mm and 0.713 ± 0.026 mm in the maxilla and mandible ($p > 0.05$), respectively; bone-level changes were significant over time ($p = 0.035$ and $p = 0.033$). Peri-implant bone loss was more aggressive around titled distal implants versus mesial actual position implants. The effect of smoking and other underlying conditions showed significantly higher ($p < 0.05$) bone resorption levels when assessed on an individual implant-level, while during patient-level analysis, only a tendency was shown for higher bone loss rates for both MA and DA implants ($p > 0.05$). Within its limitations, our study has concluded that the use of All-on-Four™ prosthetic concept for total arch rehabilitation yields higher bone loss in association with tilted implants and, in some cases, on the MA surfaces at vertically positioned implants after >40 months in function.

Keywords: immediate implant placement; dental implants; alveolar bone resorption; All-on-Four™; cone-beam computed tomography; clinical study

1. Introduction

Disorders of the oral cavity are a significant cause of decreased quality of life (QoL) and they are important contributors to years lived with disability (YLDs), affecting facial aesthetics, and the capacity to eat or speak [1]. Partial or complete edentulism (the latter exceeding >10% in patients aged 50 years or older globally) is a definite condition—occurring as a long-term consequence of dental caries and periodontal disease—which has emerged as a global public health issue [2,3]. People with low socio-economic standing are disproportionally affected by tooth loss; in addition to bad oral hygiene, many modifiable risk factors (e.g., diets rich in carbohydrates, tobacco consumption, and alcohol use)—relevant in the development of other non-communicable diseases—are also critical in leading to edentulism [4,5]. The oral rehabilitation of edentulous patients involves the use of dental implants. Rehabilitation of total edentulism with a conventional implant-supported fixed restoration involves bone grafting, a sinus elevation procedure, and soft tissue management, in case of a severely atrophic alveolar process [6]. However, bone augmentation carries considerable risks of complications (infection, loss of soft tissue contours and/or volume, graft failure, and risks associated with donor materials), procedural issues, and patient morbidity, and the reconstructive surgery corresponds to higher costs and longer recovery time intervals [7,8].

This anatomical limitation may be treated with a long distal cantilever, short implants, or implants placed in a specific anatomical area [9]. Avoiding bone grafting procedures by using tilted implants in the maxilla and the mandible is a recognized alternative with no significant clinical difference in success rates compared to axially placed implants, and their acceptability by patients is also higher [10]. Clinical advantages of angled implants are associated with the extension of the distal cantilever, leading to better implant survival rates [11]. The bending effect on the single tilting implants may increase the marginal bone stress, but this may be augmented with splinting them into a multiple implant-supported prosthesis, according to a two-dimensional finite element analysis [12]. It has been shown that cervical bone stress increases proportionally with the length of the cantilever, while it is not influenced by the length of the implants. Marginal bone loss between tilted and axially placed implants demonstrated no difference and presented with no detrimental effects on osseointegration levels [13].

The principle of the All-on-Four™ concept is to apply four implants in the anterior part of completely edentulous jaws to support a provisional, fixed, and immediately loaded prosthesis [14]. During implantation on the All-on-Four™ methodology, the rehabilitation of the total arch is carried out without the need for bone augmentation and fixed prosthesis supported by two axial implants in the anterior segment, and one tilted implant anteriorly to the mental foramina and the anterior lobe of sinus on each posterior segment [15]. The tilted implants provide anchorage for the first molar occlusion with a short cantilevered segment, by reaching a more posterior implant position [16]. Maxillary and mandibular All-on-Four™ rehabilitations have a comparable cumulative survival rate [17]. Based on biomechanical analyses, major cantilever loading is the highest at the most anterior and posterior implants supporting a reconstruction, irrespective of the intermediate implants. The load supported by the most heavily loaded implant in fix restoration is independent of the number of complementary implants, according to in vivo measurements [18].

The purpose of the present study was to retrospectively assess the clinical success and the rate of proximal bone loss following the implantation of distally tilted implants according to the All-on-Four™ prosthetic concept—based on radiographic findings—in a single-center experience, in addition to the assessment of the outcomes in the context of various clinico-epidemiological correlates (e.g., age, oral hygiene, parafunctional habits, and smoking habits of the patients). Our initial hypotheses were: (i) no differences in peri-implant bone levels among axial and tilted implants during follow-ups; and (ii) no differences in peri-implant bone levels measured at the mesio-approximal and disto-approximal aspects of implants during follow-ups.

2. Materials and Methods

2.1. Study Design

The present single-center retrospective study aimed to evaluate the clinico-epidemiological and radiographic data (peri-implant bone-level changes) longitudinally from patients undergoing an implant surgical procedure with an immediately-loaded, four-implant-supported fixed prosthetic concept, following the All-on-Four™ protocol, between 1 January 2017 and 1 January 2022.

2.2. Inclusion Criteria

The study employed convenience sampling at the study center. The following inclusion criteria were set for the study:

(i). Patients aged 18 years or older;
(ii). Patients in an overall good health condition, able to undergo surgical intervention;
(iii). Patients in need for a complete rehabilitation of the edentulous maxilla or mandible, and the possibility of placing a minimum of 4 implants (at least 10 mm long);
(iv). Sufficient bone height in the sites intended for the placement of implants (min. 6 mm, evaluated by preoperative CT scans analysis).

The exclusion criteria for the study were:

(i). Presence of an acute infection at the planned implant sites;
(ii). Known coagulopathies or other hematologic diseases;
(iii). Recent occurrence of severe cardiovascular or cerebrovascular event;
(iv). Diseases affecting the immune system;
(v). Uncontrolled diabetes mellitus (DM);
(vi). Pregnancy or lactation;
(vii). Metabolic illnesses affecting the bones, bisphosphonate therapy;
(viii). Heavy smoking (>10 packs/day);
(ix). Systemic chemotherapy or irradiation of the head and neck region within the last 12 months;
(x). Presence of parafunctional habits, such as severe bruxism or clenching (assessed and identified by the clinicians, based on clinical signs and symptoms);
(xi). Inadequate oral hygiene level (full-mouth plaque and bleeding scores over 20%), poor perceived motivation on the part of the patient to maintain good oral hygiene throughout the study.

2.3. Preoperative Treatment

Prior to surgical treatment, the patients' medical and dental histories, relevant lifestyle habits (e.g., smoking), and potential drug allergies were reviewed; the preoperative assessment of the patients was carried out by a prosthodontist and a periodontist. Following the presentation of the treatment plan to the patients 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. Individuals followed an antibiotic regimen per os (clindamycin 300 mg q.i.d.) three days prior to the surgical procedures in cases where teeth had to be extracted simultaneously. Preceding surgery, local anesthesia was administered (4% articaine containing 1:100,000 epinephrine).

2.4. Implant Placement Protocol

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 individual received (i) 2 distally tilted implants in the posterior region and, after that, (ii) 2 anterior implants in the maxilla or the mandible. In the maxilla, tilted implants were positioned just anterior to the maxillary sinus, while in the mandible they were positioned anterior to the mental foramen. The placement of implants was according to the All-on-Four™ treatment concept, using the All-on-Four™ surgical guide (Nobel Biocare; Kloten, Switzerland); comprehensive details regarding the procedure have been described elsewhere [19]. Regarding bone regeneration, universal clinical protocols for immediate implant placement were used [20]. Localized bone grafting was performed to cover exposed threads and/or other osseous defects associated with extraction sockets, as needed with demineralized allografts. For the fabrication of the master cast to create the patients' provisional restoration, open-tray multi-unit impression copings were placed on the multi-unit abutments to make an impression using precision impression material (Flexitime, Heraeus Kulzer, Hanau, Germany).

Following the operative procedure, patients were instructed to abstain from brushing in the first 7 days post-op, and to rinse using warm water. For 24 h post-io, instructions and recommendations were given for a soft diet (cold or at room temperature), to be followed by a semisolid diet for the following three months. Patients were supplied with antibiotics (amoxicillin 500 mg t.i.d. or clindamycin 300 mg t.i.d. for seven days) and analgesics (non-steroid anti-inflammatory drugs) to control post-operative pain and inflammation as per standard guidelines and protocols in oral surgery. To confirm implant positions, and the positions of the prosthetic components, a CBCT scan was taken immediately postoperatively.

2.5. Restorative Protocol

Prior to the surgical intervention, a heat-cured acrylic resin (Ivocap High Impact acrylic, Ivoclar Vivadent, Amherst, NY, USA) was prefabricated, which was amended to the master model directly after the surgery. Fabrication was carried out using cold curing material (Probase, Ivoclar Vivadent, Amherst, NY, USA). Following 3–4 h after the completion of the operation, the provisional all-acrylic prosthesis was seated. Routine follow-ups were scheduled for the patients after surgery at 7, 14, and 28 days and 3 months after surgery, and on a yearly basis thereafter. Following the 3-month appointment, fabrication of the definitive prosthesis was initiated, consisting of a milled titanium frame with a wrap-around heat-cured acrylic resin (Nobel Procera Implant Bridge titanium framework veneered with composite). The antagonist denture was a fixed denture/implant supported restoration in all cases. A long-cone paralleling method was applied to obtain matched and calibrated orthopantomogram (OPT; panoramic X-ray) images at the 3-month appointment and at the subsequent appointments continuously. The 3-month radiographs after the time of placement of the definitive prosthesis were utilized as a baseline (T_0) to assess the bone levels longitudinally. At the respective follow-ups, the implants were assessed for signs of peri-implantitis, plaque, and bleeding on probing (BOP), based on clinical routine guidelines.

2.6. Radiographic Assessment: Calculation of Marginal Bone Loss

Peri-implant bone-level changes were measured by matched and calibrated OPT images taken at the 3-month appointment (i.e., baseline) 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. An independent researcher—not affiliated with the primary center and investigators—evaluated the OPT images. Radiographs were digitized in a 640 (H) × 480 (V) pixel matrix image with an 8-bit depth. The density and contrast were then adjusted for optimal visualization of the marginal bone, and the digital images were saved as a TIF extension image. The 2D images were then exported and analyzed using the CLINIVIEW image analysis software

(MI Dental, Knowsley, Prescot, UK). Calibration for image analysis was performed on an individual implant-level ($n = 288$) to achieve the most accurate results possible, where the known size and specifications of the individual documented implants were used as the basis for calibration to allow for the calculation of marginal bone level changes in the area. Assessment of bone levels were carried out and captured separately on the MA and DA sides of the implant. 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.

2.7. Outcome Variables Assessed

The following outcome variables were ascertained during the study:

(a). Survival of implants (%): defined as implants being stable and functional (implant stability was assessed using pressure from two opposing instruments following the unscrewing of the prosthesis), lack of peri-implant radiolucency on radiographs, lack of suppuration or pain associated with the implant site, no signs of peri-implantitis, and lack of neuropathies or persistent paresthesia.
(b). Changes 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 post-implantation.

Marginal bone level changes were studied in the context of the following correlates and sub-groups:

(i). Maxillary vs. mandibular implants;
(ii). Tilted (posterior) and axial (anterior) implants;
(iii). Mesio- (MA) and disto-approximal (DA) aspects of implants;
(iv). Patients presenting with underlying conditions/parafunctional habits.

2.8. Statistical Analysis

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 by the SPSS v. 22.0 (IBM Corp., Endicott, NY, USA): the normality of variables was tested using the Shapiro–Wilk test; inferential statistics were performed using independent-sample *t*-test, one-way ANOVA with Tukey's post hoc test and Pearson's correlation. p values < 0.05 were considered statistically significant.

2.9. Ethical Considerations

The 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.

3. Results

3.1. Patient Characteristics, Clinical Outcome

During the study period, $n = 36$ patients (24 males and 12 females) with complete records of periapical radiographs underwent implant placement using the All-on-Four™ concept and have been rehabilitated; overall $n = 144$ and $n = 144$ implants (Nobel B) were place in the maxilla and mandibles of patients, respectively, i.e., the analysis of individual implant data for $n = 288$ was performed. The mean age of patients at the time of fixture installation was 58.75 ± 13.71 years (range: 19–90 years). Out of the thirty-six patients involved, six 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 five 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 (these patients will be grouped together for subgroup analyses). Among smokers, the daily average tobacco consumption of was 8.2 ± 2.6 cigarettes. During the 42-month study period no implants have failed, resulting in 100% overall survival rate (not affected by the clinico-epidemiological parameters of the patients), highlighting the success of the All-on-Four™ concept. All patients complied with the set timetables, no patients (n = 0) were lost to follow-up at either follow-ups (at 18 months, 30 months, and 42 months post-restoration); the status of all n = 36 patients were followed for the entirety of the study period.

3.2. Marginal Bone-Level Changes across Different Correlates

The radiographic mean bone loss levels at baseline (T_0) were 0.181 ± 0.011 mm (mean ± SEM; maxilla (n = 144): 0.178 ± 0.017 mm vs. mandible (n = 144): 0.184 ± 0.015 mm; $p > 0.05$); in the subsequent analyses, marginal bone level changes (ΔBL) at T_1, T_2, and T_3 follow-up times were compared to these initial values. Levels of marginal bone loss according to different correlates are presented in Table 1 (maxilla vs. mandible), Table 2 (axial vs. posterior implants) and Table 3 (MA vs. DA); in addition, the extent of bone loss on an individual implant-level is represented in Tables 4 and 5.

The average rate of bone loss after the 1.5-year follow-up was 0.558 ± 0.029 mm and 0.484 ± 0.024 mm, while by the 3.5-year mark, bone loss was 0.770 ± 0.029 mm and 0.713 ± 0.026 mm regarding the implants placed in the maxilla and mandibular bone, respectively; bone-level changes were significant over time ($p = 0.035$ and $p = 0.033$, respectively), while the alterations observed around the maxilla and mandibular implants did not differ significantly ($p > 0.05$) (Table 1). In patients presenting with underlying conditions/habits (described previously), a tendency was shown for higher bone loss rates in the maxilla (T1: −0.633 ± 0.056 mm, T2: −0.780 ± 0.056 mm, and T3: −0.830 ± 0.053 mm) and the mandible (T1: −0.535 ± 0.048 mm, T2: −0.700 ± 0.054 mm, and T3: −0.763 ± 0.051 mm), however none of these differences were statistically significant ($p > 0.05$).

Table 1. Marginal bone-level changes around implants located in the maxilla and mandible during the 42-month study period.

	Marginal Bone Level Changes (ΔBL) (mm ± SEM)		
Follow-Up	Maxilla (n = 144)	Mandible (n = 144)	p-value (between groups) **
T1	−0.558 ± 0.029 ^{a}	−0.484 ± 0.024 ^{a}	$p > 0.05$
T2	−0.747 ± 0.030 ^{b}	−0.678 ± 0.036 ^{b}	$p > 0.05$
T3	−0.770 ± 0.029 ^{b}	−0.713 ± 0.026 ^{b}	$p > 0.05$
p-value (between follow-ups) *	***p* = 0.035**	***p* = 0.033**	

* based on ANOVA analysis, significant differences ($p < 0.05$) among groups (as demonstrated by post hoc tests) are indicated by different superscript letters (a and b); ** based on independent-sample t-test; p-values below 0.05 are shown in ***boldface.***

Table 2. Marginal bone-level changes around axial and tilted implants during the 42-month study period.

	Marginal Bone Level Changes (ΔBL) (mm ± SEM)		
Follow-Up	Axial (Anterior) (n = 144)	Tilted (Posterior) (n = 144)	p-value (between groups) **
T1	−0.405 ± 0.021 ^{a}	−0.637 ± 0.027 ^{a}	***p* = 0.008**
T2	−0.592 ± 0.024 ^{b}	−0.676 ± 0.028 ^{a}	***p* = 0.048**
T3	−0.606 ± 0.022 ^{b}	−0.833 ± 0.029 ^{b}	***p* = 0.002**
p-value (between follow-ups) *	***p* = 0.041**	***p* = 0.039**	

* based on ANOVA analysis, significant differences ($p < 0.05$) among groups (as demonstrated by post hoc tests) are indicated by different superscript letters (a and b); ** based on independent-sample t-test; p-values below 0.05 are shown in ***boldface.***

Table 3. Marginal bone-level changes on the mesio- (MA) and disto-approximal (DA) aspects of the implants during the 42-month study period.

Marginal Bone Level Changes (ΔBL) (mm ± SEM)			
Follow-Up	Mesio-Approximal (MA) Aspect (n = 144)	Disto-Approximal (DA) Aspect (n = 144)	p-value (between groups) **
T1	−0.519 ± 0.024 ^{a}	−0.522 ± 0.029 ^{a}	$p > 0.05$
T2	−0.697 ± 0.025 ^{b}	−0.728 ± 0.032 ^{b}	$p > 0.05$
T3	−0.729 ± 0.024 ^{b}	−0.793 ± 0.029 ^{b}	$p > 0.05$
p-value (between follow-ups) *	***p* = 0.029**	***p* = 0.035**	

* based on ANOVA analysis, significant differences ($p < 0.05$) among groups (as demonstrated by post hoc tests) are indicated by different superscript letters (a and b); ** based on independent-sample *t*-test; p-values below 0.05 are shown in ***boldface.***

Table 4. Marginal bone-level changes around individual implants in the maxilla during the 42-month study period.

	Marginal Bone Level Changes (ΔBL) (mm ± SEM)							
Follow-Up	12DA (n = 18)	12MA (n = 18)	14DA (n = 18)	14MA (n = 18)	22DA (n = 18)	22MA (n = 18)	24DA (n = 18)	24MA (n = 18)
T1	−0.378 ± 0.051 ^{a}	−0.489 ± 0.063 ^{a}	−0.728 ± 0.093 ^{a}	−0.567 ± 0.074 ^{a}	−0.361 ± 0.061 ^{a}	−0.439 ± 0.055 ^{a}	−0.844 ± 0.095 ^{a}	−0.538 ± 0.053 ^{a}
Range (mm)	−0.0–0.7	−0.0–1.1	−0.2–1.4	−0.0–1.2	−0.0–0.8	−0.0–1.0	−0.4–1.8	−0.0–1.2
T2	−0.583 ± 0.042 ^{b}	−0.661 ± 0.051 ^{b}	−0.950 ± 0.105 ^{b}	−0.733 ± 0.072 ^{b}	−0.489 ± 0.062 ^{b}	−0.605 ± 0.067 ^{b}	−1.033 ± 0.087 ^{b}	−0.722 ± 0.056 ^{b}
Range (mm)	−0.3–1.0	−0.1–1.1	−0.3–1.7	−0.2–1.2	−0.1–0.8	−0.4–1.4	−0.6–1.8	−0.1–1.3
T3	−0.711 ± 0.061 ^{c}	−0.717 ± 0.054 ^{b}	−1.001 ± 0.101 ^{b}	−0.772 ± 0.074 ^{b}	−0.553 ± 0.053 ^{b}	−0.667 ± 0.065 ^{b}	−1.066 ± 0.081 ^{b}	−0.789 ± 0.066 ^{b}
Range (mm)	−0.3–1.1	−0.2–1.1	−0.3–1.7	−0.3–1.5	−0.1–0.8	−0.4–1.4	−0.6–1.8	−0.1–1.3
Statistical significance [1]	*	*	*	*	*	*	*	*

[1] based on ANOVA analyses, level of significance: * denotes $p < 0.05$; significant differences ($p < 0.05$) among groups (as demonstrated by post hoc tests) are indicated by different superscript letters (a, b, and c).

Table 5. Marginal bone level changes around individual implants in the mandible during the 42-month study period.

	Marginal Bone Level Changes (ΔBL) (mm ± SEM)							
Follow-Up	32DA (n = 18)	32MA (n = 18)	34DA (n = 18)	34MA (n = 18)	42DA (n = 18)	42MA (n = 18)	44DA (n = 18)	44MA (n = 18)
T1	−0.256 ± 0.051 ^{a}	−0.550 ± 0.078 ^{a}	−0.622 ± 0.052 ^{a}	−0.494 ± 0.058 ^{a}	−0.344 ± 0.054 ^{a}	−0.422 ± 0.066 ^{a}	−0.344 ± 0.054 ^{a}	−0.538 ± 0.053 ^{a}
Range (mm)	−0–0.6	−0.1–1.1	−0.2–1.0	−0.1–0.9	−0–0.8	−0.1–1.0	−0.2–1.0	−0.1–1.4
T2	−0.388 ± 0.053 ^{b}	−0.689 ± 0.082 ^{b}	−0.827 ± 0.053 ^{b}	−0.678 ± 0.063 ^{b}	−0.494 ± 0.046 ^{b}	−0.627 ± 0.062 ^{b}	−0.494 ± 0.046 ^{b}	−0.722 ± 0.056 ^{b}
Range (mm)	−0.1–0.7	−0.1–1.4	−0.4–1.3	−0.2–1.0	−0.1–0.8	−0.2–1.2	−0.3–1.1	−0.3–1.4
T3	−0.444 ± 0.051 ^{c}	−0.722 ± 0.081 ^{b}	−0.872 ± 0.044 ^{b}	−0.717 ± 0.059 ^{b}	−0.555 ± 0.051 ^{b}	−0.694 ± 0.051 ^{b}	−0.555 ± 0.051 ^{b}	−0.789 ± 0.066 ^{b}
Range (mm)	−0.1–0.8	−0.1–1.4	−0.6–1.3	−0.3–1.1	−0.2–0.9	−0.4–1.1	−0.3–1.3	−0.4–1.5
Statistical significance [1]	*	*	*	*	*	*	*	*

[1] based on ANOVA analyses, level of significance: * denotes $p < 0.05$; significant differences ($p < 0.05$) among groups (as demonstrated by post hoc tests) are indicated by different superscript letters (a, b, and c).

Measured bone loss was significantly higher in posterior implants throughout the follow-up period (Table 2); in addition, bone-level changes were significant over time ($p = 0.041$ and $p = 0.039$). Similarly to the previous result, in patients presenting with underlying conditions/habits, bone loss rates that are numerically higher—but not statistically significant—were observed for axial (T1: −0.422 ± 0.038 mm, T2: −0.596 ± 0.038 mm, and T3: −0.641 ± 0.036 mm) implants, while bone loss was significantly higher for tilted (T1: −0.733 ± 0.056 mm, T2: −0.907 ± 0.061 mm, and T3: −0.949 ± 0.057 mm) implants ($p < 0.05$).

No significant differences were observed in the measured bone-level changes on the MA and DA aspects of the implants throughout the study period ($p > 0.05$ in all cases; Table 3), while bone loss increased consistently during the follow-up periods in both the MA ($p = 0.029$) and DA ($p = 0.035$) aspects. During subgroup analysis, a tendency was shown for higher bone loss rates for both MA (T1: −0.586 ± 0.043, T2: −0.716 ± 0.046, and T3: −0.767 ± 0.042) and DA (T1: −0.545 ± 0.051, T2: −0.757 ± 0.063, and T3: −0.825 ± 0.060), however these differences were not statistically significant ($p > 0.05$).

The degree of bone resorption was also assessed on an individual implant-level, separately in the maxilla and mandible, presented in Tables 4 and 5, respectively. In the case of the maxilla, higher bone loss was observed for the teeth 14DA (with −1.001 ± 0.101 mm at T3, range: −0.3–1.7 mm) and 24DA (with −1.066 ± 0.081 mm at T3, range: −0.6–1.8 mm), which were significantly higher than the values compared to most other teeth ($p < 0.05$) (Table 4). The highest rates of bone loss in the mandibles were shown for the teeth 34DA (with −0.872 ± 0.044 mm at T3, range: −0.6–1.3 mm) and 44MA (with −0.789 ± 0.066 mm at T3, range: −0.4–1.5 mm); bone resorption rate was significantly higher at 34DA than that observed for other teeth ($p < 0.05$), with the exception of 32MA and 44MA. Significantly increasing levels of bone loss were seen in all respective cases, both for maxilla and mandibular implants ($p < 0.05$). The effects of smoking and other underlying conditions were also assessed on these results; although we had a limited number of patients to pool from for aggregated data, significantly higher ($p < 0.05$) bone resorption levels were observed for 14MA (T1: −0.760 ± 0.137, T2: −0.900 ± 0.129, and T3: −0.940 ± 0.117), 24DA (T1: −1.100 ± 0.231, T2: −1.240 ± 0.211, and T3: −1.260 ± 0.219) and 44DA (T1: −0.700 ± 0.143, T2: −1.050 ± 0.183, and T3: −1.117 ± 0.168), while only numerical tendencies were shown for the other teeth.

We have tested whether the age of the patients was a relevant correlate regarding bone resorption levels; overall, we did not find any significant linear correlation between the degree of bone resorption and age. However, in case of 12MA in the maxilla, a positive (but non-significant) tendency could be observed.

4. Discussion

Following the introduction of dental implants, their stability may be characterized by two distinct processes: primary (mechanical) implant stability influences the immediate outcome of the surgery (influenced by bone quality, preparation of the implant bed, and implant geometry), while secondary (biological) stability is a dynamic physiological process (influenced by the underlying factors of the patients and implant microtopography), leading to the formation of the implant-bone interface [21]. Previously, conventional loading protocols were carries out after a healing period of 2–3 months; however, recently, the immediate loading protocols (highly relying on implants reaching high primary stability) have been extensively investigated for their clinical applicability, showing that their overall survival rates and patient satisfaction are comparable to two-stage protocols [22]. Only around two-thirds of patients are completely complication-free following the restoration of the implant-supported fixed prostheses; these complications may include biological adverse events (e.g., peri-implantitis or loss of alveolar bone) and technical complications (screw loosening, retention loss, or fractures in the superstructures), that may lead to implant failure [7,23,24]. The clinical utility of the All-on-Four™ treatment concept has been demonstrated in numerous clinical studies, showing that this technique is distinguished by a predictable, positive prognosis and high patient satisfaction rates [14,25]. The superiority of this concept is associated with the implementation of an atrophic maxilla or mandible, less complicated surgery and upkeep, and masticatory forces in the satisfactory range [14].

The principal aim of the present retrospective study was to provide data on the clinical outcomes associated with distally tilted implants according to the All-on-Four™ therapeutic concept, and to assess the rates of marginal bone loss as a function of time elapsed and patient characteristics using radiographic findings. Various procedures preceding implant placement (e.g., impression, drilling, and introduction of tools) lead to inflammation and, consequently, a baseline level of bone resorption will inevitably occur [26]. Additionally, current publications provide evidence that repeated abutment manipulation—in case of implants with platform-switching—leads to detrimental changes in soft and hard tissues (i.e., tissue remodeling as measured by mucosal margins, implant shoulder, apical extension of the long junctional epithelium and most coronal bone-level in contact with the implant) [27]. Thus, on one hand, the use of implants with fixed abutments (“one abutment–one time” concept) may greatly stabilize peri-implant soft and hard tissues, while immediate implant placement may significantly reduce the initial unavoidable bone loss [28].

The 3.5-year-long follow-up period involved thirty-six patients, with an overall survival rate of 100%. High implant survival rates have been consistently reported for this technique; a comprehensive clinical study by Maló et al. reported a 98.2% cumulative implant survival rate, while based on the literature summary performed by Durkan et al., the overall success rate ranges between 92.2–100%, with no differences between tilted and axial implants in clinical success rates [14,29]. Based on our measured bone loss levels at baseline (T_0; ~0.18 mm) and at the three follow-up points (T_1, T_2, and T_3), bone loss showed the kinetics characteristic for a saturation curve, i.e., showing relatively high ΔBL values at the first-follow-up, with bone-levels changes “flattening out” the curve. By the third follow-up, mean bone loss in our patients was around 0.7–0.8 mm in both the maxilla and mandible, with specific positions in the maxilla and the mandible disproportionally affected; while a tendency for higher measured peri-implant bone loss was seen on the DA aspects, no significant differences were shown MA vs. DA aspects during follow-ups. Bone resorption measured on the MA aspects may be mediated by the chewing forces generated on extension surfaces and the negative torque generated by the bucco-lingual forces, which exerts tensile stresses on these surfaces (previously verified via finite element analyses), which can enhance bone resorption [30]. The cortical bone is most mechanically resistant to compressive forces, less resistant to tensile force, and the least resistant to shear forces [31].

The literature shows wide variation for bone-loss among studies, which is also considerably influenced by the follow-up period associated with the study. Similar kinetics in bone-loss where observed by Hürzeler et al. [32], showing marginal bone loss levels of 1.5 mm in the first year post-implantation, followed by 0.2 ± 0.5 mm in the subsequent years (in a 5-year follow up study), and Widmark et al. [33], with bone loss levels of 1.0 mm in the first year post-implantation, followed by 0.2 mm in the subsequent years (with follow-ups ranging between 3–5 years). In a study involving thirty-nine patients, Makary et al. assessed the clinical success of an early loading protocol by controlling for thread depth according to the bone density of the implant site. They showed a decrease in Implant Stability Quotient (ISQ) values in the early periods of healing—associated with the transition from mechanical to biological stability—following the surgical intervention, with the average marginal bone loss recorded at 0.12 ± 0.12 mm at 12 months post-loading with a 100% survival rate. No differences were shown between the MA and DA aspects of implants [34]. Similarly to this study, no differences were observed between bone loss at the MA and DA aspects by Barone et al. (0.4 mm vs. 0.5 mm) and Iasella et al. (1.0 mm vs. 0.8 mm) [35]. In a retrospective, CBCT-based study, Roe et al. reported a 0.82 ± 0.64 mm vertical, and 1.23 ± 0.75 mm horizontal bone height reduction at 1-year follow-up after immediate implant placement [36]. Interestingly, the study of Maló et al. reported implant failure in similar positions where our study presented with the highest levels on an individual implant-level [37].

On the other hand, bone loss levels were significantly higher around tilted implants compared to axial implants at every time-point. Tilted or short implants provide viable alternatives to bone grafting; on the other hand, they may lead to increased stress on the surrounding bone due to bending [12,38]. A finite-element analysis performed by Almeida et al. showed that the presence of distally tilted implants in an All-on-Four™ concept would result in higher maxillary bone stress compared to vertical implants [21]; these results were corroborated by the study of Rubo et al., additionally highlighting that the proportion of increased stress in proportional to the increased length of the cantilever [39]. In contrast, the paper by Durkan et al. reports bone loss levels within the range of 0.34–1.14 mm for axial, and 0.43–1.13 mm for angled implants, with no significant differences between them [14]. Implant length may also considerably affect implant survival and marginal bone loss, as demonstrated by the meta-analysis conducted by Fernandes et al.: based on the randomized controlled studies (RCTs) included in the analysis, survival rate of extra short ($\leq$6 mm) and longer (6 mm) implants were similar (93.12% vs. 95.98%). In addition, average marginal bone loss at 1-year-, 3-year-, 5-year- and 8-year follow-ups were -0.71 mm, -0.42 mm, -0.69 mm, and -1.58 mm for extra short implants, while -0.92 mm, -0.43 mm, -0.46 mm, and -2.46 mm for longer implants, respectively. Overall, published clinical studies have shown that bone loss was lower in extra short implants [40]

As an additional aim of this research, the bone loss levels in patients presenting with underlying conditions and lifestyle factors were assessed as a sub-group within the patients involved in this 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 [41]. Among the patients, eleven were impacted by of these factors, which were also analyzed separately: while a tendency for higher bone loss values were shown around the implants in these individuals, significant differences were not shown. A retrospective, comparative study by Chrcanovic et al. found that the odds of implant failure was almost three times higher (OR: 2.71; 95% CI: 1.25, 5.88) in bruxers compared to non-bruxers; however, the level of differences showed a decreasing trend with increases in implant length and in cases of rough-surface implants [42]. The study of Glasuer et al. came to similar conclusions, with implant failure being 4.9-times more common (95% CI: 1.75, 13.71) in identified bruxers [43].

The study of Mohanty et al. classified patients based on the presence of the potential underlying factors affecting implant health: they have found that out of n = 425 dental implants studied, implant failure was observed in 29%, 27%, 15.2%, and 13% in the diabetes group, smoking group, periodontitis group, and the bruxism group, respectively [44]. Marginal bone loss levels around implants placed in maxillary sinus grafts were studied by Herzberg et al. in 4.5-year follow-up: their results showed that immediate loading was associated with lower baseline bone loss (0.08 ± 0.24 mm vs. delayed implantation 0.31 ± 0.62 mm), smoking considerably affected the average yearly marginal bone loss (0.24 ± 0.49 mm vs. non-smokers, 0.09 ± 0.32 mm). This study—showing a 95.5% cumulative survival rate—also highlighted the significant association between smoking status and >0.2 mm/year bone loss (p = 0.011), while the number of cigarettes did not have a modifying effect; no such association was seen for bruxism [45]. In a 5-year retrospective cohort study involving 100 smoking and 100 non-smoking patients, Maló et al. assessed the outcome of full-arch mandibular fixed prosthetic rehabilitations based on the All-on-Four™ concept: implant survival did not differ among the two groups (96.9% vs. 99.0%), while marginal bone resorption rate was significantly higher among smokers (1.68 ± 0.76 mm vs. non-smokers 1.98 ± 1.02 mm; p = 0.045); on the other hand, relevant differences in bone resorption around and anterior and posterior implant were not shown [46].

5. Conclusions

Within its limitations (i.e., retrospective study design, number of subjects, and follow-up period), our study has concluded that the use of All-on-Four™ prosthetic concept for total arch rehabilitation yields higher bone loss in association with tilted implants and, in some cases, on the MA surfaces at vertically positioned implants after >40 months of function. 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. Overall, our present study highlights the areas of concern during prosthetic rehabilitation with the All-on-Four™ concept; in the future, results of our study may be extended as a randomized, controlled trial (RCT) with a longer follow-up period and larger number of patients.

Author Contributions: Á.L.S. and Z.B. conceived and designed the study. Á.L.S., Á.L.N., C.L. and Z.B. were involved in the treatment of the patients, the collection of radiographic data, and data analysis. M.G. and P.B. performed statistical analysis. Á.L.S. and Á.L.N. wrote the initial draft of the manuscript, M.G., K.K. and Z.B. revised the full paper. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The 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]).

Informed Consent Statement: Written informed consent was obtained from all participants involved in the study.

Data Availability Statement: All data generated during the study are presented in this paper.

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