Immediate Versus Delayed Loading of Two Unsplinted Implants Supporting a Locator™ Retained Mandibular Overdenture. A Randomized Controlled Study

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Master of Dental Science Thesis

Immediate Versus Delayed Loading of Two Unsplinted Implants Supporting a Locator™ Retained Mandibular Overdenture. A Randomized Controlled Study

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1. Introduction

Progressive bone resorption of the edentulous ridge is a major concern when rehabilitation of the mandible with a complete denture is considered. Complete mandibular dentures seem insufficient in re-establishing oral function, chewing efficacy and bite force [1]. The introduction of implant-retained overdenture prostheses (OVD) has led to a paradigm shift in the management of complete edentulism. Hence, implant-retained OVD have been proposed as the gold standard treatment for the fully edentulous mandible [2].

The long-term efficacy, clinical efficiency and patient satisfaction with this type of restorative solution have been successfully established in many retrospective and longitudinal trials [2, 3]. Following the traditional loading protocol, dental implants should be connected to the prosthesis when the process of osseointegration is complete. The recommended healing timelines before loading of maxillary and mandibular implants with OVD are 6 and 3 months, respectively [4]. For a long time, immediate loading of dental implants was considered detrimental for osseointegration. The evolution of implant systems, designs and surfaces has enabled shortened healing times without jeopardizing osseointegration and implant success rate [5]. The utilization of these enhanced surfaces may improve implant success in patients with systemic conditions such as diabetes and osteoporosis, in compromised sites and when an immediate or early loading protocol is considered [6, 7]
The use of immediate loading protocols may offer several advantages when compared to a delayed loading approach. These benefits include a shortened treatment period, improved function, reduced chair time for provisional relining, improved patient acceptance and no need for a second surgical intervention. A recent systematic review reported similar implant success rates with immediate loading protocols versus conventional approaches but the authors advocated for more data based on randomized controlled clinical trials to improve the quality of the evidence [8]. Immediate loading of dental implants using 2 or 4 implants splinted with a bar supporting mandibular OVD has been validated and documented by case series and prospective studies [3]. However, limited evidence exists based on randomized controlled clinical trials comparing 2 unsplinted implants supporting OVD with immediate loading versus a conventional approach.

Therefore, the aim of this single-blind, randomized controlled clinical trial was to clinically and radiographically evaluate the performance of 2 unsplinted implants supporting a Locator™ retained mandibular OVD using either an immediate or delayed loading protocol.

2. Background and Significance

2.1 Complete Edentulism

2.1.1 Causes and Prevalence

Complete edentulism is the terminal outcome of a multifactorial process involving biological and patient-related factors [9]. While largely the result of genetic or microbial diseases that have strong individual and behavioral influences, total tooth loss can be the
result of iatrogenic, traumatic, or therapeutic causes. Patient neglect and poor oral hygiene contribute significantly to edentulism. According to an oral health survey in 2008 predicted that in 2010, 26% of the US population between the ages of 65 and 74 would be completely edentulous [9]. Sound epidemiological data support predictions that the prevalence of edentulism is falling in the industrialized world [10], however, growth in population and prolonged life expectancy will offset this decrease resulting in an increase in the overall need for complete dentures [11].

### 2.1.2 Consequences of Edentulism

Edentulism can substantially affect oral health, general health as well as overall quality of life [12]. A negative impact on social life, depression and personality changes are established psychological effects of loss of teeth [13] [14] [15]. Physiological impairment can be exemplified by progressive residual ridge resorption, which has been considered one of the most important sequelae of edentulism. The most significant resorption occurs in the first year [16]. Moreover, natural tooth loss could cause temporomandibular disorders and muscular hypotonicity that affect structures related to mastication and mandible stabilization [17]. As a result, chewing efficiency decreases and the patient’s ability to eat nutrient-rich foods becomes significantly lower. This dietary change may explain possible links between edentulism and systemic conditions such as cardiovascular disease, stroke, cancer and mortality [18].

### 2.1.3 Complete Denture and Overdenture

Traditionally, the complete denture has been the gold standard of care for complete edentulism. If proper techniques are used to capture all the anatomical landmarks, a
complete denture can be relatively stable and allow satisfactory function [19]. However, once the physiological alteration process commences, dentures lose retention, support and stability, causing difficulty in reestablishing chewing efficacy and biting forces [20] [21]. In order to overcome these challenges, the concept of the OVD was introduced.

The OVD is defined as a removable partial denture or complete denture that covers and rests on one or more remaining natural teeth, the roots of natural teeth and/or dental implants [22]. The concept of OVD is age old. Ledger in 1856 suggested utilizing natural teeth to stabilize removable prostheses. A century later, Miller introduced the tooth-retained OVD technique [23]. However, when natural teeth were used as abutments, periodontal disease, periapical lesions, caries and fractured teeth frequently resulted in failure of the OVD [24].

2.2 Dental Implants

2.2.1 Implant Supported/Retained Prosthesis

Since 1985, when Branemark introduced osseointegrated implants, the therapeutic possibilities for edentulous patients have been drastically improved. Currently, implant prostheses are generally categorized into: the fixed ceramometal prosthesis, the fixed detachable prosthesis and the implant-supported OVD [25]. Crucial factors such as esthetics, phonetics, comfort, and function must be analyzed with accurate records during the treatment planning stage before the final prosthesis can be determined [26, 27]. With the rapid advancement of CAD-CAM system, options are further expanding.

Complete dentures had been the standard of care for edentulous patients for a long period
of time despite the introduction of OVD. However, current evidence suggests the restoration of the edentulous mandible with a conventional denture is no longer the most appropriate first choice prosthodontic treatment. A two-implant OVD should become the gold standard of care and be the primary choice of treatment [2] [28].

Implant OVD therapy requires the use of attachments to connect the implants to the prosthesis. There are many different attachments provided by a large number of manufacturers around the world. The attachments currently available can be broadly divided into two major categories: splinted / bar attachments (e.g., dolder bar, hader bar) and non-splinted / solitary / stud attachments (e.g., ball attachments, magnets, locators). The choice of attachment depends on the clinical situation at hand [29]. Splinted bars cannot be used in cases where the inter-occlusal space is limited. On the other hand, non-splinted solitary attachments require less inter-arch space, need minimal to no laboratory support, are less technique sensitive and can be fabricated at a lower cost.

While the introduction of implant-retained OVD has alleviated the risks associated with tooth-supported OVD, the success of the prosthesis relies on proper osseointegration of the implants.

2.2.2 Biology of Osseointegration

Osseointegration was defined by Branemark as a direct structural and functional connection of a load-carrying implant [30] and consists of direct histological bone-implant contact without an intervening layer of fibrous tissue [31] [30, 32].

There are numerous materials, such as metals, alloys, ceramics, carbons and polymers,
currently utilized in the medical field to facilitate osseointegration throughout the human body. Commercially pure titanium and Ti-6Al-4V (titanium alloy) are the most commonly used materials today for dental implants [33]. Titanium has physical properties that provide adequate ductility and strength to bear the load in function. Furthermore, titanium and its alloys belong to a bio-inert class incapable of causing chemical insult to the body. Corrosion products such as hydroxide, oxide and hydrous oxide may be toxic for cells and tissues but titanium in pH 6.5-7.0 is fully inert to the redox reaction. This is due to a specific mechanism that causes the titanium surface to be covered with a dense oxide film where the unwanted reaction product TiO$_2$ becomes a potent barrier against metal dissolution [34]. Histological foreign body reaction studies on animals and humans show that tissues surrounding titanium implants are vital and show no signs of inflammation or allergic reactions [35] [36].

Titanium is capable of achieving osseointegration through a complex mechanism. When the implant surface is in contact with water, electrochemical events take place on the surface of the implant and the titanium dioxide layer gets hydroxylated. This will cause the oxide layer to double or triple in thickness. The electrochemical reactions also lead to the incorporation of biological ions, such as calcium, phosphorus, and sulfur ions. On the biological side, water molecules and hydrated ions from blood associate with the implant surface. The presence of the substrate locally alters the organization of water molecules and this may subsequently affect adsorption of biomolecules. A complex, time-dependent cascade of events involving adsorption, displacement, and exchange then takes place and eventually result in bone formation [37] [38].

*Davies et al.* [39] also describe the process of peri-implant tissue formation as a result of
two separate biological events: contact osteogenesis and distance osteogenesis. Contact osteogenesis consists of two phases. The first phase is osteoconduction. When an osteotomy is performed, bleeding is elicited. Once the implant surface comes into contact with blood, platelet activation is generated and a clot forms acting as a scaffolding structure for further recruitment and migration of osteogenic cells to the area. The second phase, *de novo* bone formation, results in a mineralized interfacial matrix, which is immature woven bone on the implant surface equivalent to that seen in the cement line in natural bone tissue. Contact osteogenesis only occurs when the surface morphology of the implant is appropriate. Numerous studies have researched the optimal implant surface characteristics to maximize contact osteogenesis and Wennerberg et al. [40] concluded that an average surface roughness (SA) ranging between 1 to 1.5 µm seems to provide a significantly higher bone-to-implant contact when compared to either smoother or rougher surface topographies. In addition to surface geometry, the chemical modification of the metal surface seems to influence the rate of bone deposition, favoring faster bone maturation [41] [42].

Distance osteogenesis occurs when bone forms from the cut bone surface of the osteotomy toward the implant surface [39]. In distance osteogenesis, the osteocytes within the bone edges cut during osteotomy preparation, extending 100-500 µm, die due to the thermal injuries [43]. Differentiating osteoblasts migrate to the surface of the reabsorbed bone and form a noncollagenous cement line similar to that on the implant surface [43]. Hence, contact osteogenesis and the distance osteogenesis together ultimately lead to formation of the bone–implant interface. Over time, there is a changeover from primary stabilization, which results from the initial friction fit of the
implant within the host bone at the time of implantation, to secondary stabilization resulting from the formation of the woven bone around the implant [44].

### 2.2.3 Factors Influencing Osseointegration

During the process of osseointegration, implant stability is the key to a successful outcome. There should be no movement of the implant throughout the process. Micromotion during the early healing phase can cause fibrous tissue formation around the implant, resulting in failure of osseointegration [45] [46].

Primary stability relies on the initial frictional mechanical stability from the implant surface coming into contact with the severed bone [47]. Therefore, primary stability depends on the quality of bone and the implant design itself. Primary stabilization declines over time, as the host bone that is in direct contact with the implant is resorbed by osteoclasts [39]. However, despite this temporary loss of hard tissue contact, the implants remain clinically stable at all times. This is due to the mechanical anchorage of the implant that is replaced with a biological attachment including *de novo* bone formation. This includes the establishment of woven bone on the surface of the titanium device. Thus, it is crucial to have implant surface topography to be a three dimensional complex that consist of pores and undercuts that will provide better scaffolding for the woven bone formation around the implants and fasten the shift from primary stability to the secondary stability.

Hence, bone quality, implant design and implant surface characteristics are all important parameters that influence primary and secondary stability.
2.2.3.1 Primary Stability

*Quality of bone:*

Bone tissue is categorized into two macro architectural forms: 1) trabecular or cancellous and 2) cortical or compact. One of the most popular classification systems for jaw shape and quality for dental implant treatment was proposed by *Lekholm and Zarb* in 1985 [48]. Their classification was dependent upon the relative proportions of cancellous and cortical bone. This allowed the quality of bone tissue to be related to the stability of an implant. The bone quality is categorized into four types: Type I, predominantly cortical; Type II, thick layer of compact bone surrounding a dense cancellous core; Type III, thin layer of compact bone surrounding a cancellous core; and Type IV, very thin compact layer around a low density trabecular bone [48].

*Figure 1:* Jaw bone quality according to Lekholm and Zarb [48]

Poor bone quality is believed to be one of the most important risk factors for early implant failures [49] [50]. Recent systematic reviews have shown that the survival rates
of dental implants according to the bone density were lowest in Type IV bone and highest in Type I bone [51]. This can be explained by the fact that cortical bone has a higher modulus of elasticity, is harder to deform and provides greater resistance to motion [52]. Thus, with less cortical bone, the implant is subject to lower primary stability, to increased micromotion, resulting in fibrous tissue formation. In a retrospective study, Friberg et al. [50] evaluated survival of 4,641 Branemark implants and found that the majority of failures occurred in maxillae where sites with extremely soft bone and/or initial implant stability was not achieved. Similar results were obtained by Jaffin et al. [49]. In his retrospective study of 1,054 Branemark implants, 35% of the fixtures placed in Type IV bone failed. In order to overcome this problem, several surgical techniques were introduced.

Summer et al. [53] demonstrated the osteotome technique to be used in posterior maxillae where Type IV bone mostly exists. This technique attempts to retain all of the bone that is present, and to take advantage of the softer bone quality by relocating the bone to suit the needs of the surgery. In addition, pushing or tapping the osteotomes into place will compact the osseous layer around the osteotomy, which will form a denser bone interface with the implant. Later, Nkenke et al. [54] confirmed with animal study that the osteotome technique increases new bone formation and leads to an enhanced osseointegration of dental implants in poor quality bone. However, in contrast to these results, Buchter et al. [55] found in an animal study that the bone to implant contact (BIC) ratio of sandblasted, large grit, acid etched (SLA) implants placed with osteotomes was lower than that of those placed conventionally. Also, the removal torque value and interfacial stiffness were significantly higher for the conventionally installed implants.
compared to those installed using osteotomes. Furthermore, in another animal study, Stavropoulos et al. [56] observed all the implants installed using the osteotomes were lost before or shortly after immediate loading despite good initial stability whereas the conventional drilling sites had no failure. Thus he concluded that the preparation of the implant bed with osteotomes neither improved osseointegration nor increased the predictability of immediate loading compared to conventional drilling.

Another surgical technique to improve the primary stability was to underprepare the osteotomies. A retrospective study by Friberg et al. [57] investigated three different diameters of Branemark implants, with special focus on the 5.0-mm-diameter implants. The results showed lower failure rates than their previous study and they concluded that the favorable outcome in bone of poor quality can be achieved by the use of an adapted preparation technique. This concept was also confirmed by Turkyilmaz et al. [58] where they found higher mean maximum insertion torque and resonance frequency analysis (RFA) value for corresponding test groups where the osteotomies were prepared with thinner drills and concluded that the underpreparation may improve the primary stability in poor quality bone.

**Implant Design:**

Macroscopic features of implant design include the shape, type of threads and neck design at the implant-abutment interface. A human cadaver study of different implant shapes demonstrated the greatest initial stability with 1 degree tapered implants compared to cylindrical implants. This finding was attributed to the wedging effect of the tapered configuration [59].
Implant thread design is another geometric feature that could influence primary stability. The presence of threads increases the surface area available for mechanical interlocking, thereby allowing a more secure fixation [5]. A smooth, non-threaded implant relies purely on press-fit and frictional forces for initial stability, which are significantly less effective in osseointegration. Furthermore, the pitch of the threads also influences primary stability. Decreasing pitch results in increasing surface area, providing more bone-to-implant contact [60]. In addition, when micro-threaded modifications are made to cover the implant surface to the neck of the implant, greater maintenance of the marginal bone level results and an increased resistance to marginal bone loss has been reported [61] [62].

2.2.3.2 Secondary Stability

Implant surface:

Whereas the macroscopic features of implant design affect primary stability, the microscopic nature of the implant surface influences secondary stability in the process of osseointegration.

The early dental implants had a turned surface with a minimally roughened configuration and some residual periodic microgrooves. These smooth machined surfaces demonstrated great long-term clinical success, with over 96% survival in Type I-III bones [4]. However, as previously mentioned higher failure rates of machined implants were observed in Type IV bone [49] [50]. Thus numerous studies were conducted throughout the years to improve the quality of the surface. These alterations to the surface accelerated bone healing and anchorage to the implant, resulting in improved
osseointegration and yield higher rates of success even in Type IV bone [63] [40].

Typically, modifications to the implant surface are made to achieve better topographic, physical, and chemical properties for optimal osseointegration.

The surface topography relates to the degree of roughness of the surface (Sa) and the orientation of the surface irregularities (Sdr) [7]. A systematic review by Wennerberg and Albrektsson et al. [40] analyzed the available surface morphological modification data and concluded that moderately rough (Sa = 1 - 2 µm) surfaces showed stronger bone responses compared to smooth (Sa < 0.5 µm) and minimally rough (Sa = 0.5–1 µm) surfaces [40].

Several approaches are currently available to achieve ideal surface quality. In the subtractive strategy for surface modification, the irregular interface is physically created through ablating/subtraction approach. [63]. Common methods for ablating implant surfaces include grit blasting, acid etching, and grit blasting followed by acid etching [38].

At the micrometer level, a rough surface presents a higher developed area than a smooth surface and thus increases bone anchorage and reinforces the biomechanical interlocking of the bone with the implant. At the nanometer level, the roughness increases the surface energy, improving matrix protein adsorption, bone cell migration and proliferation, and finally osseointegration [40].

Studies have reported that the cellular attachment and proliferation, production of cytokines, release of growth factors and synthesis of extracellular matrix are all
influenced by these micro-roughened, altered implant surface topographies. Boyan et al. examined the role of surfaces in regulating bone cell response and found that osteoblasts and chondrocytes are sensitive to subtle differences in surface roughness [64]. They concluded that the surface micro-topography determines the pattern of cell adsorption, attachment and alignment along the implant surfaces. Schneider et al. also observed in vitro that there was an increase in Runx2 and osteocalcin gene expression in cells cultured on rough and grooved implant micro-topographies [65].

Another surface modification approach involves chemically incorporating inorganic phases such as calcium phosphate, fluoride or magnesium ions on or increasing the TiO$_2$ layer. Similarly, biochemical modification refers to the incorporation of organic molecules, such as proteins, enzymes and peptides, to induce specific cell and tissue responses. Both of these treatments are believed to stimulate the surface to become bioactive and promote bone regeneration and increase the biomechanical interlocking between bone matrix proteins and surface materials [63] [7]. While a machined surface was essentially anchored in bone via mechanical bond, a bio-active modification could have a biochemical bond with living tissues.

Ellingsen et al. [42] reported significantly greater bone-to-implant contact and higher removal torques with fluoridated surfaces in a rabbit study. The same group of authors recently [66] investigated the biologic factors involved in the improved retention of fluoridated implant surfaces. They observed that new peri-implant cortical bone attached to 0.01% hydrofluoric acid-treated implants showed the most suitable balance in gene expression between these biological factors (higher in osteocalcin, collagen-I for bone formation and also TRAP for bone resorption) [66].
Another interesting evidence supporting improved bone healing with surface modification shows more hydrophilic surfaces provide enhanced bone-to-implant contact. This is due to the fact that biologic fluids, tissues and cells interact more readily with hydrophilic surfaces. This finding has been confirmed in animal models [67] [68]. Furthermore, increased expression of bone-associated genes including alkaline phosphatase, osteocalcin, type I collagen and osteoprotegerin was observed on hydrophilic compared to hydrophobic surface in vitro [69]. Thus data confirm that the rate of protein adsorption and adhesion of osteoblasts to implant surfaces can be influenced by increased wettability and surface energy.

Currently, there are over 1300 available implant types with various surface properties [68]. Surface subtractive techniques generally increase micro-roughness while surface additive technique generally aid in improved biologic behavior. Many biochemical, physiochemical and morphological alterations of the implant surface exist through various techniques such as blasting, etching, oxidation, or combination of techniques. Some of these techniques have been studied in animal and human models while others have not and are considered experimental. New implant surface modifications are constantly being refined. Faster and more reliable osseointegration due to these advances in implant macro- and microstructure provides more flexibility with the timing of implant loading.

2.2.4 Loading of Implant Prosthesis

2.2.4.1 Traditional protocols
For years, the standard protocol for the timing of implant loading required 3 and 6
months of healing for mandible and maxilla, respectively, from the time of implant placement. This loading protocol was intended to prevent disruption of the healing process. Premature loading could result in the formation of fibrous tissue surrounding the implant, thus interfering with peri-implant osteogenesis. However, advancements in implant systems, surface modifications and surgical techniques have resulted in modifications of the aforementioned conventional loading protocols.

2.2.4.2 Immediate Protocols

Immediate loading, defined as prosthetic restoration loaded on the implant within one week of implant placement [70], was first introduced by Schnitman et al. in 1990. Significantly shortened treatment time and early functional, physiological and psychological rehabilitation are the benefits of immediate loading [70] [71].

In addition to shortened treatment time, immediate loading was thought to improve osteoblastogenesis at a histological level. The response of mesenchymal stem cells to mechanical strain and their resulting patterns of gene expression were studied in vivo. It was determined that the mechanical strain acted as an inducer to boost stem cell differentiation into osteoblasts [72]. Moreover, cyclic tensile strain was proven to favor formation of bone by maximizing the synthesis of osteoprotegerin and restricting the soluble receptor activator of nuclear factor kappa-B ligand (RANKL) [73]. An animal model also validated the concept of stimulated bone formation due to mechanical loading [74] [75]. Therefore, animal and in vitro studies seemed to support immediate loading over delayed loading to improve bone response during early healing. Also, clinical studies and human histology have shown a reduced amount of radiographic bone level
change and higher percentage of bone to implant contact around immediately loaded implants when compared to implants loaded with conventional protocol [76] [77] [78]. However, the question still remains whether there is enough evidence in humans for this modality of treatment to be used safely and effectively in all patients. According to a recent systematic review of different loading protocols (delayed, early and immediate) in completely edentulous patients, immediate loading of mandibular dentures is clinically well-documented but not scientifically validated [3].

2.2.4.3 Immediate Loading of Mandibular Overdentures

Many prospective studies have documented the success of immediate loading of mandibular OVD. A longitudinal study by Chiapasco et al. [79] evaluated the success of mandibular OVD immediately loaded on four implants utilizing a splinted bar attachment. The results showed that the success and survival of the immediately loaded prosthetics were equivalent to those documented for the conventionally delayed loading overdentures. A multicenter cohort study by Grandi et al. in 2012 revealed a 100% cumulative survival rate with changes in bone level of only 0.3 mm surrounding immediately loaded implants by ball attachments retained OVD [80]. Another prospective cohort study by Alfadda et al. analyzed immediate loading versus historical conventional controls with delayed loading at five years and reported identical results for the two groups in terms of impact on quality of life, satisfaction, success and survival [81]. Despite promising results in many studies, some reported decreased success rates of immediately loaded prosthetics after a longer follow up period [79]. In 2010, Kronstrom et al. also advised caution in utilizing immediate loading due to an 81.8% survival rate after 36 months [82].
A ten-year clinical trial by Meijer et al., in addition to Gallucci’s systematic review, has shown that there is no difference in the clinical and radiographic performance of immediately loaded two versus four implants supporting mandibular OVD [83] [3]. Successful results have been reported for two unsplinted attachments, such as ball, in the recent literature [84] [85] [80]. Furthermore, implant success rate and marginal bone loss seem to be independent of the type of attachment used [29] [86] [87]. Thus, it seems there is no difference in outcomes with two versus four implants, splinted or unsplinted, for mandibular OVD.

At present, there are no randomized controlled trials available evaluating immediate versus delayed loading using locators supporting mandibular OVD.

3. Aims, Hypothesis and Objectives

3.1 Aims

The aim of this study is to evaluate clinically and radiographically the performance of OsseoSpeed™ implants (Astra Tech, Dentsply, USA) 12 months post-loading supporting a mandibular OVD, using either an immediate or delayed protocol.

3.2 Hypothesis

There is no difference in implant outcomes as related to timing of loading.
3.3 Objectives

3.3.1 Primary Objectives

The primary objective is to evaluate peri-implant bone remodeling using radiographic bone level changes as the variable, from baseline to 12 months, between the test and the control groups.

3.3.2 Secondary Objectives

The secondary objectives include evaluation of:

- Implant survival at 1 year
- The nature and the frequency of surgical and prosthetic complications between test and control group
- Correlation between implant length and insertion torque on marginal bone level changes

4. Study Design and Procedures

4.1 Study Design

The study was a single blind parallel arms randomized controlled clinical trial, whereby each patient received 2 implants supporting a mandibular OVD retained by Locator™ abutments. The patients were randomly assigned to either one of the following groups:

- Test group – the implants were immediately loaded (IL)
- Control group - the implants were submerged under mucosa and loaded after 3 months of healing (DL)

4.2 Patient Selection

The Institutional Review Board, at the University of Connecticut, approved the research protocol (IRB#10-305-3) and subjects were recruited among patients seeking implant-retained OVD at the University of Connecticut Health Center, Graduate Periodontology Clinic, from October 2010 to December 2012.

An initial evaluation was conducted to determine whether the patient met the study inclusion criteria. This evaluation consisted of a medical history questionnaire, a clinical exam and a radiographic assessment. Orthopantomograms were done for all patients. In cases with severe bone resorption, cone beam computerized tomography (CBCT) imaging was obtained. Also, during this preliminary screening visit, a preoperative prosthetic evaluation of the existing prostheses was made to establish the need for denture adjustments before the implant placement. Once the patient was deemed eligible, the mandibular denture was duplicated and used as radiographic / surgical guide.

4.2.1 Inclusion and Exclusion Criteria

Patients that were included in the study had to fulfill the inclusion and exclusion criteria presented in Figure 2.
4.3 Study Procedures

4.3.1 Randomization and Allocation

Every patient was given a subject identification number. An independent investigator, not involved with patient treatment, generated the allocation list. Computer software was used to randomize the subject identification numbers into one of the two groups. This
information was concealed in sealed envelopes which were opened after implants were placed. Neither the surgeon, nor the patient was aware of the group assignment until after implant insertion.

4.3.2 Study Procedure

Stage I Surgery: Implant Placement (For both groups)

The same experienced operator performed all the surgeries. Two implants 4.0 S TX OsseoSpeed™ (Astra Tech-Dentsply, USA) were inserted in each subject under local anesthesia obtained with lidocaine 2% with 1:100,000 epinephrine. Each subject received a prophylactic antibiotic medication consisting of 2 grams of amoxicillin one hour before the surgical procedure. After making a crestal incision, a full thickness flap was elevated. A vertical releasing incision at the facial midline aspect of the mandibular ridge was raised if deemed necessary (Figure 3a). The osteotomy sites were prepared following the drilling sequence provided by the manufacturer’s surgical manual. To increase the implant primary stability, the implant site was underprepared in relation to bone quality. The 3.2 and 3.7 mm twist drills were used as the final drill for Class III –IV and I – II quality bone, respectively (Figure 3b). The implants were inserted in the canine/lateral incisor position following the surgical guide (Figure 3c). During the implant insertion the maximum value of insertion torque (IT) was recorded. In case the IT was lower than 20 Ncm the implants were submerged, the patient was excluded from the study and the implant treatment completed following the delayed protocol. For the DL group a cover screw was placed and the implants were submerged under the oral mucosa. For the IL group, Locator™ abutments were secured on the implant using hand torque
and the flaps were sutured (Figure 3d). Primary closure was achieved using 5-0 nylon (Monosoft; Syneture, Covidien, Mansfield, MA, USA) interrupted sutures (Figure 3e). Patients of the DL group were not allowed to wear the denture for 14 days. Patients of the IL group had the denture connected immediately and were instructed not to remove the denture for 7 days. As post-surgical instructions, the patients were asked not to brush the operated areas and to rinse instead with 0.12% chlorhexidine solution (Peridex; 3M ESPE, St Paul, MN, USA) twice a day, for one minute for 14 days. Pain control was provided with 400 mg Ibuprofen as needed. Sutures were removed after two weeks.

a. 

![Image](image1.jpg)

b. 

![Image](image2.jpg)

c. 

![Image](image3.jpg)
Stage II Surgery: Uncovery (Control Group Only)

Subjects in the DL group were seen at 12 weeks for second stage surgery. After local anesthesia the crest was sounded to locate the cover screws. A crestal incision was made and a conservative full thickness flap elevation done. Cover screws were replaced with Locator™ abutments and the flaps secured with resorbable 5-0 chromic gut (Chromic gut; Perma Sharp, Hu-Friedy, Chicago, IL, USA) interrupted sutures.
4.3.3 Prosthetic Treatment

- **IL Group** - For the IL group, the denture was immediately connected to the implants after surgery. The Locator™ attachments were connected intraorally using cold curing resin (Super T; Amco, Philadelphia, PA, USA) To avoid contact of the resin with the sutures and the surgical wound, a circular portion of sterile rubber dam sheet was adapted on the female attachment once placed on the abutment during the pickup procedure [84] (Figure 4). Occlusion and adaptation on the residual ridges was then checked and adjusted if necessary and the patient dismissed. No limitations to chewing function were given.

- **DL group** - The subjects in the control group resumed the use of the denture 2 weeks after implant placement. The dentures were used with soft reliner until the implants were uncovered. Implant uncovering and denture connection was done 12 weeks after implant placement.

![Figure 4: Prosthetic treatment](image)

4.3.4 Follow-Ups Visits

Visit schema and study timeline of the study is presented in Figure 5. Patients were recalled at 1, 2, 12, 24 and 52 weeks (±1 week) after surgery. At the post-operative visits
the abutments were gently cleaned, occlusion, stability, and retention of the prostheses were evaluated and adjusted as required.

![Visit schema and study timelines of the study](image)

**Figure 5:** Visit schema and study timelines of the study

### 4.4 Data Collection and Analysis

#### 4.4.1 Primary outcome variables

The following clinical parameters were evaluated as primary outcome variable:

1) **Radiographic bone level change**

Radiographic bone level change (RBLC) was measured on standardized periapical radiographs (Figure 6). A calibrated blinded examiner made the measurements. Image analysis software (Image J, v 1.42., NIH, Bethesda Maryland) was used to measure the distance between the implant platform and the most coronal level of the bone deemed to be in contact with the implant surface. The first bone-to-implant contact at surgery was defined as baseline. The bone level at or coronal to the implant platform was considered as 0. The RBLC was calculated as the difference between the reading at 1 year, at 6 months and the baseline value (Figure 7). Mesial and distal bone height measurements
were averaged for each implant. The value of the average RBLC of the 2 implants for each subject was used for the analysis at patient level.

Figure 6: A customized Rinn® film holder was used to standardize periapical radiographs
Figure 7: Radiographs at baseline (T0) and at 12 months (T12). The first bone-to-implant contact at surgery was defined as baseline (B). The bone level at or coronal to the implant platform was considered as 0. RBLC was measured as the distance between the implant platform and the most coronal level of the bone deemed to be in contact with the implant surface at T12.

2) Success and failure criteria

The success criteria for the implants were:

- No radiolucency around the implant
- No mobility
- No suppuration
- No pain

Implants that did not fulfill the success criteria were considered as failed. The failed implants were removed and replaced with another implant after a minimum of eight weeks of healing of the implant site. The replaced implants were loaded after three months of undisturbed healing.

4.4.2 Secondary outcome variables

The following clinical parameters were evaluated as secondary outcome variables:

1) Patient demographics

Gender, age, smoking status and the restoration of maxillary arch of each patient was recorded.

2) Prosthetic maintenance and complications
A record of the number of maintenance visits made in addition to the anticipated visit schema was documented for every patient. The reason for the maintenance visit, nature of complaint, measures taken to manage the issue were also recorded.

3) Maximum insertion torque

During the implant placement, IT was recorded during the seating of the most coronal implant threads by means of the surgical unit (W&H, Burmoos, Austria) and reported in the 20, 30, 40, 50 Ncm category. In case the torque to insert the implant was superior to the maximum value measurable with the surgical unit (50 Ncm) the hand wrench was used and the IT was recorded in the >50Ncm category.

4) Implant length

Implant lengths were recorded for each group; lengths used were 8, 11, 13 and 15mm.

4.4.3 Statistical Analysis and Data Presentation

A RBLC of 0.5 mm was considered to be of clinical relevance [88]. Sample size analysis was calculated based on an $\alpha$ error of 5% and a power of 80%. A minimum sample size of 14 subjects (28 implants) for each group was needed to detect a difference of 0.5 mm between the groups with a standard deviation of the change of 0.5 mm (Primer of Biostatistic 5.0, Statistical package). Considering 20% attrition, 18 subjects per group were enrolled. Kolmogorov-Smirnov goodness of fit test was computed for the response
variable to assess whether the parameters were normally distributed. The patient was considered a statistical unit. Parametric data were compared using Student-t test for independent groups and paired-t test for intra group comparison. Non-parametric data were compared using Mann-Whitney Rank Sum test and Wilcoxon Signed Rank test for independent groups and intra group analysis respectively. Data relative to patient demographics, number of extra visits, prosthetic complications and implant failure rates were considered as nominal and presented with descriptive statistics. Nominal data were compared using a Chi-square analysis of contingency table. Correlations between IT and implant length to RBLC were evaluated using Spearman Rank Correlation test. The level of significance was set at 5% for all statistical tests.

5. Results

5.1 Patient Demographics and Enrollment

Thirty-two patients were consecutively treated. All patients participated until the end of the study, no clinical dropout occurred. All subjects healed with minor discomfort. No swelling or surgical complications were reported. Sixty-four implants were placed. Two implants in 1 patient in the IL group did not reach IT of 20 Ncm at the time of placement. The implants were submerged and the patient was treated with a delayed protocol and excluded from the study. A total of 15 subjects and 30 implants per group were available for statistical analysis at the 12 months visit. Patient flow and allocation of the study is presented in Figure 8.
Demographic characteristics of the treatment groups are reported in Table 1. Four subjects were smokers, 2 in the DL and 2 in the IL group, respectively. All the subjects in the study were wearing a complete denture in the maxillary arch with the exception of 2 subjects in the DL. One subject had natural dentition and the other had an implant supported fixed prosthesis.

**Table 1**: Demographic characteristics of treatment group

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Gender</th>
<th>Smoking Status</th>
<th>Opposing Arch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>DL (n=15)</td>
<td>66.2 (8.6)</td>
<td>57-85</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>IL (n=17)</td>
<td>66.6 (10.2)</td>
<td>53-79</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Total (n=32)</td>
<td>66.4 (9.3)</td>
<td>53-85</td>
<td>20</td>
<td>12</td>
</tr>
</tbody>
</table>
5.2 Implant Success and Failures

No implants were lost in the DL group (0/30) for a cumulative survival rate (CSR) of 100%. In the IL group 2 implants failed in 1 subject (2/32) for a CSR of 94%. The difference in CSR between the groups was not statistically significant ($p=0.5$ Chi-square). The failed implants were 13 mm long, inserted with >50 Ncm IT in a 70 year old man, non-smoker, with history of previous implant failure. The implants were found mobile and were removed at 4 weeks visit. The patient refused to have the implant replaced and remained with his complete denture. As per intent to treat, the data relative to the failed implants were included in the analysis for IT and implant length.
5.3 Implant Length distribution

Implant length distribution relative for DL and IL groups is reported in Table 2. A statistically significant difference was observed for the implant length between DL and IL ($p=0.034$ Mann-Whitney Rank Sum test), with shorter implants in the IL group. A Spearman Rank test was carried out to evaluate the effect of implant length on RBLC and no correlation was observed. (DL; $r=0.6$, IL; $r=0.13$, Spearman Rank Correlation test)

<table>
<thead>
<tr>
<th>Implant length</th>
<th>8mm</th>
<th>11mm</th>
<th>13mm</th>
<th>15mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL n. of implants (%) (n=30)</td>
<td>0</td>
<td>10 (33.5%)</td>
<td>14 (46.5%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>IL n. of implants (%) (n=32)</td>
<td>2 (2%)</td>
<td>14 (48%)</td>
<td>16 (50%)</td>
<td>0</td>
</tr>
</tbody>
</table>

5.4 Insertion Torque Distribution

IT distribution amongst DL and IL groups is reported in Table 3. No difference was observed for IT between DL and IL implants ($p=0.92$; Mann-Whitney Rank Sum test). Spearman Rank Correlation test was carried out to evaluate the RBLC in relation to IT and the correlation was not statistically significant (DL; $r=0.26$, IL; $r=0.65$ Spearman Rank Correlation test).

<table>
<thead>
<tr>
<th>Peak IT (Ncm)</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>&gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL n. of implants (%) (n=30)</td>
<td>3 (10%)</td>
<td>6 (20%)</td>
<td>11 (37%)</td>
<td>4 (13%)</td>
<td>6 (20%)</td>
</tr>
</tbody>
</table>
### 5.5 Radiographic bone level change (RBLC)

RBLC distribution at patient and implant level for DL and IL is reported in Table 4.

**Table 4: Distribution of RBLC**

<table>
<thead>
<tr>
<th></th>
<th>Implant level</th>
<th>Patient level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RBLC (mm)</td>
<td>n. of patients (%)</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.5</td>
<td>0.5 - 1</td>
</tr>
<tr>
<td>DL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n. of patients (%) (n=30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n. of patients (%) (n=15)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The intra-group comparison of RBLC from baseline to 6 months and from baseline to 1 year showed loss of marginal bone in both IL and DL group and the difference was statistically significant (Figure 9).
RBLC from baseline to 6 months was 0.39 mm (±0.3) and 0.27 (±0.4) for DL and IL respectively. The mean RBLC from baseline to 1 year was 0.54 (±0.5) mm and 0.26 (±0.5) mm for DL and IL respectively (Table 5).

Since the RBLC data for the IL group resulted non-normally distributed ($p<0.001$ Kolmogorov-Smirnov goodness of fit test) the median RBLC values between DL and IL were compared using Mann-Whitney Rank Sum test.

A statistically significant difference was observed at 12 months interval ($p<0.02$ Mann-Whitney Rank Sum) with a smaller RBLC in the IL group.
Table 5: Comparison of RBLC between groups

<table>
<thead>
<tr>
<th></th>
<th>DL Mean (SD)</th>
<th>IL Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ 6 months</td>
<td>0.39 mm (0.33)</td>
<td>0.27 mm (0.47)</td>
<td>p = 0.1 (Mann-Whitney)</td>
</tr>
<tr>
<td>(n=15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆ 12 months</td>
<td>0.54 mm (0.55)</td>
<td>0.26 mm (0.55)</td>
<td>p = 0.019 (Mann-Whitney)</td>
</tr>
<tr>
<td>(n=15)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.6 Prosthetic Outcome

Prosthetic complication and maintenance visits are reported in Table 6.

Prosthetic maintenance was required in 17 (56.6%) out of 30 patients. Four of these patients had a midline fracture of the prostheses while others reported for minor denture adjustments due to denture sores, losing retention due to the wear of the plastic inserts or abutment loosening. The fractured prostheses were laboratory processed, relined and redelivered to the patients. The worn plastic inserts were exchanged to new ones and loose abutments were re-tightened. There was no statistical difference in the number of visits made by patients in the two groups. (p=0.488, Chi Square Test)

Table 6: Prosthetic complication and maintenance visits

<table>
<thead>
<tr>
<th></th>
<th>DL</th>
<th>IL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denture fracture</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Insert change</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Abutment loosening</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Denture adjustment</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>TOTAL</td>
<td>18</td>
<td>21</td>
</tr>
</tbody>
</table>
6. Discussion

In this single blind parallel arms randomized controlled clinical trial, we compared clinically and radiographically, 2 fluoride-modified micro-rough titanium surface implants supporting a Locator™ retained mandibular OVD, loaded immediately or following a conventional approach. The overall CSR of the implants was 97% one year after surgical placement. No implant failure was reported in the DL group whereas 2 implants failed in the IL group for a CSR of 94%.

The present CSR data are in agreement with previous investigations. The overall CSR reported in the literature for immediate loading of unsplinted implants with mandibular OVD ranges between 81 to 100% [89] [90] [91] [92] [93]. Elsyad et al. [94], using a similar study design, reported 2 implants failed in 1 subject in the immediate loading group for a CSR of 93%. A CSR of 100% was reported in a case series with 8 subjects and 16 implants by Roe et al. [93, 95]. These authors tested the same implant material used in the present study. Although immediate loading may provide similar CSR when compared to delayed loading, a trend toward a higher implant failure has been reported with immediate loading, as indicated in a recent systematic review and meta-analysis [96].

Implant primary stability is considered a very important factor when immediate loading is applied [8]. IT value correlates with implant primary stability [97] [98-100]. Also, IT is a function of the pressure needed to insert the implant in the osteotomy site and is
correlated to bone mineral density [101] [100] [98, 99]. Hence, we used IT as parameter to quantify implant primary stability and bone quality at time of insertion. Under-preparation of the osteotomy site was proposed as meaning to increase the IT value [57]. This technique was used in the present investigation to maximize primary stability. Some authors have raised concerns on the use of high insertion torque as possible cause of compression necrosis of the bone [102] [103]. However, animal and human studies have showed no detrimental effect of high IT (>50 Ncm) on peri-implant bone healing [104] [105] [106] [98]. The lower limit of IT to allow immediate loading of implants has not yet been determined. Ottoni et al. suggested an IT of ≥32 Ncm [107]. Norton et al. [108], reported a 100% CSR of implants immediately placed and loaded with single crowns in the aesthetic zone using an IT <25 Ncm. In our study the IT value between the groups was similar. The lower IT value used for IL was 20 Ncm. About 38% (12/32) of the implants in the IL group were placed with ≤30 Ncm IT and none of the implants placed with this IT value were lost. Furthermore, no correlation between IT values and loss of marginal bone was observed.

The use of long implants may help obtaining higher primary stability. Hence, implant length has been considered a critical factor for the success of immediate loading protocols. Several studies recommended implant length of at least 13 or 15 mm [85, 95, 97] when immediate loading of unsplinted implants is performed. In the present investigation we used implants at least 8 mm long with a diameter of 4 mm. In addition, the IL group had shorter implants when compared to the DL group. Fifty percent of implants placed in the IL group were <13 mm long and none were lost during the observation period. Furthermore, implant length did not correlate with RBLC 12 months
after placement. Hence, our findings do not support the use of long implants to increase clinical success with immediate loading protocols.

The primary outcome variable used in this study was RBLC. RBLC is a generally accepted parameter to assess implant success [109] [110] and bone response to occlusal loading [111]. The mean RBLC reported in this study for the IL group was 0.25 mm±0.5. This result is consistent with previous data obtained using OsseoSpeed™ implants [95] [112]. However, higher RBLC values were reported by others using different implant designs and surface configurations [84] [85] [94]. In our sample the number of implants presenting a RBLC <0.5mm was 57% and 87% in the DL and IL group, respectively. The number of implants with a RBLC <1mm was 87% and 94% for DL and IL groups, respectively. The implant design and the surface properties may in part explain the small RBLC in this study. The OsseoSpeed™-TX implants feature a switching platform connection. Several animal and human studies provide evidence that implants with switching platform connection showed significantly less RBLC [113]. Also, the micro-threaded design in the most coronal aspect of the implant may justify the improved marginal bone response. Orsini et al [60] showed the pitch of the implant threads seems to influence the osseointegration process: the smaller the pitch, the higher the bone to implant contact. Clinical trials indicated greater resistance to marginal bone loss and maintenance of bone levels when the micro-threaded design is extended to the neck of the implant [61, 62]. The fluoride-modified micro-rough implant surface used in this trial has shown improved bone to implant contact both in vitro and in animal studies [42] [37]. In particular, bone deposition seems to be increased during the early stage of
bone healing. Though, the enhanced early bone formation may have contributed to the small RBLC observed both in the DL and IL group.

When comparing the RBLC between IL and DL group, a statistically significant difference was observed. A smaller change of marginal bone level was recorded for the IL group. This result is consistent with previous data from our center evaluating immediate loading and conventional loading of implants supporting single crowns in the mandibular molar region [76]. Similarly, Assad et al. [114] reported significantly less RBLC for implants immediately loaded using a bar retained OVD when compared to conventional loading. These observations have been further confirmed in a recent meta-analysis reporting a statistically significant smaller RBLC on immediately loaded implants when compared to delayed loading [96]. A biological explanation of the positive effect of loading improving the initial phase of bone healing has been shown in both in-vitro and in-vivo studies [73] [72] [115] [116]. Qi et al. [72] evaluated the response of mesenchymal stem cells to mechanical strain and their consequent gene expression patterns. Their results suggested that mechanical strain might act as a stimulator to induce differentiation of stem cells into osteoblasts. Indeed, cyclic tensile strain has been shown to increase osteoprotegerin synthesis and decrease soluble receptor activator of nuclear factor kappa-B ligand (RANKL) [117], thus favoring bone formation. This theory was tested in a rabbit model by Duyck et al. [74], who concluded mechanical loading stimulated bone formation and led to higher bone fraction.

Our findings are in conflict with a recent randomized controlled study comparing 2 unsplinted implants supporting a ball retained mandibular OVD either loaded immediately or following conventional loading [94]. The implants loaded immediately presented
significantly higher bone loss in the distal and facial aspect when compared to the
delayed loading group after 1 and 3 years of function. These outcomes and our results
are difficult to compare since a different methodology was used to measure the bone
levels around the implants. In the previous study, the measurements of bone changes
were done on a multi-slice CBCT taken at 1 year and 3 years without a baseline
reference. When compared to standardized periapical radiographs, the use of CBCT
provides the advantage of detecting bone levels at the lingual and buccal aspect of the
implants. However, the measurements taken with this method should be interpreted with
cautions. Recent reports showed CBCT has limitations in detecting bone level around the
implant when bone thickness at the bone to implant interface is smaller than 0.8 mm
[118].

To optimize the clinical performance of implant supported OVD, the prosthesis should
have adequate soft tissue support and stable occlusion [119, 120] [84]. Many reports
indicate that maintenance requirements for implant supported OVD are higher during the
first year of function [121]. The main reasons for maintenance appointments were
contour modification and attachment repair or replacement [121]. One of the limitations
of our study is that dentures were fabricated with different techniques by outside
providers. This may explain the higher number of extra visits for denture adjustment
reported in this study when compared to others [95]. However, when evaluating the
number of maintenance visits between the IL and DL group, no difference was observed.
The number of maintenance appointments could have been reduced by using a more
consistent and controlled approach in the fabrication of the prosthesis.
7. Conclusions

Within the limits of the present trial, immediate loading of 2 unsplinted implants supporting Locator™ retained mandibular OVD seems to be a suitable alternative treatment option.

A significantly smaller RBLC after 1 year of loading was observed on IL implants when compared to implants placed with conventional protocol. However, this small difference may not be clinically relevant. Furthermore, in our sample neither implant length nor IT values seemed to have an effect on RBLC, 12 months after surgical placement. Further investigations are needed to confirm these results.

8. Bibliography


82. Kronstrom, M., B. Davis, R. Loney, J. Gerrow, and L. Hollender, A Prospective Randomized Study on the Immediate Loading of Mandibular Overdentures


