SELF-REPORTED PENICILLIN ALLERGY AND DENTAL IMPLANT THERAPY OUTCOME, A CLINICAL RETROSPECTIVE STUDY

by

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Abstract

Objectives: The histologic, clinical, and radiographic findings together indicated infection as a major etiology of implant failure. Antibiotics have been prescribed following implant surgery to control infection. Inability to take penicillin seems to be a determining factor in implants failure in particular, with certain types of implant-related procedures. The aim of this study was to investigate retrospectively whether self-reported allergy to penicillin contributes to higher rate of implant failure.

Methods: The survival of 5576 implants (985 Nobel Biocare and 4591 Straumann) placed surgically by an experienced periodontist was assessed in patients with the age range of 20-89 (mean: 60 years old) and with the follow-up period of up to 10 years. 4132 implants followed for at least one year. The survival was defined as the implant remaining in the jaw. Pearson $\chi 2$ test and Logistic regression were applied to examine the relation between pairs of variables. All tests were 2-tailed with a significance level of 0.05.

Results: Out of 5106 implants placed for patients taking penicillin, 0.8% failed, while out of 470 implants placed for patients with self-reported allergy to penicillin, 2.1% failed with statistically significant difference (P= 0.002). Odds of failure for implants placed in patients allergic to penicillin were 3.2 times higher than those for non-allergic patients while controlling for the other variables. Immediate implant placement in fresh extraction socket has 10-times higher rate of failure in patients with self-reported allergy to penicillin. Significant association between

smoking and implant failure was found (p=0.005). Implants in the area of second/third molars have the highest failure rate with more frequency in maxilla relative to mandible.

Conclusion: Inability to take penicillin may contribute to higher rate of implant failure and thus, penicillin allergy test could be implemented in clinical settings to increase the likelihood of prescribing penicillin relative to its alternates.

Preface

The contents in Chapters 3 and 4 are based on dental implants placed at Dr. David French's private periodontal office, in Calgary, Alberta. Dr. Batoul Shariati from the UBC Faculty of Dentistry completed the statistical analysis in chapter 3.

Ethics approval was provided by the Clinical Research Board of the University of British Columbia (Certificate number: H13-01664).

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List of Abbreviations

ASA American Association of Anesthesiologists

RN Regular neck

WN Wide neck

CI Confidence interval

CSR Cumulative Survival Rate

OR Odds Ratio

RR Relative Risk

HR Hazard Ratio

ISQ Implant Stability Quotient

IT Insertion Torque

IIP Immediate Implant Placement

DP Delayed Placement

Ncm Newton/Centimeter

DF David French

PENN Penicillin

GBR Guided Bone Regeneration

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I would like to thank my wife, Sara, for her love, kindness, patience and boundless support she has shown during the past three years it has taken me to finalize this thesis and the specialty program.

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Dedication

This work is dedicated to my wife Sara whose sacrifices, which were realized by our loss of precious time together, were for me the most painful and humbling of all.

Chapter 1: INTRODUCTION

The introduction of the "modern dental implant" to dentistry has revolutionized the approach to patient care. The edentulous patient with severely resorbed ridges for whom there were few to no viable treatment options or the patient who would require heroic and expensive dental treatment to save a single tooth, now have what has become successful and predictable alternatives to care[1]. A medical implant is defined as a device made from one or more materials that is intentionally placed within the body, either totally or partially buried beneath an epithelial surface[2]. Ancient recorded history documents the use of various materials to replace missing teeth such as teeth from other humans or animals, or those carved from animal tusks or seashells. One of the most significant archeological finds occurred in 1931 in Honduras by Dr. and Mrs. Wilson Popenoe. They discovered a fragment from a female Mayan mandible dating back to 600 A.D, which had tooth-shaped shells implanted into the sockets of three lower incisor teeth. From a radiographic analysis of the fragment, Professor Amadeo Bobbio described the presence of dense cortical bone encapsulating two of the shell teeth. He concluded that the shell teeth must have been placed while the Mayan woman was living, and not at the time of death as had been the ancient custom[3]. The first industrial implants were made from materials that consisted of gold, silver, platinum, aluminum, or porcelain[2]. These first implants caused foreign body reactions with the formation of fibrous tissue. The next generation of materials, used presently was made out of biocompatible materials which, osseointegrate and has high survival and success rates[2]. Osseointegration is characterized as "a direct structural and functional connection between ordered, living bone and the surface of a load- bearing implant"[2]. Modern dental implants have become increasingly a routine part of modern dentistry to provide anchorage for a

variety of prostheses to replace missing teeth. It is clear that dental implants can be a reliable method of replacing missing teeth. Light and electron microscopic studies have shown that dental implants have a high degree of biocompatibility to the surrounding hard tissues in the form of a direct structural and functional connection to the surrounding bone, known as osseointegration[4]. Endosseous implants of commercially pure titanium have been demonstrated to give success rates of more than 90 per cent over 10 years of follow-up. This high level of clinical function depends on an implant direct anchorage in bone without any interposed soft tissue layers and on a reaction-free soft tissue surrounding the abutments. Provided a correct protocol is followed, such osseointegrated dental implants may be looked upon as a routine procedure in the treatment of edentulism[5].

Several attempts have been made to define certain criteria to determine the survival and success of implant therapy based on clinical, histological and radiographic presentations. The terms survival and success have been used interchangeably in some literature. Albrektsson et al. in 1986 defined the criteria of successful implant therapy outcome as the absence of pain, mobility when tested clinically, radiolucency, peri-implant bone loss, suppuration and bleeding and presence of patient satisfaction[6]. Implant survival is often equated with implant success; however, survival has been defined as the implant remaining in the jaw and failure is defined as implant loss. Albrektsson et al. described implant success as immobility when tested clinically and vertical bone loss less than 0.2 mm/year after the first year[6]. Based on these criteria, the success rate for implants were 85% after the first 5 years and 80% after the first 10 years[6] . The survival rates of dental implants are found to be approximately 90% over 10 years and therefore are a predictable and effective treatment option for patients. However, many failures still occur

and several limitations still exist with respect to dental implants as a viable treatment modality; therefore, more comprehensive research is yet to be done in order to enhance implant therapy outcomes[7]. Metabolic disorders or immune deficiencies can give rise to surgical complications and may also interfere with bone apposition and/or remodeling at the implant–bone interface. Similarly, radiation therapy in the surgical area may significantly reduce cellularity and vascularity, and hence affect the healing of oral implants. In compromised patients, implant-based treatment may be a questionable choice[8].

The histologic, clinical, and radiographic findings together indicated that 3 major etiologies that might have been implicated in the failure processes: impaired healing ability of the host bone site, disruption of a weak bone-to-implant interface after abutment connection and infection in situations with complicated surgery[9]. Antibiotics have been prescribed either prophylactically or post operatively following implants surgeries to control infection and to enhance the success rate of the treatments especially when the surgical procedure is prolonged due to its difficulty, high number of implants placed or operator's inexperience[10]. Various types of antibiotics have been tried and empirically, penicillin has shown to be the most effective one against human oral microbiota[11,12]. Clinicians frequently withhold antibiotics that contain penicillin based on patients' self-reported clinical history of an adverse reaction to penicillin and the clinicians' own misunderstandings about the characteristics of a true penicillin allergy. Penicillin allergy seems to be a determining factor in implants failure in particular, with certain types of implant-related procedures such as bone grafting, lateral window sinus augmentation and immediate implant placement in fresh extraction socket[13] . Wallace et al. concluded that in more than 15 years of sinus grafting, more than 95% of observed or reported infections occurred in patients unable to

take penicillin due to self reported allergy and instead taking clindamycin[14]. In general, the sinus graft infection rate appears to be higher in penicillin-allergic patients[14]. Wagenberg et al. showed inability to take penicillin post-surgically as a risk factor for implant failure as they concluded patients unable to utilize postsurgical amoxicillin were 3.34 times as likely to experience implant failure as patients who received[13].

Only 10% to 20% of patients reporting a history of penicillin allergy are truly allergic when assessed by skin testing[15]. Taking a detailed history of a patient's reaction to penicillin may allow clinicians to exclude true penicillin allergy, allowing these patients to receive penicillin. Patients with a concerning history of type I penicillin allergy who have a compelling need for a drug containing penicillin should undergo skin testing. Virtually all patients with a negative skin test result can take penicillin without serious sequela[15,16,17].

The aim of the study is to investigate retrospectively the potential impact of inability to take penicillin prior to/following implant surgery on implants survival rates. The hypothesis is penicillin allergy may contribute to higher rate of implant failure, as patients taking penicillin alternatives may tend to develop higher implant failure rate. This study may indicate whether penicillin allergy test should be implemented in clinical settings prior to implant therapy to distinguish the true allergy from unproven allergy to increase the number of patients who can benefit from penicillin prescription and subsequently to improve the survival rate of implant therapy and minimize the failures due to infection.

Chapter 2: REVIEW OF THE LITERATURE

2.1 ANATOMICAL REVIEW

Buccal plate as a component of the alveolar process is very responsive to changes in the dental structure it supports[18]. Constant remodeling of the buccal plate (a combination of bone-resorption and bone-apposition processes) occurs to adapt to physiologic and pathological changes affecting the teeth, such as tooth eruption, natural or forced tooth movement, variable stress intensity and frequency, development of infection foci and surgical trauma[18]. The buccal bone plate is a structure comprised of an external (buccal) lining of cortical bone and an internal (oral) socket wall made of compact bone, also known as alveolar bone proper, and is identified as 'lamina dura' on radiographs. A core body of cancellous bone that lies between these two layers has been found to be generally thinner than its palatal/lingual counterpart and therefore more prone to osseous dehiscences and fenestrations and subsequent soft-tissue recession[19]. The oral component of the alveolar bone proper forms part of the tooth socket and is composed of bundle bone, which serves as an anchor point for the periodontal Sharpey's fibers. The presence of bundle bone relies on the presence of an adjacent tooth, and tooth loss or removal leads unavoidably to the loss of bundle bone and consequently to partial resorption of the buccal bone plate. The vascularization of the buccal bone plate originates from the superior and inferior alveolar arteries. The nourishing canals of those arteries run through the bony structures within the Haversian canals and the Volkmann canals. Anastomoses are frequent. Although several nerves run through the jaw bones or on its surface, the bone itself does not contain neural terminations[18].

Three different bone remodeling processes has been described that determines the dimensional changes of the alveolar bone under normal physiological conditions: bone remodeling following tooth extraction, bone remodeling due to surgical trauma and bone remodeling due to biologic width violation (saucerization)[18].

2.1.1 BONE REMODELING LEADING TO DIMENSIONAL CHANGES FOLLOWING TOOTH EXTRACTION

Cardaropoli et al. followed bone healing following tooth extraction in mongrel dog model. They reviewed histological sections made at days 1,3, 7, 14, 30, 60, 90, 120 and 180 postextraction. Day 1: the alveolus is filled by a coagulum covered with a layer of inflammatory cells. Day 3: the marginal part of the coagulum is replaced with vascularized granulation tissue. Day 7: zones of coagulative necrosis are present. Osteoclasts appear in the marrow spaces and in the Volkmann canals. Day 14: an outer layer of richly vascularized connective tissue appears. The periodontal ligament disappears. Day 30: a well-organized fibrous connective tissue lined by a keratinized epithelium is present. The socket is now filled almost entirely with newly formed bone. Day 60: a woven bone bridge, separating the socket from the marginal mucosa, appears. Day 90: the woven bone is in the process of being replaced with lamellar bone. Day 120: gradual replacement of the woven bone bridge with lamellar bone. Day 180: well-organized bone marrow holding a large number of adipocytes and few inflammatory cells is present. The formation of trabeculae of lamellar bone is starting. Marked bone resorption should be expected in proximity of intrasocket healing during this process[20]. Several studies have shown this bone remodeling mainly leads to horizontal bone reduction (5-7 mm) with more limited vertical reduction (2-4 mm)[21,22].

Sufficient alveolar bone volume and favorable architecture of the alveolar ridge are essential to obtain ideal functional and esthetic prosthetic reconstruction following implant therapy. Loss of alveolar bone may occur prior to tooth extraction because of periodontal disease, periapical pathology, or trauma to teeth and bone. Damage of the bone tissues during tooth extraction procedures may also result in bone loss. Alveolar bone resorption after tooth extraction is a well-known phenomenon[23]. Extraction of single or multiple teeth leads to changes in structure of the alveolar ridge. The consequent loss of teeth and change in function of the extraction site ultimately causes alterations of the edentulous alveolar bone[24]. Human re-entry studies showed horizontal bone loss of 29-63% and vertical bone loss of 11-22% after 6 months following tooth extraction. These studies demonstrated rapid reductions in the first 3-6 months that was followed by gradual reductions in dimensions[24]. Schropp et al. in 2003 studied bone formation in the alveolus and the contour changes of the alveolar process following tooth extraction. The tissue changes after removal of a premolar or molar in 46 patients were evaluated in a 12-month period by means of measurements on study casts, linear radiographic analyses, and subtraction radiography. The results demonstrated that major changes of an extraction site occurred during 1 year after tooth extraction[23]. Measurements taken immediately after the extraction, 3, 6 and 12 months following extraction showed that all vertical bone loss occurred over the fist three months after the tooth removal; however, two thirds of horizontal bone loss took place over the first three months with nearly 50% of the buccal-lingual width reduction at 12 months. The buccal plate was located about 1.2 mm apical to the palatal plate[23]. They found little or no change in regard to the changes in the vertical dimensions. On average there was a gain of 0.3 mm buccally and a loss of 0.8 mm orally. The reason that vertical bone deficiency was not

significant in Schropp study could be due to the fact that study was limited to single tooth extractions, with the neighboring teeth usually still being present. The presence of neighboring teeth is known to reduce extensive resorption in the vertical dimension[25,26].

An experimental study in dog evaluated the dimensional ridge alterations following tooth extraction. At 1 week, the marginal ridge of the lingual wall of the extraction socket was significantly wider at 1.4 mm, than the buccal wall at 0.6 mm. The buccal crest was found to be coronal to the lingual crest at this interval. At 2 weeks, newly formed bone was found at the apex of the extraction socket and at four weeks the lingual bone was wider than the buccal bone (1.6 mm and 0.7 mm respectively). Ultimately, at 8 weeks the lingual bone was significantly wider than the buccal bone and consistent with previous findings, the level of the buccal crest was 2 mm apical to the level of the lingual crest[27]. Marked dimensional alterations occurred during the early phase – 8 weeks – following the extraction of mandibular premolars. Marked osteoclastic activity resulting in resorption of the crestal region of both the buccal and the lingual bone wall occurred over this period of time. Vertical reduction of height was more noticeable at buccal plate comparing to the lingual plate[27]. This difference is linked to two factors: first, the thickness of the buccal plate, which is thinner than its palatal or lingual counterparts and thus has a greater tendency to show dimensional changes consequent to bone remodeling; and, second, the importance of bundle bone in the marginal segment of the buccal cortical plate, compared with a much reduced prevalence in the lingual plate[18]. The tooth is anchored to the jaws via the bundle bone into which the periodontal ligament fibers insert. Following the removal of a tooth, the bundle bone, as a part of periodontium, loses its function and subsequently is replaced by woven bone. The crest of the buccal plate is only composed of bundle bone compared to the lingual

plate. Rapid remodeling of the bundle bone after tooth extraction gives rise to significant vertical reduction in the buccal crest; as bundle bone presence hinges on presence of tooth[27].

Another animal study showed that the removal of a single tooth (root) during healing caused a marked change in the edentulous ridge with minor dimensional changes in the apical and middle portions of the socket site and substantial reduction of the hard tissue volume in the coronal portion of the ridge. It appears that the type procedure to remove the tooth, either flapless surgery or elevation of flap, did not significantly influence the long term healing outcome as comparable hard tissue loss was observed in both procedure[28].

Van der Weijden et al performed a systematic review of the human studies to assess the alveolar bone dimensional changes of post-extraction sockets in humans. During the post-extraction healing period, the weighted mean changes as based on the data derived from the individual selected studies show the clinical loss in width (3.87 mm) to be greater than the loss in height, assessed both clinically (1.67–2.03 mm) as well as radiographically (1.53 mm)[29].

A systematic review of post-extractional hard and soft tissue volume changes in humans by Tan et al in 2012 showed horizontal dimensional reduction (3.79 ± 0.23 mm) was greater than vertical reduction (1.24 ± 0.11 mm on buccal, 0.84 ± 0.62 mm on mesial and 0.80 ± 0.71 mm on distal sites) at 6 months. Percentage vertical dimensional change was 11–22% at 6 months. Percentage horizontal dimensional change was 32% at 3 months, and 29–63% at 6–7 months. Soft tissue changes showed 0.4–0.5 mm gain of thickness at 6 months on the buccal and lingual aspects. Horizontal dimensional changes of hard and soft tissue (loss of 0.1–6.1 mm) was more

considerable than vertical change (loss 0.9 mm to gain 0.4 mm) during observation periods of up to 12 months, when study casts were used to analyze the changes. Human re-entry studies showed horizontal bone loss of 29–63% and vertical bone loss of 11–22% after 6 months following tooth extraction. These studies demonstrated rapid reductions in the first 3–6 months followed by gradual reductions in dimensions[24].

Significant body of evidence reiterate the fact that substantial dimensional alteration in hard and soft tissue occurs following dental extraction with the greatest resorption on buccal aspect and in the first three months. These changes may hinder prosthodontically driven, ideal three-dimensional implant placement, which necessitates ridge augmentation prior to implant placement.

2.1.2 BONE REMODELING LEADING TO DIMENSIONAL CHANGES FOLLOWING SURGICAL TRAUMA

Several studies has shown that over course of surgery exposure of the alveolar bone during flap elevation will result in increase in osteoclastic activity and bone resorption with the mean crestal bone loss between 0.4 mm to 0.8 mm following full thickness flap elevation[30–36]. Partial thickness flap has been associated with increase in osteoclastic activity and bone remodeling but to lesser extent when compared to full thickness flap[18].

2.1.3 BONE REMODELING LEADING TO DIMENSIONAL CHANGES CAUSED BY BIOLOGICAL WIDTH VIOLATION

The concept of biological width has been applied to implants as well as to teeth[18]. That explains

how a constant distance has to be maintained between the base of the periodontal or peri-implant pocket/sulcus and the marginal bone crest to defend against pathological microorganisms and their toxic products Hence, it is advocated that whenever this biological width is violated, marginal bone would resorb in order to recreate an adequate safety distance. Likewise, it is believed that in healthy periodontium marginal bone resorption triggered by an external insult will cause soft-tissue recession in an attempt to reestablish biologic width. Unsupported soft tissues with no adequate underlying bone support tend to be more fragile and much more prone to recession in the event of trauma compared with their supported counterparts. The biological width around implants has been found to be slightly greater than that around teeth and about 3–3.5 mm in length, comprising a 2 mm junctional epithelium and a connective tissue of 1–1.5 mm. Furthermore, the presence of a thin mucosa, extrapolating an insufficient biological width, would unchangeably lead to spontaneous bone loss in order to reestablish the minimal biologic width encompassing junctional epithelium and connective tissue[37,18].

2.2 WOUND HEALING FOLLOWING IMPLANT PLACEMENT

2.2.1 PERI-IMPLANT SOFT TISSUE HEALING

Dental implants are surgically placed directly into native or regenerated bone as opposed to the natural teeth that develop in harmony with the surrounding periodontium. This limits the number of cell types that migrate to, attach and differentiate on the implant surface during healing[1]. Nonetheless, soft and hard tissue healing following implant placement lead to marginal soft tissue attachment and osseointegration. Marginal soft tissue adaptation plays a pivot role in establishing a mechanical seal between the oral environment and the bone surrounding

implant[38,39] which subsequently, is expected to prevent microbial organisms and contaminated products from the oral cavity environment to reach the underlying bone. Limiting migration of bacteria and bacterial products along the implant surface reduces the risk for peri-implantitis and implant failure. Additionally, a stable peri-implant soft tissue attachment, in the presence of bone support, has a critical impact on the long-term esthetic outcomes of implant therapy. In addition, it has been suggested that the attachment between the peri-implant soft tissue and the implant surface plays an important role in both establishment and maintenance of the desired soft tissue contour around dental implants[1]. Formation of the direct connection between the viable bone surrounding the implant with the implant titanium surface with the absence of interpositional connective tissue fibers provides solid mechanical support for the implant which enables implants to bear functional loads from dental prosthesis[1]. Ever since implant osseointegration is considered highly predictable, the focus has been directed toward achieving aesthetic outcomes through paying more attention to peri-implant issue structure and composition. In order to achieve predictable long-term tissue stability, functional, biologic and esthetic factors should be taken into account. A variety of clinical and radiographic parameters have been identified to predict and evaluate long-term success from biologic (stability and tissue health) and an esthetic (subjective and objective parameters) aspects[6,40,41.] Factors to be considered include: (i) the biologic width, (ii) the papilla height and the soft-tissue level (mucosal margin) on the buccal side of the implant, (iii) the amount of soft-tissue volume, (iv) the amount of keratinized tissue, and (v) the biotype of the mucosa[42]. Following implant placement a series of cellular and molecular events occur on the oral mucosa adjacent to the newly placed implant, leading to the formation of a peri-implant mucosa[1]. Berglundh et al. has shown in an animal study that immediately after implant placement, blood coagulum separates the implant surface from

osteotomy bony walls. Large numbers of neutrophils infiltrated and degraded the coagulum that occupied the compartment between the mucosa and the implant during the initial phase of healing. At 2 weeks after surgery, fibroblasts were the dominating cell population in the connective tissue interface but at 4 weeks the density of fibroblasts had decreased. Furthermore, the first signs of epithelial proliferation were observed in specimens representing 1-2 weeks of healing and a mature barrier epithelium occurred after 6-8 weeks of healing. The collagen fibers of the mucosa were organized after 4-6 weeks of healing. Migration and proliferation of epithelial cells lead to the formation of a peri-implant epithelium, which in turn, further lengthens the contact interface between the implant surface and the peri-implant mucosa. Maturation of the peri-implant mucosa occurs between 6 to 12 weeks following implant placement and is mainly characterized by formation of a mature epithelial barrier and organization and alignment of collagen fibers[43]. This sequence of healing events leads to the formation of a peri-implant mucosa. The peri-implant mucosal attachment to the implant surface is 3 to 4 mm high and consists structurally of a junctional epithelium supported by an underlying connective tissue coronal to the alveolar bone[44,]. Peri-implant mucosa has some common characteristics with dentogingival complex adjacent to natural teeth such as external well keratinized oral epithelium and non keratinized sulcular epithelium with 5-15 layers of basal and suprabasal cells tightly attached together through desmosomes[45]. Junctional epithelial cells flatten; align parallel to the long axis of the implant surface and attaches to the implant surface via hemidesmosomes[1]. Junctional epithelial attachment is likely to act as a physical barrier against microbial penetration. Moreover, epithelial attachment to the implant surface is expected to contribute to the stability of soft tissue contours around dental implants[1]. The connective tissue attachment is comprised of dense collagen fibers with scattered inflammatory cells and

fibroblasts. The direction of the collagen fibers is vertical extending from alveolar process and supra-alveolar periosteum up to the oral epithelium[46]. The zone of connective tissue attachment starts apical to the zone of junctional epithelium. This connective tissue is divided into inner and outer regions based on its composition and proximity to the implant surface[47]. The inner connective tissue zone with approximately 40 μm width lies adjacent to the implant surface and is formed from collagen fibers (65%), mostly originated from crestal bone in parallel or circumferential direction to the implant surface with no physical insertion into implant surface, fibroblasts (35%), and a small number of thin capillary-like vascular structures (0.2%). The outer layer consists of larger blood vessels with higher collagen fibers spreading in all directions and less number fibroblasts[47]. It has been demonstrated that thin peri-implant mucosa is associated with more underlying bone loss over the period of soft tissue healing around implants, most likely due to establish the biologic width[48,46,1].

2.2.2 PERI-IMPLANT HARD TISSUE HEALING

Placement of a dental implant into the alveolar bone is followed by a sequence of healing events that result in the establishment of osseointegration, characterized by a direct contact between vital bone and the implant surfaces[1]. Studies in animal models have shown that immediately after surgical placement of a dental implant, the peripheral part of the implant treads are in close contact with the recipient bone and thereby provide primary implant mechanical stability during the early phases of healing[49]. The space formed between the implant surface and the surrounding alveolar bone in osteotomy bed becomes occupied with a fibrin coagulum comprising erythrocytes, polymorphonuclear neutrophils, and few macrophages[50,51]. Debris of cortical and trabecular bone are frequently found at wound sites during early phases of healing, and

characterize remnant bone residues of osteotomy site. Osteogenic cells with micro blood vessels originated from adjacent alveolar bone penetrate the coagulum leading to formation of the granulation tissue[51,52.] First signs of bone formation has been demonstrated as early as 4 days after implant placement around hydrophilic implants (i.e. SLActive) that stimulate formation of a dense network of blood vessels [50]. Following one week of wound healing, bone debris with no osteocytes are still detectable immediately laterally to the implant pitch threads [53]. Osteoclasts migrate to these sites starting the process of osteoclastic resorption/remodeling of the boney fragments leading to their union into freshly produced woven bone[51]. Granulation tissue is subsequently replaced by provisional connective tissue matrix rich in osteogenic cells. A great portion of these cells line up parallel to the implant surface leading to formation of collagen bundles. A great percentage of these fibroblasts soon differentiate to osteoblast cells with ability to secret collagen fibers that mineralize[54]. Newly formed woven bone consisting of mineralized collagen fiber matrix associated with an inorganic (hydroxyapatite) matrix is deposited within the provisional connective tissue[54]. Most of the newly formed woven bone spreads from the existing old lamellar bone, in a development mentioned as appositional bone formation or distance osteogenesis[55], and is found in continuity with the surgical bone bed[43,51,52]. In distance osteogenesis, the recipient bone bed provides osteogenic cells that secrete a collagen-containing bone matrix, which grows, mineralizes and slowly progresses toward implant surface. Histological observation has shown newly formed bone in close proximity to the implant surface far away from the parent lamellar bone. This bone formation has been attributed to the contact osteogenesis, a process by which differentiating osteogenic cells, derived from perivascular connective tissue cells, migrate to the implant surface, differentiate into osteoblasts, and secrete a granular afibrillar organic matrix that provides nucleation sites for mineralization[55].

Davies et al has shown that peri-implant bone healing, which results in contact osteogenesis (bone growth on the implant surface), can be divided into three distinct phases that can be addressed experimentally. The first, osteoconduction, relies on the migration of differentiating osteogenic cells to the implant surface, through a temporary connective tissue scaffold. Anchorage of this scaffold to the implant surface is a function of implant surface design. The second, de novo bone formation, results in a mineralized interfacial matrix, equivalent to that seen in cement lines in natural bone tissue, being laid down on the implant surface. Implant surface topography will determine if the interfacial bone formed is bonded to the implant. Third tissue responses, that of bone remodeling, will also, at discrete sites, create a bone-implant interface comprising de novo bone formation[55]. After four weeks of wound healing the newly formed woven bone extends from the cut of the bone bed into the implant surface[51] occupying close to 30% of this distance[52,56,1]. The recently formed woven bone is increasingly remodeled and replaced over the course of one to three months by lamellar bone encompassing bone marrow adipocytes, blood vessels, collagen fibers and insignificant amounts of leukocytes [1,50,56,57]. As the volume occupied by the mineralized tissue increases from the early to the late phases of healing, the volume occupied by lining osteoblasts and osteogenic mesenchymal cells gradually decreases[45]. Moreover, increases in tissue mineralization occurring over the course of the healing are accompanied by rises in the bone to implant contact [52], which allows for the functional loading of implants. Villar et al. indicated that bone does not interface the entire length of the implant and that the presence of 100% bone-to-implant contact is inconsistent with results from preclinical and clinical studies[1]. Bone modeling and remodeling continues at a slow rate over the first year of implant placement and contributes to higher implant resistance to shear

forces[54]. This continuous process of bone modeling and remodeling is regulated by the local mechanical stress, as loading regulates proliferation and differentiation of osteoblasts and the bone healing process[1].

Based on a recent structured review of the literature concerning molecular assessment of osseointegration at the level of cell-surface topography interactions, growing body of evidence supports the role of surface topography in the direct influence of cellular phenotypes as linked to process of osseointegration[58]. Particular topographic hints can be specifically incorporated among the many extracellular signals received by the cell in its signal transduction network. Links between the character of the implant surface and adherent cellular responses, including cells from extravasated blood such as platelets and of the immune system like monocytes have been defined by functional and mechanistic investigations[58]. These interactions may affect cellular adhesion, survival, proliferation, differentiation, matrix formation, bone mineralization and resorption[58]. Application of platelet-rich fibrin increased implant stability during the early healing period supported by higher ISQ values indicating faster osseointegration[59].

2.3 ALVEOLAR RIDGE PRESERVATION/ AUGMENTATION

One of the main criteria for osseointegration and long-term success of implant therapy is presence of adequate volume of bone in horizontal and vertical direction for ideal three dimensional implant placements. As discussed earlier, alveolar bone resorption is the inevitable sequelae of tooth loss[23]. In situations where the bony walls of socket remains intact following tooth extraction and the alveolar dimension is adequate for ideal implant insertion, ridge preservation using a variety of biologic material is indicated. In the presence of large defects in

the bony walls of socket such as presence of extensive fenestration or dehiscence, guided bone regeneration may be indicated by reflection a larger flap and placing a biologic membrane beyond the boundaries of the bone defect. It has been suggested in the literature that buccal bone thickness less than 2 mm following extraction of the tooth may disappear due to loss of the bundle bone and hence, ridge preservation is indicated. Ridge preservation can also prevent sinus pneumatization in the area of maxillary molars in particular when multiple teeth are extracted. This is another indication for the ridge preservation procedure in the posterior maxilla in molar area despite the fact that the buccal bone thickness may remain thick enough following extraction socket healing[60]. Rasperini et al in a clinical study examined the effect of ridge preservation on sinus pneumatization. In the experimental group, the maxillary molar sockets were preserved using the anorganic bovine bone and collagen sponge and in the control group there was no ridge preservation was done. One out of 6 sites in the test group required sinus augmentation prior to implant placement while 3 out of 8 sites in the control group had to get sinus augmentation to enable standard implant placement[61].

Various techniques have been used to augment the bone horizontally and vertically including but not limited to guided bone regeneration using autologous, allogenic, xenogenic and synthetic biomaterial, split ridge technique, distraction osteogenesis, sinus augmentation and interpositional and onlay block graft to reconstruct the bone deficiency.

The best-documented and most widely used method to augment bone in localized alveolar defects is guided bone regeneration. Based on a series of experimental studies, a biological principle of periodontal tissue regeneration was discovered by Nyman & Karring in the early

1980s[62]. Based on their studies, cells, which first inhabit a wound area, determine the type of tissue that eventually dominates the original space. From this knowledge, they developed a technique, utilizing barrier membranes, which prevented unwanted cells from reaching the wound and, at the same time, allowed cells with the capacity to produce the desired tissue to reach the wound space. This technique was termed guided tissue regeneration and it led to novel possibilities to regenerate periodontal tissues, including new root, cementum, periodontal ligament and alveolar bone[62,63,64]. Soon after, guided tissue regeneration was directed toward regeneration of bone. Several animal and human studies have shown successful methods of bone augmentation using the same principle. Different variety of bioactive agents and biologic materials have been indicated for guided bone regeneration including but not limited to autogenous (taken from same patient), allograft (bone harvested from cadaver), xenograft (bone from animals usually bovine) and alloplastic (synthetic bone)[65,66].

2.3.1 LONG TERM RESULTS

Several studies have shown that survival rate of implants placed in augmented sites either before the implant placement or concurrently with implant insertion is comparable to the implant survival in native bone[67,68]. Hammerle et al. performed a systematic review to assess the survival rate of implants placed in GBR sites in partially edentulous patients[68]. The majority of the studies in the systematic review showed higher than 90% of implant survival in grafted bone at least one year or even more in function[68]. Nonetheless the survival rate of implants placed in augmented bone is comparable to those placed in native bone, however, the long-term stability of the augmented bone has not been studied in details.

Chiapasco et al. in 2012 evaluated survival and success rates of Straumann bone level implants placed in alveolar ridges augmented by autogenous cortical only bone grafts and to analyze related complications. 18 subjects in good general health presenting with severe vertical atrophy of ridges participated in the study. Autogenous only bone grafts were harvested from ramus or calvarium. 4-7 months after grafting, 60 Straumann bone level implants were placed in the grafted sites. 2-3 months after that, healing abutment and prosthesis was placed. Inclusion/exclusion criteria were pre-established (eg. inadequate space for 6mm implant). Documentation included periapicals, panoramic and CT. Prophylactic and post op antibiotics were given. Depending on the size of defect, bone was harvested from either ramus (for smaller defects) or calvarium (larger defects). Bio- Oss was used to fill spaces between grafted and native bone. Membrane was used to cover bone blocks to reduce resorption. 4-7 months after reconstructive surgery, second surgery was done for screw removal and implant placement. Cover screws were placed and primary closure achieved. Clinical parameters including bone resorption, implant survival and success were evaluated. Albrektsson criteria were used for success of implants. Mean resorption of grafts prior to implant placement was 0.42 mm for ramus and 0.18 for calvarium. All 60 implants were osseointegrated successfully and prosthetically loaded. Follow up after prosthetic loading was 12-36 months (mean follow up of 19 months). Mean peri-implant bone resorption was 0.52 mm for ramus and 0.41 mm for calvarium. Implant survival rate was 100%. Implant success rate according to Albrektsson criteria was 90.3% for implants placed in calvarial grafts and 93.1% for ramus grafts[69].

2.4 DENTAL IMPLANTS: DEFINITION OF SURVIVAL AND SUCCESS

Dental implants are increasingly becoming the mainstream treatment to replace missing teeth. Since Branemark's research in 1967 validated the concept of osseointegration defined as "a direct functional and structural connection between living bone and the surface of a load carrying implant"[70], there has been numerous studies on the longevity and predictability of dental implants. Various authors have suggested different criteria to outline the success of implant therapy. In many studies the term success and survival are being used interchangeably. They report the implant success criterion in terms of survival rate meaning implant remains physically in the jaw. While the proponents of this method believes this is the most objective criterion to define implant success, others debate that implants in need of removal due to presence of peri-implant diseases or pain are improperly reported as success[71].

One of the most commonly accepted success criteria for dental implants which is distinguishable from survival is the Albrektsson's criteria which define successful implant therapy when the implant is immobile when checked clinically; no evidence of periapical radiolucency is present around the implant; implant does not show greater than 0.2 mm bone loss annually after first year in function and implant is not associated with pain and/or discomfort[6]. Having said that the success criteria remain difficult to describe.

The consensus conference of the international Congress of Oral Implantologists in 2008 introduced the ICOI Pisa Implant Quality of Health Scale based on implant clinical evaluation. This scale enables practitioners to assess dental implants based on the listed criteria and to classify implants in category of health or disease and subsequently treat them accordingly. Based

upon this consensus three major categories are defined as success, survival and failure. While implants in the ideal clinical conditions (health) belong to the category of success, functional implants in less than ideal conditions belong to the category of survival and implants which need to be removed or have been already explanted are defined as failure[71]. There are four groups of implants based on the clinical demonstrations. Group I in optimal health is defined as implants with no pain or tenderness upon function, 0 mobility, < 2mm radiographic bone loss from time of surgery and no history of exudation. Group 2 is defined as satisfactory survival described as no pain on function, 0 mobility, 2-4mm radiographic bone loss with no history of exudates. Group III is defined as compromised survival with possible sensitivity on function, greater than 4 mm bone loss but less than ½ of implant body and with probing depth >7mm and possible history of exudates. The failure group is outlined as presence of any of these clinical parameters: mobility, pain on function, radiographic bone loss > ½ length of implant, uncontrolled exudate and no longer in mouth[71]. More clinical studies are yet to be done to confirm the sensitivity and specificity of these groupings. Crestal bone loss is common after implant placement and loading, and traditional criteria defining implant success permitted 1 to 1.5 mm of bone loss during the first year following loading and 0.2 mm annually thereafter[72].

2.5 PERI-IMPLANT BONE LOSS

2.5.1 EARLY IMPLANT BONE LOSS (EIBL)

Initial breakdown of the interface between implant and surrounding hard and soft tissue occurs at the crestal region regardless of the surgical protocol (submerged or non-submerged). Oh et al. defined the early implant bone loss as resorption of peri-implant crestal bone occurring from the

time of fixture placement to one year after the prosthetic loading[73]. They categorized six etiological factors that plausibly could explain the early peri-implant bone loss[73]. These six factors can be divided into two major groups: biological and biomechanical etiologies[74]. The biological factors are: 1) surgical trauma and subsequently healing response, 2) biologic width formation, 3) micro-gap/junction effect and 4) peri-implant infection (peri-implantitis). The biomechanical factors include 1) occlusal overload and 2) implant crest module[73, 74].

2.5.1.1 BIOLOGIC ETIOLOGIES

2.5.1.1.1 SURGICAL TRAUMA

Surgical trauma has been mentioned one of the main reasons of the implant failure. Implants could become encapsulated by fibrous connective tissue or apical proliferation of junctional epithelium, leading to lack of osseointegration and consequently implant failure. Heat generated at the time of implant placement, elevation of periosteal flap and disproportionate pressure at the crestal bone when inserting implant may contribute to bone loss during the healing period[73]. Eriksson and Albrektsson in 1984 defined the critical bone temperature of 47º C for 1 minute or 40º C for 7 minutes above which overheating of the bone is highly likely leading to implant failure[75]. Overheating of the bone may occur at the crestal region by applying excessive pressure, most likely due to heavy forces during the insertion of implant[76]. However, some studies have questioned the impact of high insertion torque on implant failure. Elevation of mucoperiosteal flap has been mentioned as a contributing factor for the crestal bone loss around implant. Mean 0.8 mm of horizontal bone loss has been reported in dental literature following periodontal surgery with raising the full thickness mucoperiosteal flap[77]. The reparative capability is greatly

dependent on the amount of cancellous bone under the existing cortical bone[77].

2.5.1.1.2 BIOLOGIC WIDTH FORMATION

Gargiulo et al study on cadavers showed constant dimension of dentogingival complex consisting of 3 components: gingival sulcus (mean depth of 0.67 mm), epithelial attachment (0.97 mm in average) and connective tissue attachment (1.07 mm in average) around natural teeth[73]. Likewise, the soft tissue around implants consists of epithelial attachment and connective tissue as a biologic seal to prevent the bacterial insult and food debris ingress into the implant-bone interface. The collagen fibers are parallel to the implant surface with less vascularity as opposed to the perpendicular collagen fibers attached to root surface with higher vascularity. The epithelial attachment is made of hemidesmosomes and basal lamina (lamina lucida and lumina densa zone) around natural teeth and implants with weaker adhesion around implants and abutments[73]. Following exposure of implants to the oral cavity, crestal bone loss occurs to establish the biologic width around the implant. The amount of bone loss to establish the biologic width varies based upon factors such as the thickness of peri-implant mucosa, the relative position of the polish-rough interface of non submerged implants to the crestal bone level and also the relative location of the microgap to the crestal bone. However, all the crestal bone loss cannot be attributed to the biologic width establishment[73].

2.5.1.1.3 MICROGAP EFFECT

Implant placement is generally divided in two categories: submerged (two stage) or non submerged (one stage). In two-stage protocol the implant is fully covered by overlying soft tissue and is exposed to oral cavity following completion of osseointegration. In one-stage protocol

implant is exposed to the oral cavity through the presence of healing abutment or provisional crown. Following the connection of the abutment to the implant platform, a microgap exists at or below the crestal bone. Microbial species cultivated from the internal surface and restorative components of the submerged implants were found and they were mainly coccoid cells (86.2%) and non-motile rods (12.3%). Motile organisms (1.3%) or spirochetes (0.1%) were only sporadically registered. This microbial contamination origin was linked to the microbial leakage from the area of the abutment-implant interface leading to peri-implant infection[78]. 0.5 mm of inflamed connective tissue below and above the implant-abutment gap with presence of 0.5 mm crestal bone only two weeks after the placement of abutment was documented in dental literature[44]. The crestal bone level is highly dependent on the relative location of the microgap to the bone crest at the time of implant placement. When two-piece matched implants are exposed to the oral environment, due to presence of microgap, 1-5-2.5 mm of vertical bone loss and 1.5 mm of horizontal bone loss can be observed radiographically 4 weeks after the insertion of the abutment[79]. Hermann et al has shown that the implant-abutment microgap has direct effect on peri-implant crestal bone loss independent of surgery protocols due to bacterial contamination of internal cavity of implants regardless whether one stage or two stage surgery protocol was used[79]. This study suggested that apical migration of epithelium to establish the biologic width could be the reason for the crestal bone loss found about 2 mm below the microgap[79].

2.5.1.2 BIOMECHANICAL ETIOLOGIES

2.5.1.2.1 OCCLUSAL OVERLOAD

As opposed to natural teeth, which are surround by periodontal ligament with shock absorbing

and mechanoreceptor function, osseointegrated implants are directly ankylosed to bone. The marginal bone can be a fulcrum of the lever movement when a bending force is applied to the implant. As a result, implants are subject to more crestal bone loss due to mechanical forces[73]. A retrospective clinical study by Rangert et al. has specified potential causal factors associated with excessive occlusal overload on implants such as posterior prosthesis supported by one or two implants, substantial deviation of the implant alignment from the line of action, high crown/implant ratio, excessive cantilever length, discrepancy in dimension between the occlusal table and implant platform and presence of parafunctional habits[96]. Compact cortical bone is believed to have least resistance against the shear forces caused by overbending forces potentially leading to progressive marginal bone loss and even deosseointegration[97]. An experimental animal study has shown loss of osseointegration due to occlusal overloads and significantly more marginal bone loss around those implants remained osseointegrated but was subjected to occlusal overload. They concluded occlusal overload and peri-implant infection are causative factors for implant failure[98]. The impact of occlusal overload on marginal bone loss and implant failure is debatable as the literature shows controversial results based upon on the amount, direction and duration of forces applied with or without presence of inflammation[73]. A histological study in monkeys evaluated the influence of the controlled occlusal overload on peri-implant tissues. All monkeys were subject to excessive 100 μm superstructure leading to occlusal overload for the a period of 4 weeks in the absence of any tissues inflammation due to providing good oral hygiene. They found no gross bone loss around the implants subject to occlusal overload for a period of 4 weeks in the absence of inflammation[99] . The same group has shown that peri-implant marginal bone loss occurs significantly when the height of the superstructure exceeds 100 μm. Thy concluded the threshold of the excessive superstructure

height at which the peri-implant tissue breakdown due to occlusal overload begins is 180 μm even in the absence of any clinical inflammation[100]. The final report from the same group concluded that the coexistence of occlusal overload and inflammation or severe occlusal overload alone intensify the peri-implant bone resorption[101]. Biomechanically, titanium has 5 times higher modulus of elasticity compared to the alveolar bone, leading to significant stress contour increase in the interface of the implant and bone with consequent crestal bone loss phenomenon most likely due to micro-fractures in the immature peri-implant bone[73].

2.5.1.2.2 IMPLANT CREST MODULE

Crest module is the transosseous part of the implant which s subject to crestal stress after the implant loading. Different types of crest module have been designed around the modern implants. Cortical bone is strongest to compressive forces, 30% weaker to tensile stress and 65% weaker to shear forces compared to compressive forces. Smooth, parallel-sided crest module may contribute to shear stresses whereas, angled crest module more than 20º with surface micro-texture (with subsequent increase in bone-implant contact) may provide combination of compressive and tensile stress contributing to decrease in the risk of bone loss[102].

Hermann et al. have showed benefits of rough surface textured crest module on crestal bone preservation. In their study, implants were divided into two groups; in group 1, the interface of the smooth and rough surface placed at the crestal bone and in the other group the interface was placed 1.5 mm apical to the crestal bone. 6 months later the bone level around the implants with smooth-rough interface at the crestal bone remained at the original height whereas 1.5mm bone loss occurred around the implants with smooth-rough interface below the crestal bone[79].

2.5.2 PERI-IMPLANT INFECTION: PERI-IMPLANTITIS

Peri-implant mucositis is defined as reversible inflammatory reaction confined to the peri-implant mucosal tissues with no evidence of bone loss. Peri-implantitis is associated with bone loss around dental implants with presence of deep pockets, bleeding on probing and suppuration[73]. Mombelli et al has described the clinical features of peri-implantitis including radiographic demonstration of vertical destruction of peri-implant crestal bone, formation of peri-implant pockets in association with radiographic bone loss, bleeding after gentle probing possibly with presence of suppuration, mucosal swelling and redness and no pain[103]. Peri-implantitis has been defined as site-specific infection with common microbiota with chronic periodontitis[104]. Microbiota associated with healthy implants are scarce and mostly consists of coccoids, whereas microbiota obtained from failing implants consists of large proportion of gram-negative anaerobic rods with black pigmented Bacteroids and Fusobacterium species[104]. Study by Lee et al examined the impact on the peri-implant microbiota of crown restorations; implant type; length of time of loading; history of implant or periodontal infections; and whether implants replaced single or multiple teeth in 43 partially edentulous subjects[105]. They concluded history of periodontitis has more significant impact on peri-implant microbiota compared to implant loading time. The microbiota associated with remaining teeth significantly impacted the composition of the peri-implant microbiota. Despite implants osseointegration, the red complex periodontal pathogens e.g. P.gingivalis and T. Forsythus associated with the remaining teeth colonized several implants[105]. An experimental animal study has shown greater, faster tissues destruction around implants compared to natural teeth in a ligature induced tissue breakdown. The parallel direction of the collagen fibers in peri-implant mucosa with no adhesion to the

implant surface and also less vascularity of the peri-implant mucosa have been suggested to explain the more rapid and pronounced pattern of tissue breakdown around implants in comparison with natural teeth[106]. Although Peri-implantitis is affecting implants in long run; it may not be justified that peri-implantitis is the main causative factor for early bone loss around implants since the rate of bone loss is dramatically reduced following the first year of prosthetic loading[73].

2.6 TIMING OF IMPLANT PLACEMENT

Since the implant therapy has grown dramatically over the past two decades, several different treatment-timing approaches have been suggested. Immediate implant placement into fresh extraction socket has been advocated to reduce the number of surgeries and overall treatment time in addition to decrease in patient morbidity[91] and also to preserve the height and width of alveolar ridge at the extraction site[92,93] and possibly to place implants in ideal position[94] and to achieve optimal soft tissue aesthetics[92] . On the contrary, there is some evidence indicating that immediate implant placement into extraction socket may be adversely affected due to presence of infection at site, absence of tissue closure and flap dehiscence over the extraction socket in particular, when concomitant guided bone regeneration is being done using barrier membranes. Thin tissue biotype with inadequate volume of soft tissue[95] and the presence of gap between implant body and socket bony walls due to incongruity of implant body shape and socket morphology may adversely affect the implant therapy outcome[96]. Having said that, majority of studies agree that implant osseointegration, survival rate and the interdental bone is not negatively affected by immediate implantation; however, there are few studies reporting on outcome on peri-implant soft tissue health and aesthetics. In order to minimize the consequences

of these issues, different timing protocol has been suggested in different intervals from the time of tooth extraction[96].

2.6.1 CLASSIFICATION OF TIMING OF IMPLANT PLACEMENT AFTER TOOTH EXTRACTION

There have been some variations in terms of classification of implant timing. Hammerle et al. recommended a classification based on desired clinical outcome during healing rather than restricted descriptive terms on rigid time frames[97] . They introduced four type of implantation protocol[97]:

Type I (Immediate): immediate Implant placement into fresh extraction socket concurrently with extraction with no healing of either soft tissue or bone.

Type II (Immediate-delayed) (typically 4-8 weeks of healing): Implant placement following substantial soft tissue healing and before any clinically significant bone fill in the socket.

Type III: (Typically 12-16 weeks of healing). Implant placement following clinically and radiographically significant bone fill in the extraction socket.

Type IV (Late: more than six months after extraction): Implant placement in fully healed extraction socket.

2.6.2 ADVANTAGES AND DISADVANATEGES OF IMPLANT PLACEMENT TIMING

With immediate implant placement right after the extraction of tooth, the number of surgical procedures and overall treatment time is reduced; there is possibility of providing the provisional restoration at the same visit pending adequate implant primary stability. The gap between the

implant and socket is considered 2-3 wall intrabony defects, which is amenable to regenerative therapy; however, immediate implant placement is more technically demanding due to morphology of socket and implant-socket dimension discrepancy. There is an increase risk of mucosal tissue recession on buccal aspect with dire esthetic consequences and loss of facial bone contour. If primary soft tissue closure is desired for instance, when extensive buccal bone augmentation is required, lack of soft tissue increases the difficulty of obtaining tension free closure. Coronal advancement of the flap to acquire the flap primary closure alters the mucoginival junction location with subsequent aesthetic dilemmas. Bone remodeling following dental extraction is unpredictable[97].

In Type II (4-8 weeks following extraction), substantial soft tissue healing has taken place with increase in tissue volume leading to easier flap manipulation/advancement to cover the bone graft and barrier membranes. In the period of 4-8 weeks, slight flattening of the facial bone is observed which facilitates flap advancement and augmentation of the buccal bone with low-rate bone substitutes and tension free primary closure. Due to absence of bone fill in the extraction socket the challenge of implant placement in correct position with adequate primary stability remains.

In Type III protocol, with clinically and radiographically substantial bone fill in the extraction socket, surgical placement of implant with adequate primary stability is more readily attainable; significant increase in soft tissue volume with more predictable tension free primary closure is available. The defect around the implant is amenable for regeneration. The extended healing time allows for extended healing of pathological defects/infections to take place. However, significant

amount of bone remodeling and turnover takes place during this period, which may hinder implant placement in ideal position impossible without extensive bone regeneration.

In the type IV protocol, substantial bone loss occurs in the extraction area which increases the likelihood of insufficient bone for implant placement necessitating extensive bone regeneration procedures[97.]

Several studies have reported the success and survival of implants placed with different timing protocol. In a systematic review on survival and success rates of implants placed immediately into fresh extraction socket following first year, a total of 46 prospective studies with mean follow up of 2 years were included. Survival was defined as implants remaining in situ at the follow-up examinations, irrespective of their conditions. Failure was defined as implants that were lost after immediate implant placement. The estimated annual failure rate of implants placed in extraction sockets was 0.82% (95% CI: 0.48–1.39%) corresponding to a 2-year survival rate of 98.4% (97.3–99%). Among the five factors analyzed (reasons for extraction, antibiotic administration, implant location [anterior vs. posterior, maxilla vs. mandible), loading protocol), only the regimen of antibiotic use impacted the survival rate statistically significantly. The annual implant failure rate was lower after 5–7 days postoperative antibiotic course (0.51%) compared to a single dose of pre-operative antibiotics (1.87%) ($P = 0.002$)[98]. 20% of patients receiving immediate implant placement with delayed restoration experienced suboptimal aesthetic outcomes due to buccal soft tissue recession in studies with 3 years of follow-up or more. One randomized clinical trial showed immediate restoration in cases of immediate implantation may prevent buccal mucosal recession; however, further studies are indicated and

the effects of tissue biotype and buccal-lingual position of implant on buccal soft tissue level should not be underestimated[98]. 110 immediate implants with no bone grafting in 72 patients were evaluated retrospectively 5 years after the insertion. 105 implants had uneventful healing with 4 implants were lost in the first three months and one implant failed one year after the first year of functional loading of the prosthesis with the estimate survival rate of 95.5%[99] . In a prospective randomized study in 50 patients, 25 implants placed immediately into extraction socket (IP) and 25 implants were placed after healing period of three months (DP). Two implants in the IP group failed with survival rate of 92% for the IP group versus 100% for the DP with no statistical significance. Immediate implant placement was considered a viable option, however, the delayed protocol may be preferred in aesthetic zone due to buccal mucosal recession. The implant success, radiographic implants bone level one year after the loading and mean ISQ was not associated with presence of periapical micro flora of the extraction socket[100]. Block et al. evaluated the soft and hard tissue response to immediate implant placement and assessed the crestal bone level in immediate implant group versus delayed implant group. 76 patients were randomized in two treatment groups. In the experimental group an anterior maxillary tooth was extracted followed by immediate implant placement and immediate provisionalization and in the control group, an anterior maxillary tooth was extracted followed by socket grafting and implant placement after period of 4 months of healing. Periapical radiographs were taken at baseline and every 6 months for the period of 2-year follow-up. Crestal bone response to delayed or immediate placement of implant with immediate provisionalization in the anterior maxilla was comparable; however, there was 1mm less buccal soft tissue recession in the group of immediate placement and immediate provisionalization. Immediate extraction followed by immediate provisional preserved the buccal soft tissue 1 mm more than the control group[101]. In a Cochrane

systematic review by Esposito et al., immediate, immediate-delayed and delayed implants were assessed in terms of success rate, complication rate, aesthetic outcome and patient satisfaction. Fourteen eligible RCTs were identified but only seven trials could be included. Four RCTs evaluated implant placement timing. Two RCTs compared immediate versus delayed implants in 126 patients and found no statistically significant differences. One RCT compared immediate-delayed versus delayed implants in 46 patients. After 2 years, patients in the immediate-delayed group perceived the time to functional loading significantly shorter, were more satisfied and an independent blinded evaluator judged the level of the peri-implant marginal mucosa in relation to that of the adjacent teeth as more appropriate (RR = 1.68; 95% CI 1.04 to 2.72). These differences disappeared 5 years after loading, and significantly more complications occurred in the immediate-delayed group (RR = 4.20; 95% CI 1.01 to 17.43). One RCT compared immediate with immediately delayed implants in 16 patients for 2 years and found no differences. In the three RCTs evaluated different techniques of bone grafting for implants immediately placed in extraction sockets, no statistically significant differences were detected. There was no statistically significant difference among various bone augmentation materials. The systematic review reported insufficient evidence to conclude the possible advantages or disadvantages of immediate, immediate-delayed or delayed implants. There is a suggestion that immediate and immediate-delayed implants may be at a higher risk of implant failure and complications than delayed implants, on the other hand the aesthetic outcome might be better when placing implants right after extraction[102.]

Several studies have shown comparable survival rate, marginal bone level, prosthetic complication rate and probing depth level between implants placed immediately into the fresh

extraction socket and delayed implant placement in the healed ridge for the period of 1-5 years of follow-up [101,103,104,105] . Therefore, with proper case selection, immediate implant placement into fresh extraction socket seems to be a viable alternative to the traditional protocol.

2.7 IMPLANT LOADING TIME

One of the major advantages of immediate implant placement is decrease in overall treatment time; however implants need a period 3-6 months of healing for osseointegration which delays the process of delivering the function, aesthetic and phonetics to patients and may discourage patient acceptance of implant therapy[106]. Different loading protocols have been presented in the dental literature. The 2004 consensus statements define immediate restoration (IR) as insertion of prosthesis within the first 48 hours subsequent to implant placement with no occlusion with opposing dentition, whereas immediate loading (IL) is insertion of the restoration within 48 hours following implant placement in occlusion with opposing dentition. Based on this system of classification, early loading is insertion of the prosthesis anytime from 48 hours to less than three months following implant placement[107]. Weber et al in 2009 classified the protocol of loading as follows: Conventional loading is defined as implant loading greater than two months following implant placement. Early loading is defined as loading after the first week but not later than two months following implant placement. Immediate loading is defined as loading the implant within the first week following implant placement[108] .

Several clinical studies have shown comparable predictability of both conventional and early loading in implant survival[109,110,111]. The rational for conventional loading was providing undisturbed environment for implant integration to the bone. It was assumed that

micromovements as little as 100-150 micrometers[112] caused by loading implants during the critical period of initial healing might lead to fibrous encapsulation and subsequent implant failure[106]. Better implant designs leading to higher primary stability and better understanding of the osseointegration process has led to faster loading protocols[106]. Increase in number of implants, splinting, reduction in lateral forces and avoiding loads beyond the threshold above which implant healing is disturbed have been recommended to optimize the condition of implant immediate loading[106].

A prospective randomized comparative study evaluated the 2 year success rates of implants with the immediate provisionalization with occlusal loading (40 patients) versus implants with immediate provisionalization without occlusal loading (40 patients) versus delayed loading with one stage implant surgery protocol (37 patients). All implants were at least 10 mm long with the insertion torque of minimum 30Ncm and ISQ of greater than 60. Smokers, subjects with parafunctional habits (bruxism and clenching) and cases with severe interocclusal discrepancies with potentially unfavorable implant-crown ratio were excluded. 209 implants were immediately loaded in 80 patients with splinted provisional restorations. The two-year success rate was 93% (7 implant failures) for the implants with the immediate provisionalization with occlusal loading and 100% for the other two groups. The mean crestal bone loss was 1.2 mm with no statistically significant difference among the three groups. They concluded implants with immediate provisionalization has comparable success rates to implants with delayed loading only when not loaded in occlusion[113].

A prospective multicenter clinical study evaluated the success rate of immediate functional

loading of single implant in the area of second premolars[114]. In the test group 1, immediate functional loading of implant followed the conventional drilling osteotomy. In the test group 2, osteotome bone condensation/preparation was used followed by immediate functional restoration. In the control group conventional loading protocol was done three months after the insertion of the implants. Antibiotic prophylaxis with 1 gram Augmentin was administered in all patients. The minimal primary stability of 20 Ncm was achieved for implants from all groups. 5.5% of implants failed in the test group 2 (osteotome protocol) whereas 2% failures occurred in the test group 1 (conventional drill protocol) with no statistically significant difference in marginal bone loss among the all three groups. This study concluded that the immediate functional loading of single implants that are placed with conventional drill protocol could be as an acceptable alternative to delayed loading protocol for single implant in the premolar area as long as adequate primary stability is achieved[114.]

A split mouth randomized controlled study with thirty patients compared single short (7 mm) immediately occlusal loaded implants inserted surgically with no flap elevation with single short implants loaded at 6 weeks with a 5-year follow-up. No baseline differences in the bone quality implant diameter and position was noted between the two groups. A minimum of 40 Ncm torque was required for loading. Overall, two implants failed (one in each group) within the first two months after loading. There were no statistically significant differences for bone levels at loading and following 6 months of loading between the two groups. Even though the study sample size was small, results imply that immediate and early loading of even short implants can provide favorable results[115].

Comparable conclusions were proposed by Merli et al. in a randomized controlled trial comparing immediately restored implants in conjunction with flapless surgery (test group) with early loading implants (6 weeks) (control group) up to one year following loading. They concluded optimal clinical result might be achieved with non-occlusal immediate loading in selected patients[116].

In a systematic review of 26 randomized controlled trials including over 1200 subjects by Esposito et al. in 2012, no evidence of difference in prosthesis failure or implant failure between the immediate versus conventional loading protocol (after three months) was observed at the end of one year follow-up. A slightly better marginal bone preservation favored immediate loading in long term with some heterogeneity; however, the difference was too small to have any clinical significance. There is insufficient evidence of difference in prosthesis failure, implant failure or marginal bone loss when early and conventional loading protocols were compared together[117].

In a recent systematic review and meta analysis, 10 randomized controlled trials were meta analyzed to evaluate the annual failure rate and peri-implant marginal bone level changes of immediate loading (within 24 hours of implant placement) compared to conventional loading (greater than three months after implant placement). Only RCTs with at least one year of follow-up, minimal 20 subjects and accurate documentation of implant survival and bone level changes were considered for review. The annual failure rate was 2.3% and 3.4% for conventionally and immediately loaded implants, respectively, with no statistically significant difference (relative risk of 0.82). In terms of marginal bone level changes, the weighted mean difference was statistically significant only at the end of the year 5 follow-up in favor of conventional loading

(0.3mm P< 0.05); however, the weighted mean difference was not statistically significant for the combined period of 5-year follow-up (P>0.05). No clinically significant differences in implant failure and radiographic bone level changes can be detected up to 5 years of follow-up between conventionally loaded and immediately loaded implants[118] .

Adequate primary stability (insertion torque in the range of 20-45 Ncm and/or implant stability quotient values ≥ 60 to 65), adequate implant length/diameter, absence of large bone defects, the timing of implant placement, smoking, and the absence of parafunctional habits were common criteria in selecting a loading protocol[119].

2.8 IMPLANT PRIMARY STABILITY

Primary stability of the implant is considered a paradigm in achieving osseointegration. Primary stability is defined as engagement of the implant with the surrounding bone. Factors that may influence the primary stability could be attributed to bone quality and quantity, surgical technique, implant geometry, thread form and surface morphology[120,112]. The implant primary stability has been depicted as insertion torque or implant stability quotient (ISQ); however, there is no consensus with respect to optimal insertion torque or ISQ value. 32 N/cm of torque and/or ISQ value of ≥60 have been suggested as an indication of adequate primary stability.

Bone quality is often referred to as the amount of alveolar cortical and cancellous bone[112]. The bone quality can be evaluated radiographically and during implant osteotomy site preparation. Bone quality has been categorized into four different types defined by Leckholm and Zarb (1985): Type 1 = a thick cortical bone with entire jaw is comprised of compact bone; Type 2 = a thick layer of compact bone surrounding a core of dense trabecular bone; Type 3 = a thin layer of

cortical bone with a core of dense trabecular bone; Type 4 = a thin layer of cortical bone with a core of poor density trabecular bone[112]. Type 4 bone has been mainly associated with lower insertion torque and subsequently higher rate of osseointegration failure due to presence of more spongy bone with more tendencies for bone resorption and impaired healing[121]. Posterior maxilla tends to have more type 4 whereas, more type 1 and 2 in mandible. This difference can explain the higher implant failure rate in maxilla relative to mandible[122]. It is more difficult to obtain high insertion torque in type 4 bone due to lower bone density[123].

Meredith et al. described a non-invasive method whereby bone formation around an implant could be studied in vivo by measuring the resonance frequency of a small transducer to an implant fixture. The transducer is vibrated by exciting one of the piezo elements with a sinusoidal signal, the response being measured by the second element. The resonance frequency is registered as the peak when frequency is designed against the amplitude of the received signal.

A clinical tool was developed to analyze resonance frequency by using a new unit called implant stability quotient (ISQ). ISQ replaces hertz, which is dependent on the transducer used, and is recorded as a number between 1 and 100, 100 representing the highest degree of stability. Transducers are manufactured for specific implant types and calibrated by the manufacturer. ISQ levels for successfully osseointegrated implants are reported from 57 to 82, with a mean of 69 ISQ after 1 year of loading[124].

A total of one hundred twenty implants were placed in fresh bovine bone of three different densities representing hard, normal and soft categories. Insertion torque was assessed at five

categories (20, 35, 45, 70 and 100 N/cm). The authors concluded that in soft bone, the implants could not be placed at an insertion torque of 35 N/cm's or higher. The higher insertion torque was associated with lower level of implant micromotion. This meant that high micromotion was steadily found in soft bone, which could explain the lower survival rates found in the maxilla[123].

A study was designed to substantiate whether there was a correlation between implant stability quotient (ISQ) values, maximum insertion torque values, angular momentum and energy. 81 dental implants of two different designs in 41 patients were evaluated using ISQ values. Maximum insertion torque values were obtained during the placement procedure. A linear correlation between ISQ values and maximum insertion torque values at the initial implant surgery was found (P<0·01). There was a correlation between ISQ values and angular momentum (P<0·05). This study suggested that both ISQ values and new methods to calculate angular momentum and energy can help to predict implant stability[125].

A retrospective study aimed to assess the fitness of three stability factors - namely, insertion torque (IT), implant stability quotient (ISQ; measured by resonance frequency analysis), and Periotest (PT) values - as potential predictors for the risk of osseointegration failure of immediately loaded splinted implants. 105 implants immediately loaded in 19 patients in 11 edentulous and 8 partially edentulous maxillas. The IT and ISQ (IT 25.0 ± 12.5 Ncm and 8.4 ± 2.3 Ncm; PT -1.5 ± 3.0 and $+2.7 \pm 3.0$; and ISQ 62.6 ± 6.7 and 54.7 ± 6.2) differed significantly between the osseointegrated and failed implants ($p < .005$). The IT showed the greatest specificity at a sensitivity of 1 and the greatest area under the curve (AUC; 0.929), followed by the PT value (AUC = 0.836) and ISQ (AUC = 0.811). Among these three parameters

studied, insertion torque showed the highest specificity at a high sensitivity of 1. Therefore, insertion torque can be suggested the most valid prognostic factor for osseointegration of immediately loaded splinted dental implants[126].

An in vitro investigation on dry human mandible to determine the intra- and inter-examiner reliability and validity of the instrumental assessment of primary dental implant stability, using resonance frequency analysis (RFA) was performed with sixteen tapered implants and 16 cylindrical implants inserted in eight unfixed dry human mandibles. Implant stability quotients (ISQ; the outcome variable of RFA) and peak removal torque were recorded. Both the intra-observer reliability and the inter-examiner reliability of the RFA measurements were fair-to-good, while no significant correlations between the ISQ values and removal torque were found. The removal torque of the cylindrical implants was higher than that of the tapered implants. The smallest detectable difference was almost nine ISQ units. They concluded primary dental implant stability can be gauged reliably with RFA measurements, the concomitant validity between RFA measurements and removal torque is poor, cylindrical implants may be more stable than tapered ones and two subsequent readings of RFA measurements should differ at least nine ISQ units for statistically significant difference[127].

A study to determine the correlation between the measurements of implants stability using resonance frequency analysis (RFA) and histomorphometric analysis of bone-implant contact was done in animal models. Ten adult female foxhounds received a total of 80 implants in their mandibles 3 months after removal of all premolar teeth. At the time of implant placement, torque required for bone tapping was registered as a measure of bone density and immediately after

placement implant stability was measured using RFA. RFA measurements were done again at the time of implant retrieval after 1 month (5 dogs) and 3 months (5 dogs). Bone-implant interface was assessed histomorphometrically by measuring bone-implant contact (BIC) and the peri-implant bone volume density (BVD). RFA values at the time of implant placement did not correlate with the torque required to tap the bone for implant placement. After 1 and 3 months, RFA values were significantly increased compared with baseline values. BIC and BVD, however, had increased significantly during this interval. There was neither correlation between bone-implant contact and RFA values nor between peri-implant bone density and RFA values. It was concluded that the validity of the individual measurement of implant stability using RFA should be considered with caution[128].

A prospective case series study evaluated 4114 consecutive SLA Straumann implants to evaluate the predictability of implant stability assessment either clinically or by resonance frequency analysis (RFA). Primary stability was classified in four categories, depending on the degree of implant rotation when tightening the healing cap: A (no rotation at all), B (light rotation with a feeling of resistance), C (rotation without resistance) and D (rotation and lateral oscillation). RFA method was also used the day of the surgery (Osstell 1) and at restoration placement (Osstell 2). Survival rates were stratified according to the clinical classification categories using life table analysis. 3899 implants were classified as stable (A) and 213 as unstable (B-D). Their survival rates were 99.1% and 97.2%, respectively. The unstable implants were further classified in B (158), C (51) and D (4), with survivals of 98.1%, 94.1% and 100%, respectively, being these differences statistically significant ($P<0.009$). Using Osstell, implants were stratified in two groups according to a predefined threshold of implant stability quotient ≥ or <60. At the Osstell 1

measurement, there was no significant association between primary stability and implant survival (P<0.753). In Osstell 2, however, the association was significant (P<0.001). The authors concluded only secondary stability RFA values at the time of restoration placement were able to significantly predict implant outcomes, but not primary stability values[129].

It seems there is controversy in terms of the relation between implant osseointegration and primary stability and the presence of correlation between RFA values and implant stability.

2.9 RISK FACTORS ASSOCIATED WITH IMPLANT FAILURE

In a recent review by Chrcanovic et al., reasons for implant failure has been divided into two categories[130]: primary failure refers to implants which never osseointegrated. Poor surgery and overheating of the bone has been defied as the causes of primary failure. Frequency of such failures is considered small (1-2%). Secondary failures refer to loss of implants over the time of function due to peri-implant bone loss. The reason for onset of marginal bone loss around implants is not clearly known. Some authors have been suggested that any marginal bone loss after the first year of clinical function of implant must be related to peri-implantitis. On the contrary, the other group of authors believes marginal bone loss is not a disease phenomenon but rather, it is a complication of the treatment. Infection around implants is secondary to marginal bone loss caused by poor surgical handling, improper implant design/surface, and improper patient selection for implant therapy. Retained cements, rapidly changing loading protocols and patients with untreated disease or complex metabolic conditions have been mentioned as the other reasons for initiation of bone loss with subsequent infection around the implants if these conditions are not treated[130].

Since the introduction of implants as a viable option to replace missing teeth, there have been some indication and contraindication criteria for implant therapy defined in the literature in order to achieve and maintain osseointegration. Buser et al. divided the contraindications in two groups of local and systemic/medical. They also subdivided the group of systemic/medical contraindications into two separate groups: the first group is patients at very high risk, because of the serious systemic diseases such as rheumatoid arthritis, osteomalacia, osteogenesis imperfecta, immunocompromised patients (e.g. HIV and patients on immunosuppressive drugs), drug abusers and non compliant patients. The second group is patients with significant risk including patients with history of radiotherapy leading to irradiated bone, uncontrolled severe diabetes (in particular type I), patients with bleeding disorders (hemorrhagic disorders/anticoagulant therapy) and patients with heavy smoking[131].

In an 8-year follow-up study from 2004 to 2012, a total of 13,147 implants were placed in 4,316 patients at the Academy for Oral Implantology in Vienna. The implant survival rates after 8 years of follow-up were calculated using the Kaplan-Meier method, and the impact of patient- and implant-related risk factors was evaluated. Overall implant survival was 97% and was not associated with length or diameter of implant, jaw location (maxilla versus mandible), implant position (posterior or anterior), local bone quality, history of guided bone regeneration. Patient-related factors such as osteoporosis, age or diabetes mellitus did not statistically influence the survival of implants. However, smoking increased the risk of implant failure by 3-folds ($P<0.001$) and a positive history of periodontal disease doubled the failure risk ($P=0.001$)[132].

A systematic review and Meta analysis performed by Strietzel et al. investigated the impact of smoking on prognosis of dental implants compared with non-smokers[133]. The Meta-analysis revealed a significantly enhanced risk for implant failure among smokers [implant-related odds ratio (OR) 2.25, confidence interval (CI (95%)) 1.96-2.59; patient-related OR 2.64; CI (95%) 1.70-4.09] compared with non-smokers. Implants accompanied by bone augmentation procedure were associated with more failure compared to none smokers. The systematic review suggested significantly higher risks of biologic complications among smokers. Smoking is considered a significant risk factor for implant therapy and bone augmentation procedures[133].

Bornstein et al. in a systematic review evaluated the effects of systemic conditions as risks for dental implants. In their review, smoking has been associated with early implant failure and higher overall implant failures[134]. However, one study suggested that in heavy cigarette smokers, presence of a particular IL-1 gene complex polymorphism is associated with an increased risk for peri-implant bone loss following prosthetic reconstruction and during the supportive periodontal care, whereas presence of each of these factors (smoking or IL1 polymorphism) alone is not associated with the peri-implant bone loss[135]. Smoking has been associated with higher implant failure rate and postoperative complications such as spontaneous implant exposure.

Schwartz-Arad et al. studied 261 patients receiving dental implants and they divided the patients to three different groups: non-smokers, mild smokers (less than 10 cigarettes per day) and heavy smokers (greater than 10 cigarettes per day). The overall failure rate of implants in smokers was 4% versus 2% in none-smokers and complication rate of 46% in smokers versus 31% in non-smokers[136].

In a systematic review by Klokkevold et al., the potential influence of smoking, diabetes and periodontitis on implant therapy outcome was investigated[137]. Based on review of 35 articles, which met the inclusion criteria of the review, they concluded smoking has statistically significant adverse effects, in particular in areas of loose trabecular bone, on implant survival. No significant difference was found between implant survival in patients with and without diabetes. Similarly, no difference in implant survival was found between the groups of patients with history of treated periodontitis in comparison with patients with no history of periodontitis. Having said that, presence of history of periodontitis may have a negative impact on implant success rate especially over long period of time. However, the conclusion of this systematic review should be reviewed with caution due to limited number of studies included and heterogeneity of methodology in the included studies. Smoking, diabetes mellitus and bone metabolic disorders can impair wound healing capacity and bone turn over.

In a systematic review, smoking and history of periodontitis have been identified as risks for implant therapy with smoking as a significant risk for adverse implant outcome such as increased risk of peri-implantitis in smokers compared with non-smokers (odds ratio 3.6-4.6)[138,139]. Combination of smoking and treated history of periodontitis increases the risk of implant failure and peri-implant bone loss. Higher incidence of marginal bone loss around implants was noted in smokers compared with non-smokers and this trend was more significant in maxilla. Diabetes Mellitus is not an absolute contraindication for implants as several studies have shown comparable survival rates of implants placed in diabetic patients to the implants placed in healthy individuals[140,141]. Poor glycemic control is not always associated with implant success but

adversely affects the bone to implant contact necessitating longer period of healing. Patients with HbA1c ≥8.1 had the maximum decrease in primary stability observed 2-6 weeks following implant placement[142] .

2.10 SMOKING AND PERIODONTAL DISEASE

Periodontal disease is considered to be an infective disease as a result of interactions between the dental biofilm and the host responses, which may be modulated by genetic, environmental and acquired risk factors. Tobacco smoking has also been associated with periodontal disease and greater risk of severe periodontal attachment loss. 40-60% of chronic periodontitis cases might be attributed to smoking, with an increased odds ratio of 5.4 for chronic periodontitis in smokers. Periodontitis in smokers has different presentations when compared with none-smokers including but not limited to deeper probing depths, more deep pockets and more attachment loss, including more gingival recession[143.] Smokers also have more alveolar bone loss and more teeth with furcation involvement[144]. Smokers also tend to have a higher level of tooth loss than non-smokers after adjusting for oral hygiene, age, gender, and socio-economic level[145]. The effect of smoking on the periodontal tissues is dose-dependent[146]. Smokers still had more disease and more severe attachment loss even after adjusting the oral hygiene levels[147]. A study by Hanioka et al. showed that tobacco smoke contains carbon monoxide, leading to decrease the oxygen saturation of hemoglobin in healthy gingiva. Oxygen tension was significantly reduced in pockets in smokers favoring the growth of anaerobic bacteria even in the shallower pockets. Smoking extends a favorable habitat for periodontal pathogens such as *Porphyromonas gingivalis*, *Aggregatobacter actinomycetemcomitans* and *Prevotella intermedia* in shallow pockets of less than 5 mm[148]; however, the literature is contradictory with respect to difference in

microbiota between smokers and non-smokers. More studies has shown that smoking has chronic effects on impairing vasculature that harm healing by influencing revascularization. Smoking does not manifest its effects simply through vasoconstriction. Smoking alters the host immuno-inflammatory response to the bacterial insult leading to more severe periodontal breakdown[149]. Less bleeding on probing and less gingival redness is evident in smokers[150]. The animal study by Benatti et al. has shown the smoking is associated with lower rate of bone repair and acceleration of reduction in bone height[151]. Smoking affects host response to the periodontal pathogens. Increase in number of neutrophils in blood circulation and reduction in neutrophils in gingival sulcus has been shown in some studies[152,149]. Neutrophil-derived proteolytic enzymes, particularly MMPs and elastase, increase significantly in tobacco smokers. Phagocytosis and chemotaxis of neutrophils are also impaired by nicotine[149]. Different components of cigarettes may have immunostimulatory or immunosuppressive properties. Experimental animal studies have shown that tobacco smoke affects both humoral and cell-mediated immunity[153]. The B cell function in peripheral blood was impaired in smokers, as reflected by a decrease in proliferative response to polyclonal B cell activators and antigens. Tobacco smoke also affects fibroblasts, connective tissue matrix and bone. Proliferation, migration, matrix production, and attachment to surfaces of fibroblasts were reduced in smokers[154]. Smokers demonstrate less favorable responses to different types of periodontal treatments including non-surgical, surgical, regenerative and mucogingival procedures. Less probing depth reduction and less attachment level gain was achievable following non-surgical treatments in smokers[143,149]. One study also showed that smokers have a less favorable treatment response to non-surgical periodontal treatment, even with adjunctive use of antibiotics owing to impaired healing capacity[155]. It is believed that host immuno-inflammatory response rather than quality of microbiota is more

accountable for the less favorable treatment outcome in smokers[149]. The effect of smoking on the periodontium is reversible on smoking cessation. Gingival bleeding was significantly increased following smoking cessation, which refers to the recovery of the inflammatory response. The odds ratio for having severe periodontitis is reduced after quitting smoking. Smoking cessation may also restore the normal healing response. The treatment response was found to be similar in former-smokers and nonsmokers[149].

2.11 ANTIBIOTIC THERAPY IN CONJUCTION WITH IMPLANT SURGERY

The histologic, clinical, and radiographic findings together indicated that 3 major etiologies that might have been implicated in the early failure processes: impaired healing ability of the host bone site, disruption of a weak bone-to-implant interface after abutment connection and infection in situations with complicated surgery[9]. A group of dental implant failures may be due to bacterial contamination at implant insertion. Though a number of factors can ultimately lead to the failure of dental implants, most practitioners take extra precautions regarding infection[152]. With the mouth being an inherently "dirty field", with a multitude of flora, the incidence of bacteremia is also high. The aim is to prevent the onset of infection in the surgical wound by achieving an antibiotic concentration in the blood that will prevent bacterial proliferation and dissemination[157]. Infections around biomaterials are difficult to treat, and almost all infected implants have to be removed. The benefits of prescribing antimicrobials are, however, limited by a number of problems associated with their use for example, side effects, allergic reactions, toxicity and more importantly the development of resistant strains of microbes[158]. In general, antibiotic administration in surgery is only indicated for patients at risk of infectious endocarditis; with reduced host-response; when surgery is performed in infected sites; in cases of

extensive and prolonged surgical interventions; and when large foreign materials are implanted[65]. A variety of prophylactic systemic antibiotic regimens have been suggested to minimize infections after dental implant placement. More recent protocols recommended short-term prophylaxis, if antibiotics have to be used. Adverse events may occur with the administration of antibiotics, and can range from diarrhea to life threatening allergic reactions. Another major concern associated with the widespread use of antibiotics is the selection of antibiotic resistant bacteria.

The use of prophylactic antibiotics in implant dentistry is controversial. Antibiotics have been prescribed either prophylactically or post operatively following implants surgeries to control infection and to enhance the success rate of the treatments especially when the surgical procedure is prolonged due to its difficulty, high number of implants placed or operator's inexperience[10]. Various types of antibiotics have been tried and empirically, Penicillin has shown to be the most effective one against human oral microbiota[12]. It is clear that the anti-microbial agents should be effective against the bacteria causing any infection. These bacteria include aerobic streptococci, anaerobic gram-positive cocci and anaerobic gram-negative rods. Furthermore, the anti-microbial should be bactericidal and non-toxic. Taking these guidelines into consideration, penicillin is the first choice antimicrobial for prophylaxis in dental implant surgery. The use of prophylactic antibiotics in dental implant surgery remains controversial with different studies reporting conflicting data on their efficacy[10]. In an overview of 5,000 patients in 1997, Dent et al. reported that the risk for implant failure of osseointegration during healing (stage I) and at stage II surgery (uncovering) was two to three times higher if no prophylactic antibiotics were given preoperatively[159].

Esposito et al. conducted a Cochrane systematic review to assess the beneficial or harmful effects of systemic prophylactic antibiotics at dental implant placement versus no antibiotic/placebo administration and, if antibiotics are of benefit, to find which type, dosage and duration is the most effective. Four randomized controlled clinical trials were identified: three comparing 2 g of preoperative amoxicillin versus placebo (927 patients) and the other comparing 1 g of preoperative amoxicillin plus 500 mg four times a day for 2 days versus no antibiotics (80 patients). The meta-analyses of the four trials showed a statistically significantly higher number of patients experiencing implant failures in the group not receiving antibiotics: risk ratio=0.40 (95% confidence interval (CI) 0.19 to 0.84). The number needed to treat (NNT) to prevent one patient having an implant failure is 33 (95% CI 17-100), based on a patient implant failure rate of 5% in patients not receiving antibiotics. The other outcomes were not statistically significant, and only two minor adverse events were recorded, one in the placebo group. They concluded there is some evidence suggesting that 2 g of amoxicillin given orally 1 h preoperatively significantly reduce failures of dental implants placed in ordinary conditions. No significant adverse events were reported. It might be sensible to suggest the use of a single dose of 2 g prophylactic amoxicillin prior to dental implant placement[160]. In a systematic review by Esposito et al. in 2008 two RCTs were identified: one comparing 2 g of preoperative amoxicillin versus placebo (316 patients) and the other comparing 2 g of preoperative amoxicillin 500 mg four times a day for 2 days versus no antibiotics (80 patients). The meta-analyses of the two trials showed a statistically significant higher number of patients experiencing implant failures in the group not receiving antibiotics: RR = 0.22 (95% CI 0.06 to 0.86). The number needed to treat (NNT) to prevent one patient having an implant failure was 25 (95% CI 13 to 100), based on a

patient implant failure rate of 6% in patients not receiving antibiotics. The other outcomes were not statistically significant, and only two minor adverse events were recorded, one of which was in the placebo group. As a result they concluded there is some evidence suggesting that 2 g of amoxicillin given 1 hour preoperatively significantly reduce failures of dental implants placed in ordinary conditions. It remains unclear whether postoperative antibiotics are beneficial, and which is the most effective antibiotic. It might be recommendable to suggest the use of one dose of prophylactic antibiotics prior to dental implant placement[161]. A prospective double-blind randomized controlled trial by Nolan et al. was conducted to test the effect of prophylactic antibiotics on post-operative morbidity and osseointegration of dental implants. Fifty-five subjects scheduled for implant surgery were enrolled. The patients were randomly assigned to the antibiotic (test group) and placebo (control group). Twenty-seven patients (test group) received three grams of amoxicillin one hour pre-operatively, and twenty-eight patients (control group) received placebo capsules one hour pre-operatively. No post-operative antibiotics were prescribed. The patients kept pain and interference with daily activities diaries for one week post-operatively. Signs of post-operative morbidity (swelling, bruising, suppuration and wound dehiscence) were recorded by the principal investigators at day 2 and day 7 following the operation. Osseointegration was assessed at second stage surgery or 3–4 months post-operatively. The results of this study suggest that the use of prophylactic pre-operative antibiotics may result in higher dental implant survival rates (100% vs. 82%). Five implant failures, one in each of five patients, were reported in the placebo group and none in the antibiotic group ($P = 0.0515$). No significant differences were found for most of the signs of post-operative morbidity 2 and 7 days post-operatively. Only bruising at 2 days following the operation appeared to be higher in the placebo group ($P = 0.0511$). Post-operative pain ($P = 0.01$) and interference with

daily activities (P = 0.01) appeared to be significantly lower for the antibiotic group after 7 days. Those patients with implant failure reported higher pain (based on the VAS scores) after 2 days (P = 0.003) and after 7 days (P = 0.0005), higher pain (based on the amount of analgesics used) after 7 days (P = 0.001) and higher interference with daily activities (based on the VAS scores) after 2 days (P = 0.005). They concluded pre-operative prophylactic antibiotics appears to improve implant survival in the short term and also results in less post-operative pain and interference with daily activities[10].

The Cochrane systematic review in 2013 investigated six RCTs with 1162 participants; three trials compared 2 g of preoperative amoxicillin versus placebo (927 participants), one compared 3 g of preoperative amoxicillin versus placebo (55 participants), one compared 1 g of preoperative amoxicillin plus 500 mg four times a day for two days versus no antibiotics (80 participants), and one compared four groups: (1) 2 g of preoperative amoxicillin; (2) 2 g of preoperative amoxicillin plus 1 g twice a day for seven days; (3) 1 g of postoperative amoxicillin twice a day for seven days, and (4) no antibiotics (100 participants). The overall body of evidence was considered to be of moderate quality. The Meta analyses of the six trials showed a statistically significant higher number of participants experiencing implant failures in the group not receiving antibiotics (RR 0.33; 95% CI 0.16 to 0.67, P value 0.002, heterogeneity: Tau2 0.00; Chi2 2.87, df = 5 (P value 0.57). The number needed to treat for one additional beneficial outcome (NNTB) to prevent one person having an implant failure was 25 (95% CI 14 to 100), based on an implant failure rate of 6% in participants not receiving antibiotics. There was borderline statistical significance for prosthesis failures (RR 0.44; 95% CI 0.19 to 1.00), with no statistically significant differences for infections (RR 0.69; 95% CI 0.36 to 1.35), or adverse

events (RR 1; 95% CI 0.06 to 15.85) (only two minor adverse events were recorded, one in the placebo group). No conclusive information can be derived from the only trial that compared three different durations of antibiotic prophylaxis since no event (implant/prosthesis failures, infections or adverse events) occurred in any of the 25 participants included in each study group. There were no trials that evaluated different antibiotics or different antibiotic dosages. In general, antibiotics are beneficial for reducing failure of dental implants placed in ordinary conditions. Specifically 2 g or 3 g of amoxicillin given orally, as a single administration, one hour preoperatively significantly reduces failure of dental implants. No significant adverse events were reported. It might be sensible to suggest the use of a single dose of 2 g prophylactic amoxicillin prior to dental implant placement. It is still unknown whether postoperative antibiotics are beneficial, and which antibiotic is the most effective[65].

Wagenberg et al. in 2006 evaluated implant survival rates of 1925 immediately placed implants (IIP) into fresh extraction sockets to determine risk factors for implant failure. They showed inability to take penicillin post-surgically as a risk factor for implant failure as they concluded patients unable to utilize postsurgical amoxicillin were 3.34-times as likely to experience implant failure as patients who received amoxicillin[13]. Patients with an allergy to penicillin (8.52% of failure) were 5.7-times more likely to experience implant failures due to infection than patients without allergy to penicillin (2.95% of failure)[13].

Lambert et al. evaluated the influence of smoking on the survival of 2887 implants. At 36 months of follow-up, implants in smokers failed 14.9% of the time when pre-operative antibiotics were not given or given at an insufficient dosage. The failure rate in nonsmokers or

those who quit smoking was 7.5% of the time when not given antibiotics pre-operatively. Smokers not given prophylactic antibiotics were nearly three times more likely to develop implant failures than those who received pre-operative antibiotic coverage. The failure rate for both smokers and non-smokers/quit individuals was the same, decreasing to 4.7% when prophylactic antibiotics were administered[162].

A retrospective chart review was conducted of all patients in whom IIP was performed between January 1988 and December 31, 2004. Treatment required atraumatic tooth extraction, IIP, and mineralized freeze-dried bone allograft with an absorbable barrier to cover exposed implant threads. Implant failure was documented along with time of failure, age, gender, medical history, medications taken, postsurgical antibiotic usage, site of implant placement, and reason for implant failure. Statistical analysis was performed using chi-square and logistic regression analysis methods. A total of 1925 IIPs (1398 machined-surface and 527 rough-surface implants) occurred in 891 patients. Seventy-one implants failed to achieve integration; a total of 77 implants were lost in 68 patients. The overall implant survival rate was 96.0% with a failure rate of 3.7% pre-restoration and 0.3% post-restoration. Machined-surface implants were twice as likely to fail as rough-surface implants (4.6% versus 2.3%). Men were 1.65-times more likely to experience implant failure. Implants placed in sites where teeth were removed for periodontal reasons were 2.3-times more likely to fail than implants placed in other sites. Patients unable to utilize postsurgical amoxicillin were 3.34-times as likely to experience implant failure as patients who received amoxicillin. They concluded penicillin allergy seems to be a determining factor in implants failure in particular, with certain types of implant-related procedures such as bone grafting, lateral window sinus augmentation and immediate implant placement in fresh extraction

socket. Factors such as the ability to use postsurgical amoxicillin and reason for tooth extraction should be considered when treatment planning for IIP[13].

Wallace et al. concluded in more than 15 years of sinus grafting, more than 95% of observed or reported infections occurred in patients taking clindamycin. In general, the sinus graft infection rate appears to be higher in penicillin-allergic patients[14].

Ahmed et al. in 2012 conducted the literature review and comparison of survival rates of dental implants with regimens of no, pre or post prophylaxis using electronic databases. Retrospective or prospective controlled studies were examined for the influence of preoperative and/or postoperative or no antibiosis on dental implant success rate. Of the 11406 implants used in this literature review, cases with no antibiotics had a 92 % success rate, cases with pre-op antibiotic alone had a 96% success rate, and cases with post-op antibiotic alone had a 97% success. The results from this literature review showed ≥ 95% success rate when antibiotics are used compared to when they are not used[163].

Bafail et al. performed a systematic review including four randomized clinical trials to assess the effects of antibiotics on implant failure and postoperative infection. Based on the result of this Meta analysis, antibiotic use significantly lowered the implant failure rate (P = 0.003), with an odds ratio of 0.331, implying that antibiotic treatment reduced the odds of failure by 66.9%. The number needed to treat (NNT) to prevent one patient from having an implant failure was 48 (95% confidence interval 31-109)[164,165].

A recent systematic review and meta analysis by Chrcanovic et al. in 2014 was conducted to investigate the effects of prophylactic antibiotic regimen on implant failure rates and post-operative infection following implant placement in healthy individuals. The test for overall effect showed that the antibiotic administration significantly reduced the implant failure rates (P=0.0002) with a RR of 0.55 (95% CI 0.41-0.75). The number needed to treat (NNT) to prevent one patient having an implant failure was 50 (95% CI 33-100). No significant effects of prophylactic antibiotics on the occurrence of post-operative infections in healthy patients were shown[166].

The benefits of preoperative versus postoperative antibiotic administration are controversial in the literature. Sharaf et al. in 2011 concluded that a single dose of preoperative antibiotic therapy might slightly decrease the failure rate of dental implants. However, the current data do not support the routine use of postoperative antibiotics[12]. In a pilot study to determine the effectiveness of different Amoxicillin regimens in implant surgery, no statistically significant difference was found between different amoxicillin regimens administered prophylactically[167].

Gynther et al. retrospectively compared the outcomes of dental implant treatment with and without antibiotic prophylaxis. Two groups of patients with edentulous or partially edentulous maxillas or mandibles (or both) were treated with dental implants. One group, consisting of 147 patients (790 implants), was given prophylaxis with oral phenoxymethylpenicillin; 1 g of antibiotic was administered 1 hour preoperatively, and 1 g was administered every 8 hours for 10 days postoperatively. The other group, consisting of 132 patients (664 implants) was not given any antibiotics preoperatively or postoperatively. There were no significant differences with

respect to early and late postoperative infections or with respect to implant survival between the two groups. They concluded that antibiotic prophylaxis for routine dental implant surgery offers no advantage for the patient[168].

In a multicenter randomized controlled clinical trial, Three hundred and twenty-nine healthy adults in need of dental implants were randomly assigned to one of four groups: (i) preoperatively 2 g of amoxicillin 1 h before surgery (positive control, PC), (ii) postoperatively 2 g of amoxicillin immediately following surgery (test 1, T1), (iii) preoperatively 2 g of amoxicillin 1 h before and 500 mg three times daily on days 2 and 3 after surgery (test 2, T2), (iv) preoperatively 2 g of placebo 1 h before surgery (negative control, NC). Blinded examiners examined subjects clinically over 8 weeks after implant surgery. Visual Analogue Scales (VAS) for pain, swelling, bruising and bleeding were obtained over 14 days. They concluded in cases of standard single implant placement, prophylactic systemic antibiotics either before or after, or before and after the surgical procedure do not improve patient-reported outcomes or prevalence of postsurgical complications[169].

The choice of antibiotic in oral and maxillofacial procedures has always been a subject of debate. Penicillin is less expensive than most other alternatives, such as clindamycin and cephalosporins, and has less environmental impact on the evolution of resistant bacteria[170]. The importance of b-lactamase-producing organisms in the pathogenesis of oral infections and the unpredictability of the intestinal resorption of the drug make other antibiotics such as clindamycin a useful alternative. Clindamycin is well absorbed and has good penetration of most tissues except for the cerebrospinal fluid, and the bile when there is complete biliary obstruction[171].

In a clinical study by Lindeboom et al., 150 consecutive patients undergoing local intraoral bone grafting randomly received either an oral single dose of 600 mg clindamycin or 2 g of the penicillin phenethicillin 1 h before incision. Primary endpoint was wound infection at the recipient site within 8 weeks of surgery. Secondary outcome measurements included postoperative infections at the donor site and adverse events as a result of antibiotic administration. Mean age of the patients was 36.8+/-12.7 years (range 18–67 years), and 98 patients were females (65.3%) and 52 males (34.7%). Infections at the receptor site were seen in 4 patients (5.3%; 95% CI 0.23–10.4%) of the phenethicillin group and in 2 patients (2.7%; 95% CI 0–6.36%) of the clindamycin group. In both groups, 3 patients had an infection at the donor site. A-hemolytic Streptococci sensitive to penicillin predominantly caused postoperative infections. No significant difference was found between prophylactic single doses of phenethicillin and clindamycin with regard to postoperative infection in patients undergoing local bone augmentation procedures[172].

In a prospective double-blinded trial, penicillin and clindamycin were compared in treatment of moderate to severe orofacial infections of odontogenic origin, which yielded pus on aspiration. Among 27 patients randomized to receive penicillin, 22 (81%) had a successful outcome, and five (19%) were improved. In the 28 clindamycin-treated patients, 23 (82%) had a successful outcome, and five (18%) were improved. No failures were noted in either group. It was concluded that penicillin and clindamycin produce similar good results in treating odontogenic infection when the rate of penicillin resistance among oral anaerobic bacteria is at a relatively low level [173].

At present, there is still a lack of large-scale multicenter studies to support or refute the need for antibiotic prophylaxis with conventional implant placement. Some authors recommended antibiotic prophylaxis with the procedure based on cohort studies and anecdotal experience[159] .

2.12 AIM OF THE STUDY

The aim of this study was to investigate retrospectively the potential impact of self-reported allergy to penicillin on implant survival rate. The secondary purpose of this retrospective, non-interventional, open cohort study is to report on the long-term survival of dental implants, in private practice representing daily realities of implant therapy. The data were analyzed to recognize statistical relationships between explanatory variables and implant failure.

It was hypothesized that patients unable to receive penicillin antibiotic in association with implant therapy are more prone to develop implant failures. This study may indicate whether penicillin allergy test should be implemented in clinical settings prior to implant therapy to identify true allergies to penicillin with the aim of penicillin coverage of higher number of implant patients leading to enhanced survival rate of implants.

Chapter 3: MATERIALS AND METHODS

3.1 STUDY DESIGN

3.1.1 IMPLANT DATABASE AND PATIENT SAMPLE

This retrospective observational study consisted of 2467 patients with a total of 5906 implants placed by one of the authors (DF) in private practice from 1997 until 2010 with the follow-up period of up to 10 years. The practitioner (DF) is a Periodontist with over 15 years of experience in surgical implant dentistry. The clinic is a private practice providing surgical implant services as well as abutment and provisional restorations. Referring clinicians did all final restorations. Initial retrospective charts review indicated that of the 5906 implants placed during this time frame, 5622 implants were available for evaluation at 3 months post insertion (284 were not evaluated at 3 months = 4.8%). Of the 5622 implants followed to 3 months, there were 4132 implants followed to at least one year. Of the 5906 there were 358 patients deemed as drop outs because they were 2 years past due for evaluation for a total dropout of 6% (358/5906). In order to provide more homogenous database with less confounding variables, only 5576 dental implants from either Nobel Biocare or Straumann brand were investigated for this study and the rest from other brands were excluded.

Of 5576 dental implants reviewed, 985 were Nobel Biocare and 4591 implants were from the Straumann Company. The mean patient age at the time of surgery was 60 years old with a range of 20-89 years. The inclusion criterion was the presentation of edentulous or partially edentulous sites, and the only exclusion criterion was the use of ASA class 3 or higher[174]. Implants were

inserted according to manufacturer guidelines and used for approved indications. All potential implant locations were used, and the location of implants was determined based on individual patient's requirements; no set location or group of locations were planned or declined. Patient education and consent to implant surgery was obtained, and the study is part of an ongoing long-term evaluation of dental implants associated with the University of British Columbia retrospective clinical study on dental implants. The study was approved by the Clinical Research Ethics Board at the University of British Columbia (Vancouver, Canada). Data analysis was designed to preserve the anonymity of the patients. Surgical protocols included placement in maturely healed ridge with and without bone grafting and immediate placement in extraction sockets. Implants were placed using flap surgery except for immediate placement in extraction sockets, which were performed flapless. In sites of atrophied ridge that required bone graft, particulate graft with membrane was performed at the time of implant placement using autogenous bone, bovine xenograft or combinations with an e-PTFE or collagen membrane. Sinus procedures were divided into two groups. In one group, a lateral window sinus lift was performed prior to implant placement using a mixture of autogenous and bovine xenograft in combination with a slowly resorbable collagen membrane. In the other group, an osteotome indirect sinus lift was performed using straight wall osteotomes with no added bone graft. Loading protocols varied based on individual case requirements but were divided into three categories; immediate loading (within 48 h of placement), conventional loading (2–3 months after placement) and delayed loading (6 months after placement if very low-density bone and low insertion stability). When adjacent implants were placed, they were typically splinted together, and when 6 mm implants were used, they were always splinted to adjacent implants. The patients were evaluated at 2–3 months post-implant insertion for implant stability; via a 35

Ncm torque test and radiographic bone measurements, which provided a baseline for future assessment. Follow-up was then scheduled on 1-, 3-, and 5-year intervals. Case parameters recorded for comparative evaluation were divided into two major categories: A) patient related factors such as age at implant placement, gender, history of periodontal disease, smoking, diabetes mellitus, bisphosphonate therapy, immunosuppressant diseases and self reported allergy to penicillin B) Implant related factors such implant manufacturer, type, length and width, torque on insertion, implant placement timing (implant placement in extraction socket versus healed alveolar ridge), immediate versus delayed loading protocol, location of implant placement, additional surgical procedures such as sinus lift procedure (direct and indirect osteotome) and bone augmentation. When applicable, date and reasons for implant failure were recorded. The implants were evaluated for implant survival defined as implant remaining in the jaw and were listed as failure if implant were lost. Radiographs were taken and interpreted by the same examiner that placed the implants, using a periapical and Dexis proprietary parallel film holder (Hatfield, PA USA). The dexis radiograph software program which measures calibrated to sensor dimensions, was used to measure bone loss looking at the smooth/rough interface (beyond 2.8 or 1.8 mm collar on Straumann Standard and Standard Plus respectively and beyond 1.5 mm collar on Nobel Biocare Replace). All measurements were taken by the same examiner who placed the implants (DF). All bone loss measurements were taken from the coronal aspect of the implant shoulder to the coronal aspect of the alveolar crest at the most apical level, regardless of mesial or distal position thus measuring the side with the greatest bone loss. The amount of exposed rough implant surface would indicate the amount of bone lost from time of implant placement. Standard protocol and the manufacturer's recommendation were followed for osteotomy preparation.

All patients with no reported allergy to penicillin received either pre and/or post-operative amoxicillin whereas patients with self-reported allergy to penicillin were prescribed the alternatives, most commonly, clindamycin. In cases of immediate implant placement in fresh extraction socket, sockets were thoroughly degranulated with curretts and/or burr and carefully inspected to ensure the remnants of soft tissue fibers have been removed.

3.1.2 IMPLANT STABILITY

The insertion torque was recorded using the same electric torque device (W. & H. Implant med, Bürmoos, Austria), used for insertion of the implant. Results were recorded in increments of 5 Ncm from 10 Ncm to 40 Ncm. Implants that needed greater than 45 Ncm torque to fully seat were removed and the site re-prepared to prevent bone compression such that all implants were placed with 40 Ncm torque or less. Implant removal was performed using counter torque technique or an explant device. All cases were examined at 1-week post-operatively for signs of infection or mobility. The implants seen at three months were tested for clinical soft tissue health, radiographic integration, and stability by a forward - reverse torque test of 35 Ncm with a manual strain gauge. Implants that were not obviously loose and passed radiographic tests but rotated slightly at a torque of 35 Ncm were given another three months of healing to allow bone to mature. Implant survival was defined as an implant regarded osseointegrated after the torque test and subsequently restored.

3.2 DATA MANAGEMENT AND STATISTICAL ANALYSIS

Implant survival was analyzed by calculating the percentage of surviving implants as a function of time. The Pearson Chi-square analysis was employed to test the relationship between categorical variables such as penicillin allergy and implant failure (yes/no) for the evaluation of statistical significance. Fisher's Exact test was applied if assumptions for chi-square test were not met. Selection of variables into the final model was carried out in steps. First, we performed a univariate analysis (one by one explanatory variable), and then, all variables with a P-value < 0.15 entered into a multivariate analysis. The multivariate model enabled an estimate of the odds ratio with adjustment to possible confounders. For example, if a multivariate model includes penicillin allergy as explanatory variable and implant location as a confounder, the model actually estimates the net effect of penicillin allergy on implant failure, no matter what is the value of implant location. Bivariate analysis was done between each independent variable and implant failure to evaluate the presence of statistically significant correlation between the explanatory variables and implant failure. All variables with statistically significant correlation with implant failure were entered into logistic regression analysis for the evaluation of impact of demographic and clinical variables on implant survival. The level (alpha) of statistical significance was 0.05 using SPSS (version 20.0) statistical package.

Chapter 4: RESULTS

4.1 DESCRIPTION OF THE IMPLANT AND PATIENT COHORT

8.4% of the study population had self-reported allergy to penicillin which is in accordance with many other studies. 8.1% of Straumann implants were placed for patients unable to take penicillin versus 10.1% of Nobel Biocare implants were placed for patients unable to utilize penicillin (Table 1). The total of 49 implants failed out of 5576 implants for the overall survival rate of 99.1% and failure rate of 0.9%.

4.1.1 PENICILLIN ALLERGY AND IMPLANT FAILURE

Of the 5576 dental implants studied, 5106 (91.6%) were placed in patients with no history of self-reported allergy to penicillin whereas, 470 implants (8.4%) were placed in patients with self-reported allergy to penicillin (Table 1). Out of 49 failed implants in total, 20.4% (n=10) was placed in patients who were not prescribed penicillin and 79.6% (n=39) was placed in patients who were able to take penicillin. Out of 5106 implants placed for non-allergic group, 0.8% failed whereas, 2.1% of implants placed in Penicillin allergic group failed (Table 4). There is a statistically significant difference in implant failure rate between groups with and without self-reported allergy to penicillin (P value=0.002) (Table 5). A significantly greater implant failure rate was linked to the high infection rate in patients who were unable to use postsurgical penicillin due to self-described allergy, with penicillin-allergic patients demonstrating an odds ratio of 3.1 (95% CI: 1.5-6.4) when compared to patients who were able to utilize penicillin ($P < .01$). Patients with an allergy to penicillin were 6.8-times more likely to experience implant failures due to infection than patients without allergy to penicillin. There were also 48 sites

where there was a post-operative infection incident for the total infection rate of about 0.9% per implant.

4.1.2 PENICILLIN ALLERGY AND INFECTION RATE

Of the total 48 sites with postoperative infection, 16 (33%) out of 470 sites developed infection in patients with self-reported allergy to penicillin for the infection rate of 3.4% whereas 32 sites out of 5106 developed infection in non-allergic group for the infection rate of 0.6%. Infection rate in penicillin allergic patients was about 6-times higher than the rate of infection in non-penicillin allergic implant patients ($P < 0.05$).

4.1.3 SMOKING AND IMPLANT FAILURE

Of 5576 implants, a total number of 125 implants were placed in patients with self-described smoking habits. Of 125 implants in smokers 4 implants failed (3.2%). Nonsmokers received a total of 5451 implants of which 45 (0.8%) failed. The difference in implant failure rate between smokers and nonsmokers was statistically significant ($P=0.005$) (Table 6-7).

4.1.4 HISTORY OF PERIODONTAL DISEASE AND IMPLANT FAILURE

Of the total 5576 implants of this study, 207 were placed in patients with history of periodontal disease; 2 of which failed (4.1% of all implant failures) (Table 8). The association between history of periodontal disease and implant failure was not statistically significant ($P>0.05$) (Table 9).

4.1.5 IMMEDIATE IMPLANTATION IN EXTRACTION SOCKET AND IMPLANT FAILURE

Of the total 5576 implants, 687 implants (12.3%) were placed immediately into extraction sockets following tooth removal of which, 12 implants (1.7%) failed. 37 implants out of 4889 implants inserted in healed ridges failed for the failure rate of 0.8% (Table 10). The difference in implant failure rate between immediate implant placement in extraction socket and delayed implant placement in already healed ridge was statistically significant (P= 0.009) (Table 11).

Of 687 immediate implant placements into fresh extraction socket, 57 implants were placed in penicillin allergy group (8.3%) and 630 immediate implants placed in non-penicillin allergic patients (91.7%). A total of 12 immediately placed implants into fresh extraction socket failed (1.7%). 6 out of 57 immediate implants in penicillin allergic group failed for the failure rate of 10.5% while, 6 out of 630 immediate implants in extraction socket in the non-penicillin allergic group failed for the failure rate of only 1%. The failure rate for immediate implant placement into fresh extraction socket is 10-times higher in penicillin allergic group compared to non-allergic group (Table 12). A drastically greater implant failure rate was linked to the higher infection rate in patients who were unable to use penicillin due to self-described allergy, with penicillin-allergic patients representing an odds ratio of 3.0 when compared to patients who were able to utilize penicillin ($P < 0.01$) after adjustment for possible confounders.

4.1.6 IMMEDIATE LOADING AND IMPLANT FAILURE

Immediate loading protocol was applied only to a total of 318 implants out of 5576 (5.7%) of which none failed during the study period. The survival rate of implants with immediate loading was comparable to those implants with conventional loading (Table 14).

4.1.7 GUIDED BONE REGENERATION AND IMPLANT FAILURE

Bone augmentation procedures using variety of biologic materials have been applied in association with implant surgery either in earlier stage (prior to implant placement with healing time) or simultaneously at the time of implant placement. Of the total 5576 implants of the study, 1819 implants were placed in conjunction with bone augmentation or at the sites with previous bone augmentation (staged); 23 of which failed equal to 1.3% of all grafted sites and 47% of the all implant failures (Table 15). The failure rate of the implants placed in grafted sites or in conjunction with bone augmentation at the time of implant placement was statistically higher relative to implants with no associated bone augmentation (P=0.03) (Table 16).

4.1.8 BONE LOSS AT THE BASELINE AND IMPLANT FAILURE

Bone loss greater than 1 mm below the smooth/rough interface (beyond 2.8 or 1.8 mm collar on Straumann Standard and Standard Plus respectively and beyond 1.5 mm collar on Nobel Biocare Replace) at the second stage surgery or three months post insertion of implant was considered non-physiologic bone loss, unrelated to bone remodeling to establish biologic width. From the total of 5576 implants, 245 experienced baseline bone loss of > 1mm, 8 of which eventually failed for the failure rate of 3.3% comparing to 0.8% of failure rate for implants with baseline bone loss ≤1mm (Table 17). There is significant association between implant failures and bone loss at the baseline (P=0.001)(Table 18).

Of the total 245 implants with the baseline bone loss >1mm, 13 implants (5.3%) were placed in penicillin allergic patients (Table 19). No significant relation between penicillin allergy and baseline bone loss was found (Table 20); however, since the P value was <0.1, this variable

(baseline bone loss) was included in the final logistic regression model (Table 25).

4.1.9 IMPLANT SITE ASSOCIATION WITH IMPLANT FAILURE

A statistically significant difference in implant failure rate by area of implant placement was seen (P= .002). The region with the highest percentage of failure was the area of second molars (22.4% of all failures). The higher rate of failure could be attributed to the placement of shorter implants due to close proximity to vital anatomical structures such as maxillary sinus and inferior alveolar nerve, free standing position of the implant in this region due to absence of adjacent posterior tooth and lower quality of bone. Over 77% of the implant failures (38 of the total of 49 failures) occurred in maxilla (Table 23, 24).

Age of patients at the time of implant placement, history of periodontal disease, bisphosphonates therapy, bruxism, immediate loading and sinus lift surgery did not have statistically significant correlation with implant failure when doing bivariate analysis and hence, they were not entered into the logistic regression analysis model.

4.2 LOGISTIC REGRESSION ANALYSIS MODEL

Following statistically significant correlation with implant failure in the bivariate analysis, the following explanatory variables were entered into the logistic regression model: Penicillin allergy, smoking, immediate implant placement into fresh extraction socket, bone augmentation procedure, location of implant placement, bone loss at the baseline. The Hosmer & Lemeshow test checks the fitness of the model (whether the model is a significant fit of the data or not). The result of the Hosmer and Lemeshow test is not significant meaning that the logistic regression

model is a good fit to our data. The probability for the residual chi-square statistics is 0.280 meaning that forcing all of the variables excluded from the model into the model would not have made a significant contribution to its predictive value. All variables studied with P <0.1 were included in the logistic regression model but some were removed automatically from model meaning that they did not have any meaningful impacts on outcome (Implant failure) while controlling the other confounding variables in the model (Table 25).

4.3 IMPLANT SURVIVAL ANALYSIS

4.3.1 STATISTICAL METHODS

The main outcome variable in the current section is the "time to implant failure". Failure was defined as the removal of an implant for any reason. This variable is regarded as a censored variable since for most of the observations, the exact time to failure is not revealed during the follow-up period.

In order to describe our survival data, we calculated the Cumulative Survival Rate [CSR] according to the life table method and illustrated the results with the Kaplan-Meier Survival Curve. These methods calculate the number of patients at risk in each interval of time after excluding the censored observation from the analysis before the start of the interval.

Hazard ratios were calculated in order to estimate the association between explanatory variables and failure time. Hazard ratio for categorical variable is defined as the ratio between Hazards for implants failure among one group compared to another group. A ratio equal to one means that

hazards are equal across groups while H.R<1 and H.R.>1 means protective and risk effect, respectively. Hazard ratios were obtained by constructing the proportional hazard Cox regression model. This method allows us to estimate the Hazard ratio with adjustment to possible confounders. Selection of variable into the final model was done in steps. According to univariate analysis (one by one) we built an overloaded model, and then in backward steps non-significant variables were removed until we reached a parsimonious multivariate model.

Lastly, In order to use the Cox model, it is essential to check the underling Proportional Hazard assumption that states that Hazard ratio is constant throughout the time under investigation. In our analysis, the PH assumption was tested with the Grambsch–Therneau test. In case of violation, we included a time variant covariate. The statistical analysis was performed with SPSS software.

4.3.1.1 DESCRIPTIVE SURVIVAL ANALYSIS AT IMPLANT LEVEL

The implant cohort consists of 5576 implants. Among the cohort, we observed 32 (0.5%) failures during the surgical phase (before loading) and only 17 (0.3%) failures after loading. The table 28 presents the exact time to failures of these 49 implants.

4.3.1.2 KAPLAN-MEIER SURVIVAL ANALYSIS

Table 26 and figure 1 present the cumulative survival rate by allergy group. According to the life table analysis, the cumulative survival rates at implant level at 1-, 5- and 10-years were, 98.1%, 97.3% and 97.3%, respectively in penicillin allergic group and 99.5%, 98.9% and 98.4%, respectively in non-allergic group. Kaplan Meier (Log Rank) test revealed there was significant

difference (Chi^2=9.3; df=1; p value 0.002) between survivals of implants placed in penicillin-allergic group compared with non-allergic group. 54% (21 out of 39) of implant failures in non-allergic group have occurred during the first 6 months of implant insertion, while in penicillin allergic group this amount was 80% (8 out of 10)(Table 26).

4.3.1.3 COX REGRESSION ANALYSIS

According to a univariate Cox regression, risk of failure for implants placed in non-allergic group was 64% less than those of implants placed in patients with self-reported allergy to penicillin (RR = 0.36; 95% CI: 0.18-0.71) with statistically significant difference.

4.3.1.4 COX PROPORTIONAL HAZARDS MODEL

Risk of failure of the implants in penicillin allergic group was 2.8 times higher than the risk for non-allergic-group (hazard ratio = 2.8; 95% CI: 1.4-5.6).

Table 1: Descriptive Analysis of Data: Penicillin Allergy

Penicillin Allergy	Frequency	Percent	Valid Percent	Cumulative Percent
No	5106	91.6	91.6	91.6
Yes	470	8.4	8.4	100.0
Total	5576	100.0	100.0	

Table 2: Implant Failure and Implant Type

			Implant type		Total
			Straumann	Nobel	
Implant Failure	No	Count	4559	968	5527
		% Within implant failure	82.5%	17.5%	100.0%
		% Within implant type	99.3%	98.3%	99.1%
		% Of Total	81.8%	17.4%	99.1%
	Yes	Count	32	17	49
		%Within implant failure	65.3%	34.7%	100.0%
		% Within implant type	0.7%	1.7%	0.9%
		% Of Total	0.6%	0.3%	0.9%
Total		Count	4591	985	5576
		% Within implant failure	82.3%	17.7%	100.0%
		% Within implant type	100.0%	100.0%	100.0%
		% Of Total	82.3%	17.7%	100.0%

Table 3: Penicillin Allergy and Implant Type Crosstabulation

			Implant type		Total
			Straumann	Nobel	
Penicillin Allergy	No	Count	4220	886	5106
		% Within penicillin medication	82.6%	17.4%	100.0%
		% Within implant type	91.9%	89.9%	91.6%
		% Of Total	75.7%	15.9%	91.6%
	Yes	Count	371	99	470
		% Within penicillin medication	78.9%	21.1%	100.0%
		% Within implant type	8.1%	10.1%	8.4%
		% Of Total	6.7%	1.8%	8.4%
Total		Count	4591	985	5576
		% Within penicillin medication	82.3%	17.7%	100.0%
		% Within implant type	100.0%	100.0%	100.0%
		% Of Total	82.3%	17.7%	100.0%

Table 4: Penicillin Allergy and Implant Failure Crosstabulation

			Implant failure		Total
			No	Yes	
Penicillin Allergy	No	Count	5067	39	5106
		% Within penicillin allergy	99.2%	0.8%	100.0%
		% Within implant failure	91.7%	79.6%	91.6%
		% Of Total	90.9%	0.7%	91.6%
	Yes	Count	460	10	470
		% Within penicillin allergy	97.9%	2.1%	100.0%
		% Within implant failure	8.3%	20.4%	8.4%
		% Of Total	8.2%	0.2%	8.4%
Total		Count	5527	49	5576
		% Within penicillin allergy	99.1%	0.9%	100.0%
		% Within implant failure	100.0%	100.0%	100.0%
		% Of Total	99.1%	0.9%	100.0%

Table 5: Penicillin Allergy and Implant Failure Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	9.191[a]	1	.002		
Continuity Correction[b]	7.692	1	.006		
Likelihood Ratio	6.830	1	.009		
Fisher's Exact Test				.007	.007
N of Valid Cases	5576				

Table 6: Implant Distribution in Smokers

Smoker	Frequency	Percent	Valid Percent	Cumulative Percent
No	5451	97.8	97.8	97.8
Yes	125	2.2	2.2	100.0
Total	5576	100.0	100.0	

Table 7: Implant Failure and Smoking Status Crosstabulation

			Smoking status		Total
			No	Yes	
Implant Failure	No	Count	5406	121	5527
		% within implant failure	97.8%	2.2%	100.0%
		% within smoking status	99.2%	96.8%	99.1%
		% of total	97.0%	2.2%	99.1%
	Yes	Count	45	4	49
		% within implant failure	91.8%	8.2%	100.0%
		% within smoking status	0.8%	3.2%	0.9%
		% of Total	0.8%	0.1%	0.9%
Total		Count	5451	125	5576
		% within Implant failure	97.8%	2.2%	100.0%
		% within smoking status	100.0%	100.0%	100.0%
		% of Total	97.8%	2.2%	100.0%

Table 8: History of Periodontal Disease Frequency

Periodontal Disease	Frequency	Percent	Valid Percent	Cumulative Percent
No	5369	96.3	96.3	96.3
Yes	207	3.7	3.7	100.0
Total	5576	100.0	100.0	

Table 9: Implant Failure and History of Periodontal Disease Crosstabulation

			History of Periodontal Disease		Total
			No	Yes	
Implant Failure	No	Count	5322	205	5527
		% within implant failure	96.3%	3.7%	100.0%
		% within history of perio disease	99.1%	99.0%	99.1%
		% of Total	95.4%	3.7%	99.1%
	Yes	Count	47	2	49
		% within implant failure	95.9%	4.1%	100.0%
		% within history of perio disease	0.9%	1.0%	0.9%
		% of Total	0.8%	0.0%	0.9%
Total		Count	5369	207	5576
		% within implant failure	96.3%	3.7%	100.0%
		% within history of perio disease	100.0%	100.0%	100.0%
		% of Total	96.3%	3.7%	100.0%

Table 10: Implant Failure & Immediate Implant Placement Crosstabulation

			IIP		Total
			No	Yes	
Implant Failure	No	Count	4852	675	5527
		% Within implant failure	87.8%	12.2%	100.0%
		% Within IIP	99.2%	98.3%	99.1%
	Yes	Count	37	12	49
		% Within implant failure	75.5%	24.5%	100.0%
		% Within IIP	0.8%	1.7%	0.9%
Total		Count	4889	687	5576
		% Within implant failure	87.7%	12.3%	100.0%
		% Within IIP	100.0%	100.0%	100.0%

Table 11: Chi-Square Test (Implant Failure & Immediate Implant Placement)

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6.777[a]	1	.009		
Continuity Correction[b]	5.688	1	.017		
Likelihood Ratio	5.490	1	.019		
Fisher's Exact Test				.015	.014
Linear-by-Linear Association	6.775	1	.009		
N of Valid Cases	5576				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.04.

b. Computed only for a 2x2 table

Table 12: Implant Failure in Immediate Implant Placement Group & Penicillin Allergy Crosstabulation

			Penicillin allergy		Total
			No	Yes	
Implant Failure (IIP group)	No	Count	624	51	675
		% Within implant failure	92.4%	7.6%	100.0%
		% Within penicillin allergy	99.0%	89.5%	98.3%
	Yes	Count	6	6	12
		% Within implant failure	50.0%	50.0%	100.0%
		% Within penicillin allergy	1.0%	10.5%	1.7%
Total		Count	630	57	687
		% Within implant failure	91.7%	8.3%	100.0%
		% Within penicillin allergy	100.0%	100.0%	100.0%

Table 13: Chi-Square Test: Immediate Implant Placement Failure and Penicillin Allergy

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	27.917[b]	1	.000		
Continuity Correction[c]	22.617	1	.000		
Likelihood Ratio	14.777	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	27.876	1	.000		
N of Valid Cases	687				

a. Immediate Implant Placement in Extraction Socket = Yes

b.1 cells (25.0%) have expected count less than 5. The minimum expected count is 1.00.

c. Computed only for a 2x2 table

Table 14: Descriptive Analysis, Immediate Loading

Immediate Loading	Frequency	Percent	Valid Percent	Cumulative Percent
No	5258	94.3	94.3	94.3
Yes	318	5.7	5.7	100.0
Total	5576	100.0	100.0	

Table 15: Implant Failure & Bone Graft Crosstabulation

			Bone Graft		Total
			No	Yes	
Implant failure	No	Count	3731	1796	5527
		% within implant failure	67.5%	32.5%	100.0%
		% within bone graft	99.3%	98.7%	99.1%
	Yes	Count	26	23	49
		% within implant failure	53.1%	46.9%	100.0%
		% within bone graft	0.7%	1.3%	0.9%
Total		Count	3757	1819	5576
		% within implant failure	67.4%	32.6%	100.0%
		% within bone graft	100.0%	100.0%	100.0%

Table 16: Chi-Square Test (Implant Failure and Bone Graft)

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.610[a]	1	.032		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 15.98.

b. Computed only for a 2x2 table

Table 17: Implant Failure & Bone Loss at Baseline Crosstabulation

			Bone loss at baseline		Total
			≤1mm	>1mm	
Implant Failure	No	Count	5290	237	5527
		% within implant failure	95.7%	4.3%	100.0%
		% within bone loss at baseline	99.2%	96.7%	99.1%
	Yes	Count	41	8	49
		% within implant failure	83.7%	16.3%	100.0%
		% within bone loss at baseline	0.8%	3.3%	0.9%
Total		Count	5331	245	5576
		% within implant failure	95.6%	4.4%	100.0%
		% within bone loss at baseline	100.0%	100.0%	100.0%

Table 18: Implant Failure & Bone Loss at Baseline Crosstabulation Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	16.756[a]	1	.000		
Continuity Correction[b]	14.013	1	.000		
Likelihood Ratio	10.218	1	.001		
Fisher's Exact Test				.001	.001
Linear-by-Linear Association	16.753	1	.000		
N of Valid Cases	5576				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 2.15.

b. Computed only for a 2x2 table

Table 19: Penicillin Allergy & Baseline Bone Loss Crosstabulation

			Bone loss at baseline		Total
			≤1mm	>1mm	
Penicillin Allergy	No	Count	4874	232	5106
		% within penicillin allergy	95.5%	4.5%	100.0%
		% within bone loss at baseline	91.4%	94.7%	91.6%
	Yes	Count	457	13	470
		% within penicillin allergy	97.2%	2.8%	100.0%
		% within bone loss at baseline	8.6%	5.3%	8.4%
Total		Count	5331	245	5576
		% within penicillin allergy	95.6%	4.4%	100.0%
		% within bone loss at baseline	100.0%	100.0%	100.0%

Table 20: Penicillin Allergy & Baseline Bone Loss Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.238[a]	1	.072		

Note: No statistically significant association between penicillin allergy and baseline bone loss. Since P value is < 0.1, this variable was included in the logistic regression model.

Table 21: Implant Failure & Quadrant Crosstabulation

			Quadrant				Total
			1	2	3	4	
Implant failure	No	Count	1503	1505	1275	1244	5527
		% within implant failure	27.2%	27.2%	23.1%	22.5%	100.0%
		% within quadrant	98.8%	98.8%	99.6%	99.5%	99.1%
	Yes	Count	19	19	5	6	49
		% within implant failure	38.8%	38.8%	10.2%	12.2%	100.0%
		% within quadrant	1.2%	1.2%	0.4%	0.5%	0.9%
Total		Count	1522	1524	1280	1250	5576
		% within implant failure	27.3%	27.3%	23.0%	22.4%	100.0%
		% within quadrant	100.0%	100.0%	100.0%	100.0%	100.0%

Table 22: Implant Failure & Quadrant Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	10.539[a]	3	.014
Likelihood Ratio	11.359	3	.010
Linear-by-Linear Association	7.951	1	.005
N of Valid Cases	5576		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 10.98.

Table 23: Implant Failure & Implant Site Crosstabulation

			Implant site								Total
			1	2	3	4	5	6	7	8	
Implant Failure	No	Count	444	576	291	705	1075	1617	754	65	5527
		% within implant failure	8.0%	10.4%	5.3%	12.8%	19.4%	29.3%	13.6%	1.2%	100.0%
		% within implant site	98.4%	99.0%	98.3%	99.4%	99.4%	99.6%	98.6%	95.6%	99.1%
	Yes	Count	7	6	5	4	6	7	11	3	49
		% within implant failure	14.3%	12.2%	10.2%	8.2%	12.2%	14.3%	22.4%	6.1%	100.0%
		% within implant site	1.6%	1.0%	1.7%	0.6%	0.6%	0.4%	1.4%	4.4%	0.9%
Total		Count	451	582	296	709	1081	1624	765	68	5576
		% within implant failure	8.1%	10.4%	5.3%	12.7%	19.4%	29.1%	13.7%	1.2%	100.0%
		% within implant site	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 24: Implant Failure & Implant Site Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	23.068[a]	7	.002
Likelihood Ratio	18.102	7	.012
Linear-by-Linear Association	.470	1	.493
N of Valid Cases	5576		

a. 3 cells (18.8%) have expected count less than 5. The minimum expected count is .60.

Table 25: Logistic Regression Analysis

Variables	**B (SE)**	**95% Confidence Interval for Odds Ratio**		
		Lower	Odds Ratio	Upper
Constant	-5.42 (0.48)			
Allergy to Penicillin	1.14 (0.37)	1.52	3.13	6.41
Immediate Implantation in Fresh Socket	1.122 (0.39)	1.4	3.07	6.6
Guided Bone Regeneration	0.82 (0.30)	1.2	2.3	4.1
Site (#7)	1.7 (0.74)	1.3	5.7	24.7
Baseline Bone loss >1mm	1.16 (0.43)	1.3	3.2	7.5

Table 26: Life Table by Penicillin Allergy Status

	No Penicillin Allergy			Penicillin Allergy		
Start Time	**N**	**Events**	**C.S.R**	**N**	**Events**	**C.S.R**
0	5069	21	.9955	465	8	.9812
6	4145	4	.9945	379	0	.9812
12	3907	1	.9942	348	0	.9812
18	3493	4	.9929	314	0	.9812
24	2783	0	.9929	258	1	.9772
30	2435	2	.9921	225	1	.9725
36	2194	1	.9916	189	0	.9725
42	1847	1	.9910	174	0	.9725
48	1426	1	.9902	139	0	.9725
54	1169	1	.9893	106	0	.9725
60	965	0	.9893	93	0	.9725
66	761	2	.9864	74	0	.9725
72	609	0	.9864	43	0	.9725
78	475	1	.9840	30	0	.9725
84	330	0	.9840	26	0	.9725
90	240	0	.9840	22	0	.9725
96	168	0	.9840	16	0	.9725
102	122	0	.9840	15	0	.9725
108	59	0	.9840	6	0	.9725
114	44	0	.9840	4	0	.9725
120	23	0	.9840	3	0	.9725
126	11	0	.9840	2	0	.9725

N: Number Entering Interval

Events: Number of Terminal Events (Implant Failure)

CSR: Cumulative Survival Rate at End of Interval

Table 27: Summary of Life Table

Allergy to Penicillin	Number of Failures	1-year survival rate (%)	5-years survival rate (%)	10-year survival rate (%)
Positive (n=465)	10	98.1	97.3	97.3
Negative (n=5069)	39	99.5	98.9	98.4

Figure 1: Kaplan-Meier Survival Function by Penicillin Allergy

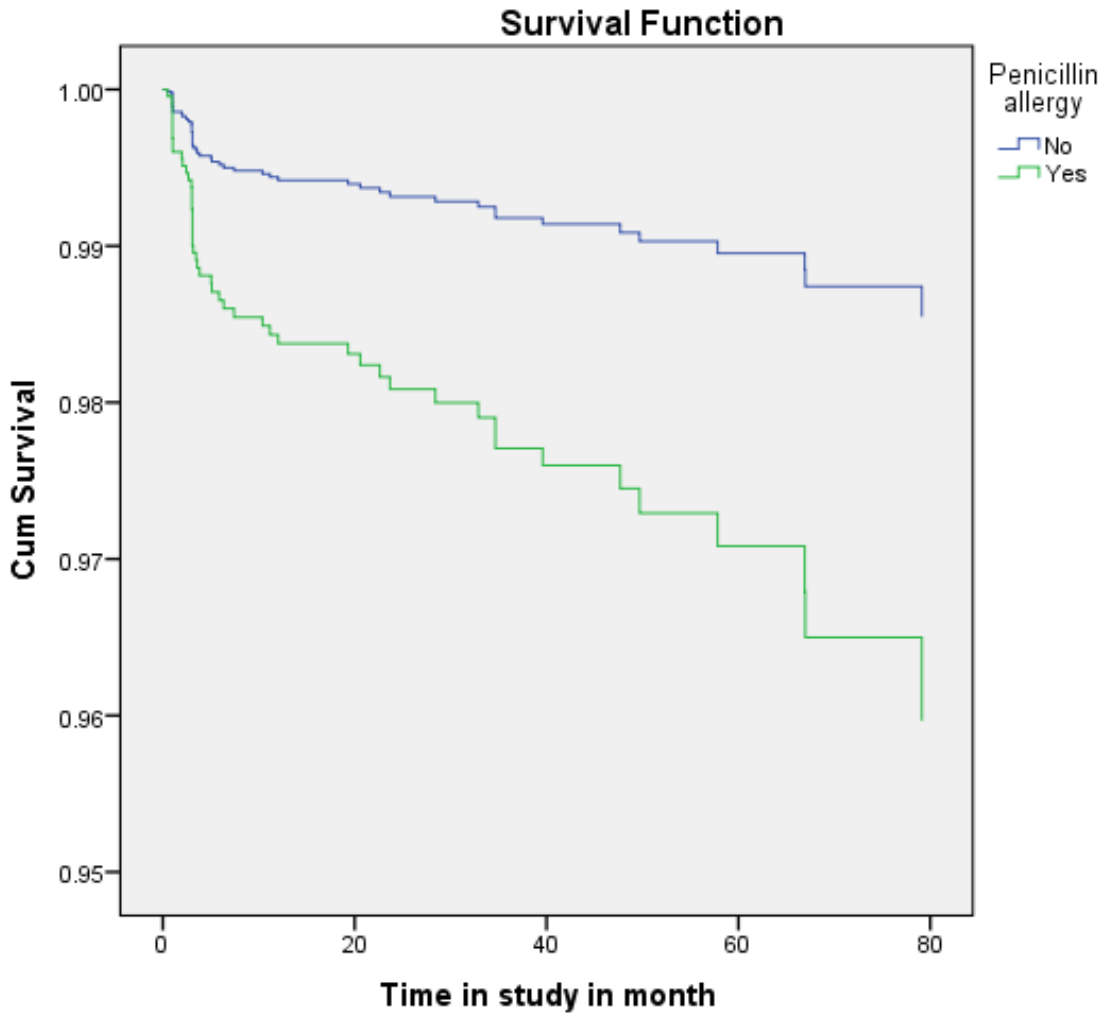

Table 28: Time to Failure for the 49 Failing Implants

Frequency	8	3	12	2	2	2	1	1	1	1	1	1	1	1	1	2	2	1	1	1	1	2	1	49
Time to Failure [month]	1	2	3	4	5	6	7	10	11	12	19	21	23	24	28	33	35	40	48	50	58	67	79	Total
Phase	Pre-loading									Post-loading														

Chapter 5: DISCUSSION

It is important to note that higher implant survival can be achievable when thoroughly tested implant materials, surfaces and designs are used, evidence-based surgical and restorative protocols are established and risk factors/indicators influencing the implant failure are identified[175]. There have been numerous studies looking at different implant-related, patient-related and surgical-related factors that may have impacts on implant therapy outcome; however, there are very few implant studies looking at potential impacts of allergy to penicillin on implant therapy outcome. One of the proposed methods to minimize infection following implant surgery is the prescription of antibiotics. The choice of antibiotics should be that it covers a reasonable bacterial spectrum to limit potential pathogens from colonizing in the vicinity of the surgical sites[98.] However, antibiotic administration in conjunction with implant surgery either prophylactically or postoperatively has been a matter of controversy in implant literatures. In a recent systematic review of controlled trials comparing amoxicillin versus placebo in 927 patients, it was noted that 2 g of amoxicillin given orally 1 h preoperatively reduced the probability of implant failure[65].

In this retrospective clinical study, 5576 dental implants placed by experienced periodontist in private practice were reviewed. All implants placed in patients receiving antibiotics either prophylactically or postoperatively or both. The antibiotic administration protocol with respect to timing (preoperatively, postoperatively or combined), dosage and duration was based on the practitioner (DF) clinical judgment and discretion. In those cases that amoxicillin was not used due to self-reported penicillin allergy, clindamycin was given as an alternate. Out of 5106

implants placed for non-allergic group, 0.8% failed whereas, 2.1% of implants placed in penicillin allergic group failed. There is a statistically significant difference in implant failure rate between groups with and without self-reported allergy to penicillin. Our reported odds ratio of 3.1 indicates a potential tripling of failure rate in patients allergic to penicillin; however, due to low numbers of implant failures, this result should be interpreted with caution. Wagenberg and Forum in 2006 evaluated implant survival rates of 1925 immediately placed implants (IIP) into fresh extraction sockets to determine risk factors for implant failure. They showed inability to take amoxicillin post-surgically as a risk factor for implant failure as they concluded patients unable to utilize postsurgical amoxicillin were 3.34-times as likely to experience implant failure as patients who received amoxicillin[13]. A recent systematic review on implant survival placed into fresh extraction sockets after at least one year of function showed among the five factors analyzed (reasons for extraction, antibiotic use, position of implant [anterior vs. posterior, maxilla vs. mandible), type of loading], only the regimen of antibiotic use affected the survival rate significantly. Lower failure rates were found in groups that were provided with a course of postoperative antibiotics[98].

It could be hypothesized that Clindamycin is bacteriostatic antibiotic with less effects on oral bacteria as opposed to penicillin with bactericidal characteristics and thus more effective antibacterial properties. There is also speculation that clindamycin over-prescription in medicine and dentistry has led to bacterial resistance. The impacts of antibiotics on wound healing are yet to be identified. Duewelhenke et al. has shown inhibition of metabolic activity and inhibition of proliferation of primary human osteoblasts and cell lines, increase in inhibition of respiratory chain and impaired mitochondrial energetics in response to high concentration of clindamycin,

macrolides, tetracycline and fluoroquinolones[176].

The difference in implant failure rate between immediate implantation in extraction socket and delayed implant placement in already healed ridge was statistically significant irrespective of penicillin allergy status (P= 0.009). The failure rate for immediate implantation into fresh extraction socket was even worse in penicillin allergic group compared to non-allergic group. A drastically greater immediate implant failure rate was linked to the higher infection rate in patients who were unable to use penicillin due to self-described allergy; with an odds ratio of 3.0 for implant failure when compared to patients who were able to utilize penicillin ($P < 0.01$) after adjustment for possible confounders. These findings are in agreement with Wagenberg and Forum study that showed inability to take penicillin post-surgically as a risk indicator for immediate implantation failure. Patients unable to utilize postsurgical amoxicillin were 3.34 times as likely to experience implant failure as patients who received amoxicillin[13]. Immediate implantation could pose higher risks of implant failure due to presence of oral infection at the time of tooth extraction. However, this should be interpreted with caution, as there are other factors such as implant stability, buccal wall integrity, implant design and geometry, patient compliance, parafunctional habits and occlusion may play a role in implant failure in immediate cases.

A statistically significant difference in implant failure rate by area of implant placement was observed (P= .002) in our study. The sites with the highest percentage of failures were the area of second molar. Of the total of 49 failed implants, 11 failures were located in the region of the second molars (22.4%). The higher rate of failure could be attributed to the placement of shorter

implants due to close proximity to vital anatomical structures such as maxillary sinus and inferior alveolar nerve, free standing position of the implant in this region due to absence of adjacent posterior tooth and lower quality of bone. Over 77% of the implant failures (38 of the total of 49 failures) occurred in maxilla. Our findings are in agreement with Koo et al. that has shown higher failure rate of implants in the second molar region compared to the first molar region[177]. It is possible that the masseter muscle involved in mastication exerts a strong force to the lateral side of the second molar and the single implant at the first molar site could distribute the delivered masticatory forces to the adjacent premolar and second molar[177]. However, the second molar could expect to experience the distribution effect only from the proximal first molar and thus, it may be disadvantageous dynamically[177]. Screw loosening has been reported to occur frequently in the molar area. Furthermore, the frequency in the maxilla is more than two times higher than the mandible[177].

In this study, the implant failure was higher in sites with guided bone regeneration. Bone augmentation procedures using variety of biologic materials have been applied in association with implant surgery either in earlier stage (prior to implant placement with healing time) or simultaneously at the time of implant placement. Of the total 5576 implants of the study, 1819 implants were placed in conjunction with bone augmentation or at the sites with previous bone augmentation (staged); 23 of which failed equal to 1.3% of all grafted sites and 47% of the all implant failures. The failure rate of the implants placed in grafted sites or in conjunction with bone augmentation at the time of implant placement was statistically higher relative to implants with no associated bone augmentation (P=0.03). However, the implant survival in GBR sites remains higher than that 95.7% reported in a systematic review of the GBR procedures to correct

peri-implant dehiscence[178] .

It is highly important to understand that implant failure is a multifactorial phenomenon with several risk factors involved. Penicillin allergy alone as a risk indicator does not cause implant failure; however, it can contribute to the failures when other risks are present as well. The results of this study should be interpreted with caution due to small number of implant failures.

Chapter 6: CONCLUSION

Within the limitation of this retrospective study:

1- Overall implant survival rate was 99.1 % with 49 implants failed.

2- Infection rate in penicillin allergic group was about 6-times higher than the rate of infection in non-allergic group.

3- Implants in patients unable to take penicillin due to self-reported allergy were 3.1-times more likely to develop failure than those placed in patients who were able to receive penicillin (P= 0.002).

4- The failure rate for immediate implantation into fresh extraction socket is 10 times higher in penicillin allergic group compared to non-allergic group. A drastically greater implant failure rate was linked to the higher infection rate in patients who were unable to use penicillin due to self-described allergy, with penicillin-allergic patients representing an odds ratio of 3.0 when compared to patients who were able to utilize penicillin ($P < 0.01$) after adjustment for possible confounders.

5- A statistically significant difference in implant failure rate by area of implantation was noted (P= .002). The area with the highest percentage of failure was the area of second molars with 11 failures (22.4%) of the total of 49 failed implants was located in this region. The failure trend was more frequent in maxilla.

6- Based on Kaplan-Meier survival analysis, there was statistically significant difference (Chi^2=9.3; df=1; p value 0.002) between survivals of implants placed in penicillin-allergic group compared with non-allergic group. 54% (21 out of 39) of implant failures in non-allergic group have occurred during the first 6 months of implant insertion, while

in penicillin allergic group this amount is 80%.

7- Risk of failure for implants placed in non-allergic group was 64% less than those of implants placed in patients with self-reported allergy to penicillin (RR = 0.36; 95% CI: 0.18-0.71) with statistically significant difference.

8- Risk of implant failure in penicillin allergic group was 2.8 times higher than the risk for non-allergic group (hazard ratio = 2.8; 95% CI: 1.4-5.6).

9- Strong association between implant failure and smoking was noted (P=0.005).

10- Further randomized controlled clinical trials are necessary to strengthen the evidence and to draw conclusive conclusion.

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