Early Wound Healing Around Endosseous Implants: A Review of the Literature

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The knowledge base of information related to early wound healing around endosseous dental implants is rapidly changing and expanding. Unless one is directly involved with creating this pool of information or has an extraordinary interest in the literature of the field, it is difficult to keep up to date with the flow of information. This article is intended to provide the clinician with a state-of-the-art review of the current literature related to early wound healing and the creation of an osseointegrated interface between living and nonliving structures. While some literature dealing with basic laboratory studies including tissue culture is discussed, the primary focus of the article is the in vivo literature, ie, animal and human studies. Int J Oral Maxillofac Implants 2005;20:425–431

Key words: *bone healing, bone-implant interface, dental implants, early wound healing, wound healing*

The intent of this review was to present the current state of knowledge related to early bone healing adjacent to endosseous dental implants. The English language literature was searched electronically using PubMed. Key terms used included "wound healing and implants," "dental implants and surface roughness," "bone remodeling and implants," "dental implant histology," "implant surfaces," and "bone-implant interface." A total of 1,095 titles published from January 1997 through June 2004 were reviewed. Additionally, 26 references were obtained from a hand search of reviewed articles. Although pertinent studies at the molecular and/or tissue culture level were included, the emphasis of this literature review was the current state of animal and human studies related to the early stages of healing at the bone-implant interface. Several key or classic articles from older sources were included primarily for background information. Sixty-three sources were examined in depth, and 50 were selected for inclusion (Fig 1).

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OSSEOUS WOUND HEALING AND OSSEOINTEGRATION

Current theories of bone biology are an extension of those formed by Marshall Urist in 1952.[1] Bone formation is a complex series of molecular changes that lead to a newly formed structural and functional entity. Endosseous wound healing can be subdivided into the stages of hematoma, clot resolution, and osteogenic cell migration, which lead to the formation of new bone at the wound site.[2]

Osseointegration was defined by Brånemark and associates as a direct structural and functional connection between ordered living bone and the surface of a load-carrying implant.[3] Histologically, this has been further defined as direct anchorage of an implant by the formation of bone directly on the surface of an implant, without an intervening layer of fibrous tissue.[4,5] Clinically, this suggests ankylosis of the implant-bone interface as described by Schröeder and colleagues.[5] This ankylotic interface is created during the healing period immediately postsurgery and is maintained in dynamic equilibrium throughout the postintegration period.

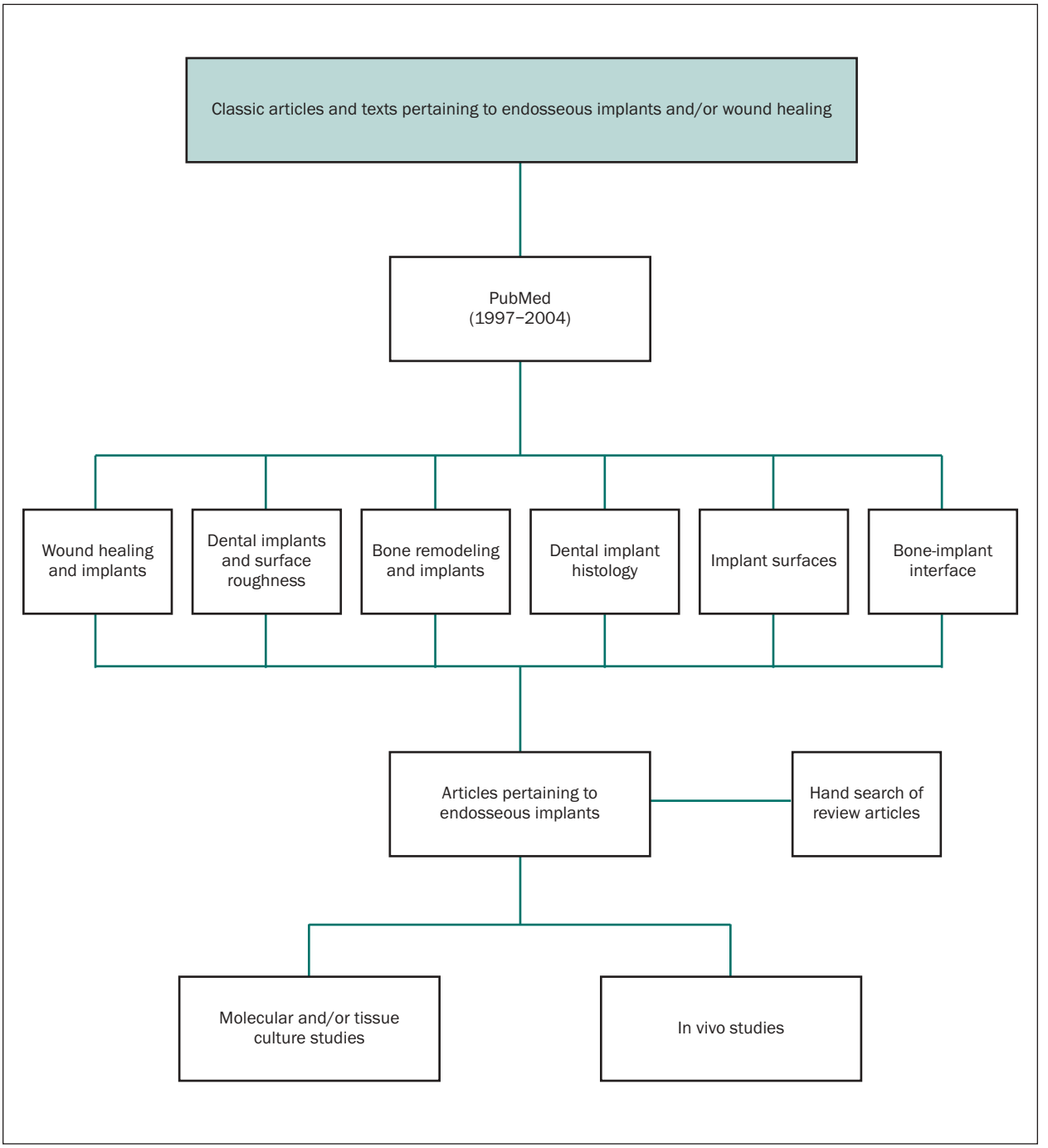

Fig 1 Flowchart demonstrating method of literature search.

OSTEOINDUCTION AND OSTEOCONDUCTION

The induction of bone formation at the site of a surgically created wound (implant site) reflects a major alteration in the cellular environment.[6] Davies[7] described peri-implant bone healing as having 3 distinct phases: osteoconduction, de novo bone formation, and bone remodeling. Albrektsson and Johansson[4] described the terms *osteoinduction* and *osteoconduction* as interrelated but not identical phenomena that occur during bone wound healing. Osteoinduction involves the phenotypic conversion of mesenchymal cells into bone-forming cells.[2] Primitive, undifferentiated, pluripotent mesenchymal cells are stimulated to develop into the bone-forming cell lineages of osteoblasts and osteocytes.[4] Osteoconduction has been defined as appositional bone

growth permitting bone formation on a surface or down into pores, channels, or pipes.[4] Davies[2] described de novo bone formation around endosseous implants as the formation of a mineralized interfacial matrix, equivalent to that found in natural bone tissue, on the implant surface.

The phenomenon of osteoconduction relies on the migration of differentiating osteogenic cells to the implant surface.[7] Undifferentiated mesenchymal cells migrate to the surface of the implant, attach, and proliferate. According to Boyan and coworkers,[8] environmental factors such as oxygen tension help determine whether mesenchymal cells will differentiate into fibroblasts, chondrocytes, or osteoblasts. Adherence can occur when the cell itself directly binds to the surface or when it binds to arginine-glycine-aspartic acid (RGD) -containing proteins that adhere to the surface.[9] During this time, the mesenchymal cells synthesize their own extracellular matrix, including growth factors and cytokines, and modify the surface of the implant. Mesenchymal cells then undergo osteoblastic differentiation.[10] Cells of mesenchymal origin are extremely sensitive to surface properties such as surface energy, roughness, and topography.[11] The new osteoblasts produce osteoid, including matrix vesicles and growth factors. Matrix calcification occurs, leading to the formation of woven bone, which is subsequently remodeled with osteoclast recruitment.[12] In an in vitro model, Davies[13] suggested that although osteoblasts have the ability to migrate, in bone-healing sites, it is usually less-differentiated cells in the osteogenic lineage or perhaps undifferentiated mesenchymal cells that migrate to and colonize the implant surface.

Osborn and Newesley[14] proposed that 2 different phenomena exist by which bone can become juxtaposed to an implant surface: contact osteogenesis and distance osteogenesis. Contact osteogenesis involves de novo bone formation directly on the implant surface. Distance osteogenesis is the formation of new bone on the surfaces of existing peri-implant bone. Berglundh and colleagues[15] studied wound healing adjacent to endosseous implants in Labrador dogs and suggested specific timelines for de novo bone formation. They observed that the placement of implants in the alveolar process elicits a sequence of healing events, including necrosis and subsequent resorption of traumatized bone around the implant body concomitant with new bone formation.

The events involved in osseous wound healing adjacent to implants appear identical to the normal events of wound healing in bone.[6] Based on investigations at the molecular level, implant substrate-osteoblast interactions may be characterized as specific, protein-mediated, dynamic, signal-generating events. Implant surface modification may modulate this cell behavior.[16] Following implantation, after hemostasis and clot formation, fibrinolysis occurs with the formation of a loose connective tissue stroma that supports angiogenesis.[6] The surface of the implant is conditioned by serum proteins, mineral ions, sugars, and lipids, as well as cytokines produced by immune cells.[10] The behavior of adsorbed proteins may be related not only to the interaction between the charge of the material and the protein, but also to the protein's potential for change once adsorbed onto the surface.[9] The static blood volume surrounding the implant will vary considerably as a function of the implant design and site.[13] Vascular ingrowth or angiogenesis is most likely mediated by extracellular matrix components and growth factors.[17] The absence or relative paucity of serum proteins such as albumin indicates a selective accumulation or deposition of molecules at the interface.[18] Because they contain RGD and polyacetic sequences, osteopontin and bone sialoprotein are believed to play roles in cell adhesion and mineral binding.[9,18] In addition, Davies[2] suggested that the implant surface provides anchorage for the fibrin clot to withstand detachment forces during cell migration and thus maintain a migratory pathway for the differentiating osteogenic cells to reach the implant surface.

IMPLANT SURFACE TECHNOLOGY

Development of the implant-bone interface is complex and involves numerous factors. These include not only implant-related factors, such as material, shape, topography, and surface chemistry, but also mechanical loading, surgical technique, and patient variables such as bone quality and quantity.[18] The original studies on osseointegration were performed using turned (machined) surface implants. Efforts to enhance implant surface technology have focused on improving the predictability, rate, and degree of osseointegration. Commonly, modifications to the implant surface have been made through the use of additive or subtractive techniques. To date, there is no consensus concerning the most appropriate implant surface topography, other than to say that turned surfaces on implants have generally given way to surfaces that are roughened using additive or subtractive processes.

Implant Surface Topography

Creating topographic variation from the mean surface plane of the implant can be achieved by additive methods such as titanium plasma spraying, hydroxyapatite (HA) coating, coating with plasma, or magnetron sputter coating. Coatings of calcium phosphate and/or apatites, as well as various attempts to coat an implant surface with biologic molecules, have also been described. Subtractive methods of surface modification include abrasion through blasting with titanium oxides or other soluble or resorbable biomaterials, grit or sandblasting with aluminous oxides, and blasting and acid-attacking or etching (with a hydrogen sulfate or hydrogen chloride). Other surface treatments include anodizing, cold working (dimpling), sintering, and bead compaction. The surface energy, composition, topography, and roughness of an implant are thought to affect bone formation and apposition.[10,12,19–33] Three articles were found that reported no apparent difference between altered implant surface textures[34–36]; however, in 2 of these studies, HA-coated surfaces demonstrated loss of coating thickness.

Some important advantages have been attributed to increased surface roughness. These include increased surface area of the implant adjacent to bone, improved cell attachment to the implant surface, increased bone present at the implant surface, and increased biomechanical interaction of the implant with bone.[37] In a survey comparing the surface topography and industrial processing of 4 implant systems, Szmukler-Moncler and colleagues[38] showed that treating titanium surfaces with acid does not create a standard topography. Each implant system tested had a specific topography that could not be mistaken. The authors further concluded that industrial processing is not fully reproducible and that clinical implications based on roughness data alone cannot be extrapolated from one surface to another. Acid treatment, for example, varies according to prior treatment, acid mixture composition, temperature, and duration of acid treatment.

Implant Surface Chemistry

The energy at the surface of a biomaterial is defined by the general charge density and is either positive, negative, or neutral. Charge, in turn, affects the hydrophilic or hydrophobic characteristics of the surface.[8] A hydrophilic, or easily wettable, implant surface is assumed to be advantageous during the initial phase of wound healing and the cascade of events that occurs during osseointegration. In a recent publication, Buser and coworkers examined the effect of altering the surface chemistry and charge of a sandblasted, acid-etched (SLA) titanium implant surface (Straumann, Waldenburg, Switzerland) on the rate of osseointegration in miniature pigs.[39] They attempted to avoid contamination of the implant surface from the atmosphere by immersing the implant into an isotonic saline solution immediately after acid etching. Their results demonstrated significantly increased amounts of bone-to-implant contact (BIC) at 2, 4, and 8 weeks. At 2 weeks, the modified SLA surface demonstrated a mean of 49.3% BIC, while the conventional SLA surface showed a mean of 29.4% BIC. The authors speculated that the creation of a hydroxylated oxide surface enhances surface reactivity with surrounding ions, amino acids, and proteins in tissue fluid.

When the surface topography of an implant is altered, its surface chemistry is also altered. Cell behavior is not dependent on topography alone; surface topography and chemistry are inseparable. Morra and associates[40] compared the chemical effects of surface treatments using 3 types of roughened surfaces and a machined surface. They found that turned surfaces contained significantly more carbon and significantly less titanium than roughened surfaces. Acid etching removes most of the carbon contaminant introduced onto the implant surface by machining, together with the outer layer of titanium. Thus, acid-etched and plasma-sprayed surfaces are generally cleaner and more reproducible than turned and sandblasted surfaces. In an in vitro study, Cassinelli and colleagues[41] compared 3 variations of acid cleaning on turned implants. They concluded that the effect of surface chemistry was independent of topography and that chemical effects operate over and above the commonly invoked topographic effects. However, Perrin and his group[42] found that surface topography (not the surface composition) alters the bone response to roughened implant surfaces. In a study investigating bone tissue reactions to various surface oxide properties, Sul[43] concluded that, either separately or together, surface chemistry and topography play important roles of bone response to the implant surface.

Implant Surface Roughness and Bone Formation

A number of in vitro and in vivo studies have been conducted to compare the effect of implant surfaces on bone formation. Novaes and colleagues,[44] comparing HA, titanium plasma-sprayed (TPS), sandblasted, and machined implants, found that in relation to BIC, the sandblasted surface was statistically superior to the turned surface and showed greater BIC than the HA and TPS surfaces after 90 days in place without loading. In an extensive review article, Cochran[45] assessed publications that evaluated

implant use in patients to determine whether differences existed in success rates of implants with relatively smooth surfaces compared to implants having roughened surfaces. He concluded that rough-surfaced implants had significantly higher success rates compared to implants with turned surfaces. Human histologic findings have demonstrated improved BIC on rough surfaced implants compared to turned surfaced implants.[24,25]

The surface roughness of titanium is one factor that helps in determining the balance between bone formation and remodeling at the bone-implant interface when comparing TPS and machined implants.[46] Buser and coworkers[19] reported that the extent of the bone-implant interface is positively correlated with increasing roughness of the implant surface. Chehroudi and colleagues[20] reported that surface topography influenced the frequency and amount of bone deposited adjacent to micromachined grooved or pitted-surface implants. Perrin and associates showed that the osteophilic properties of rough titanium surfaces appear to be related to surface topography rather than specific surface composition.[42] In their in vivo study in Land Race pigs, an SLA surface, which normally contains 20% to 30% titanium hydride, was compared to a mechanically altered SLA surface and one from which the titanium hydride was removed. No significant differences in BIC were seen between any of the surfaces. Other authors have published similar reports on the apparent benefit of a rough surface.[19–25,37,47,48] Gotfredsen and colleagues[23] demonstrated that a clear relationship exists between surface roughness and implant anchorage, which was assessed by removal torque measurements.

In addition to animal studies and human clinical trials documenting the superiority of rough implant surfaces to turned surfaces in regard to survival, there is clear evidence that rough-surfaced implants decrease the integration time and may decrease overall treatment time appreciably.[22] The topic of immediate loading of dental implants is outside the scope of this review, but it should at least be stated that implants with rough surfaces are more likely to be successful when used in immediate loading situations.[45,49,50]

TIMELINE OF OSSEOINTEGRATION

Schwartz and Boyan[10] described the events involved in bone apposition in humans as occurring in a series of discrete but overlapping stages. Immediately after implantation, serum proteins adhere to the implant. During the first 3 days, mesenchymal cells attach and proliferate. By 6 days, osteoid is produced. By 2 weeks, matrix calcification is complete. At 3 weeks, remodeling is well under way.

One of the most critical (perhaps the *most* critical) factors in successful osseointegration of an implant is stability in the bone at the time of placement. Relative motion between the implant body and the surrounding bone during the early healing phase is considered to be a high risk factor for early implant loss as failure of osseointegration occurs. Following the placement of an endosseous implant, primary mechanical stability is gradually replaced by biologic stability. The transition from primary mechanical stability, provided by the implant design, to biologic stability provided by newly formed bone as osseointegration occurs takes place during early wound healing.[15] Therefore, presumably, there is a period of time during healing in which osteoclastic activity has decreased the initial mechanical stability of the implant but the formation of new bone has not yet occurred to the level required to maintain implant stability. During this critical period, a loaded implant would be at greatest risk of relative motion and would theoretically be most susceptible to failure of osseointegration. Only by bone remodeling will there be a gradual replacement of peri-implant bone, with the possibility of de novo bone formation at the implant surface.[13]

A series of cellular events contributes to this change. Osteogenesis in vivo must find a balance between achieving adequate coverage of an implant material with osteogenic cells and the ability of those cells to differentiate into competent osteoblasts in a timely manner.[12] Berglundh and coworkers,[15] in an in vivo study of de novo alveolar bone formation adjacent to endosseous implants, described a novel model to investigate different temporal phases of wound healing that result in osseointegration. Specially designed implants with a designated wound chamber were placed in Labrador dog mandibles. Within 2 hours the wound chamber was occupied by a coagulum of erythrocytes, neutrophils, and macrophages in a fibrin network. At 4 days, along the cut surface, osteoclasts were observed and mesenchymal cells (fibroblast-like cells), vascular structures, and densely packed connective tissue cells were found within the wound chamber. At 7 days, woven bone was first seen along the implant surface and along vascular units. Trabeculae were lined with osteoblasts and a provisional matrix which had collagen fibrils and vasculature. At 2 weeks, newly formed bone appeared to be extending from parent bone. At 4 weeks, marked formation of woven bone combined with lamellar bone was seen. Finally, at 8 and 12 weeks, there were marked signs of remodeling within the wound chamber. In this animal model, osteoclastic activity was seen as early as 4 days following implant placement, and new bone

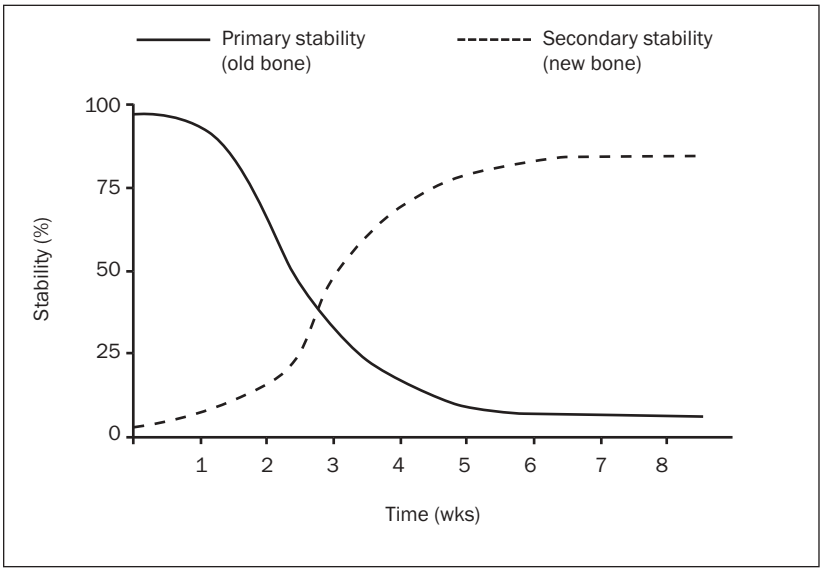

Fig 2 Changeover from primary stability created at the time of implant placement to secondary stability created by deposition of new bone (osseointegration) in humans.

formation was noted at 1 week postplacement. Replacement of the original bone that was responsible for the initial stability of the implant at placement was well underway at the 2-week mark.

Correlating the findings in the canine model of Berglundh and associates[15] with the timeline of the same events in human bone formation is difficult. A rough estimate of comparative healing rates between dogs and humans would suggest that the events of wound healing and bone remodeling happen approximately 1.5 times sooner in dogs than would occur in the human (personal communication, DL Cochran, September 2003). Assuming this to be true, the critical time frame for implant healing in humans would be 2 to 3 weeks postplacement, at least for the surface utilized in the Berglundh study.

The effect of immediate loading is not clearly understood as it relates to the timeline of osseointegration. However, it is clear that the processes of osseous remodeling and osseointegration occur simultaneously with functional loading. Interaction of these biologic and mechanical forces would seem to be critical to the successful integration of the implant (Fig 2). It appears that initial stability and continued stability during the healing phase is necessary for osseointegration to occur and that splinting of implants improves the likelihood of success.[49,50]

CONCLUSION

The recent literature was reviewed in an attempt to present the current state of knowledge of early wound healing adjacent to endosseous of dental implants.

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