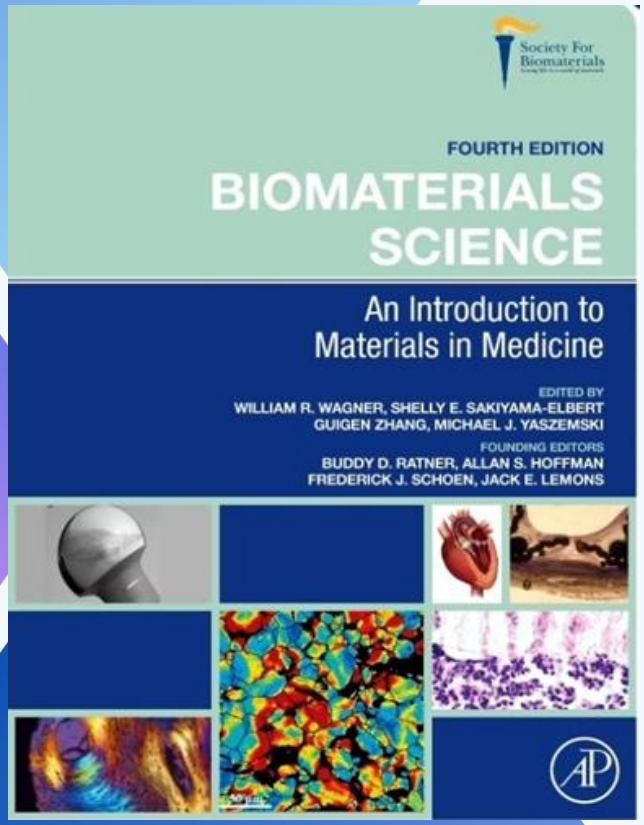
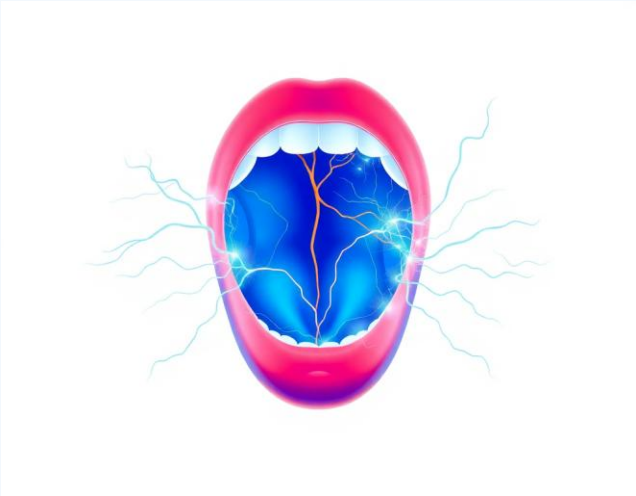


Dental Applications in Biomaterials

An In-depth Review for University Students

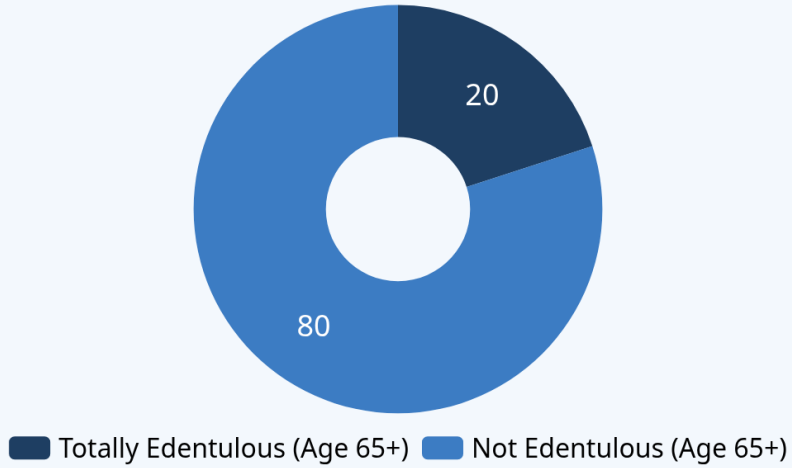
Based on Chapter 2.5.5 by DAVID H. KOHN & JACK E. LEMONS

Section 1: Overview - The Mouth as the Gateway



The mouth is the gateway to the body. The links between oral and systemic health are now widely accepted, with compromises in general health being strongly correlated with the loss of oral dentition.

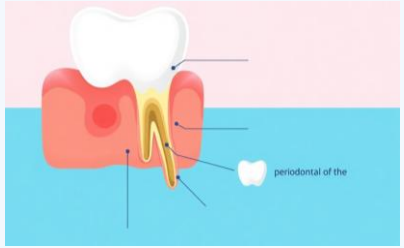
The Scale of Tooth Loss in the US



Furthermore, a substantial number of other patients are partially edentulous, having an average of 10 missing teeth. 50% of adults aged 20-64 have at least one missing tooth.

Prevalence of DOC Disorders

Beyond tooth loss, a wide range of Dental, Oral, and Craniofacial (DOC) disorders affect millions.



Periodontal Disease

15% of the US population has periodontal disease severe enough to warrant surgery.

TMJ Disorders

15 million people experience temporomandibular joint (TMJ) disorders.

Craniofacial Resection

30,000 patients a year undergo craniofacial resection surgery, often due to tumors.

Salivary Gland Disorders

4 million people suffer from salivary gland disorders, impacting quality of life.

A Global Health Challenge

Collectively, it is estimated that more than 85% of the world's population requires the repair or replacement of a dental, oral, or craniofacial (DOC) tissue at some point in their lives.

Clinical Challenges in DOC Tissue Restoration

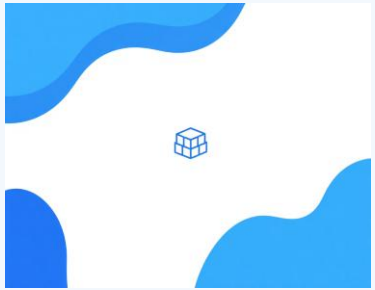
Defects in DOC tissues resulting from disease, trauma, congenital abnormalities, or tumor resection present a significant challenge to clinicians.

The replacement or restoration of these tissues is a major subject of clinical, basic science, and engineering concern.

Beyond Aesthetics: The Functional Impact

In addition to leaving patients with aesthetic deformities, defects in DOC tissues can be uncomfortable and profoundly affect function. Therefore, four key factors must be managed simultaneously.

Structure



Function

Aesthetics

Pain

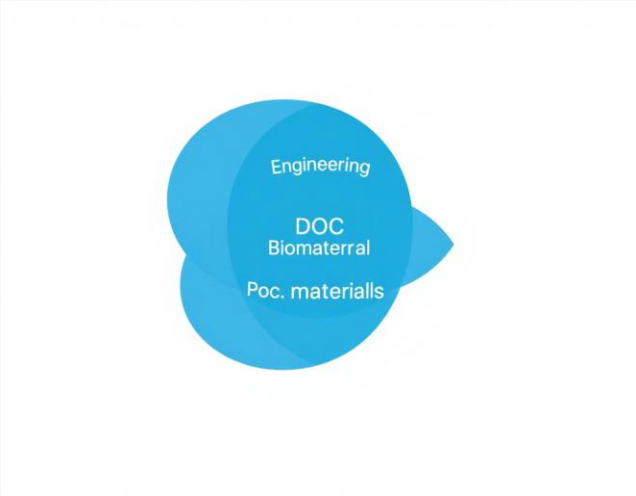
The Role of Biomaterials Science and Engineering

Biomaterials scientists and engineers working in the DOC space have developed a wide range of solutions to manage the loss of DOC tissue structure and function. This chapter will explore these advancements.

Chapter Roadmap

- Unique needs in designing materials for DOC use.
- An overview of restorative materials.
- In-depth discussion of dental implants.
- In-depth discussion of tissue-engineered medical products in dentistry.
- How dental biomaterials have informed the broader discipline.

Section 2: Unique Needs for DOC Biomaterials



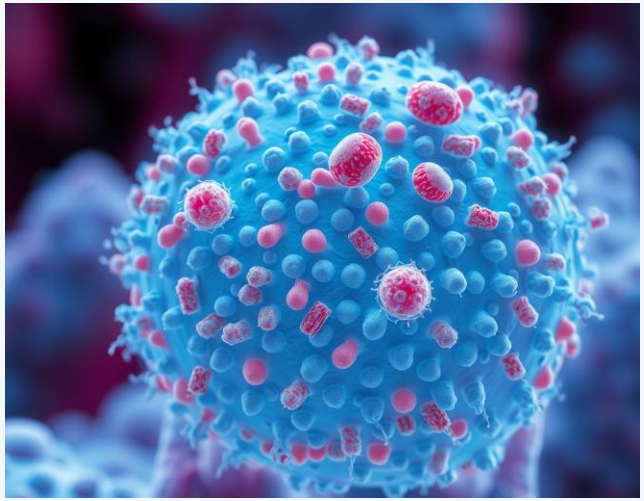
The replacement, reconstruction, and regeneration of DOC tissues require a deep synthesis of engineering, biology, and clinical sciences.

The tissues themselves are exceptionally complex.

Challenge 1: The Added Dimension of Aesthetics

In the DOC region, maintaining or restoring aesthetics, in addition to restoring structure and function, presents a more complex design problem than in many other regions of the body.

Challenge 2: The Oral Microenvironment



When designing biomaterials for use in the mouth, it is necessary to consider the unique microbial environment and the potentially altered host immune response that materials will be exposed to.

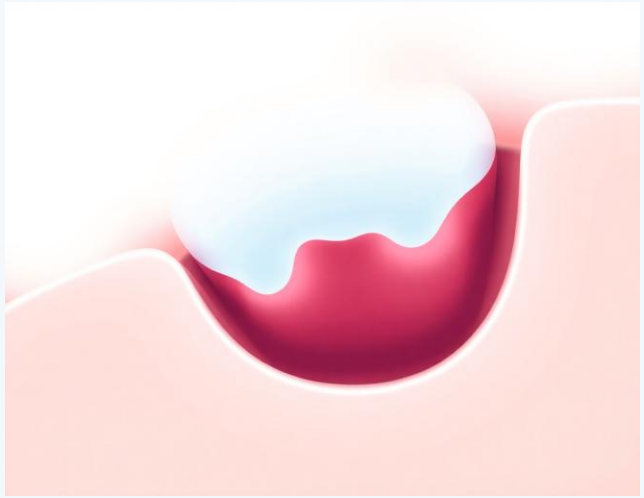
Challenge 3: Multi-Tissue Replacement

It is rare that a single DOC tissue needs to be replaced. More often, multiple, interconnected tissues are in need of repair or replacement.

Example: The Complexity of a Single Tooth

A single tooth consists of multiple mineralized tissues (enamel and dentin) surrounding a pulpal cavity that contains vasculature and innervation. It is a functionally graded material.

The Dentin-Enamel Junction (DEJ)



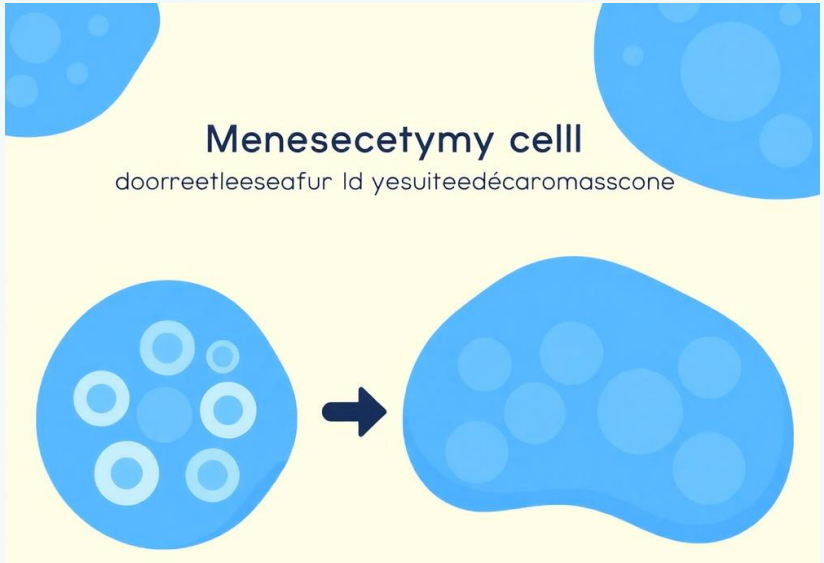
Within the mineralized tissue compartment of the tooth, there is an elegant, functionally graded transition from the hard, brittle enamel to the tougher, more compliant dentin.

This junction is critical for preventing crack propagation.

Challenge 4: Developmental Differences

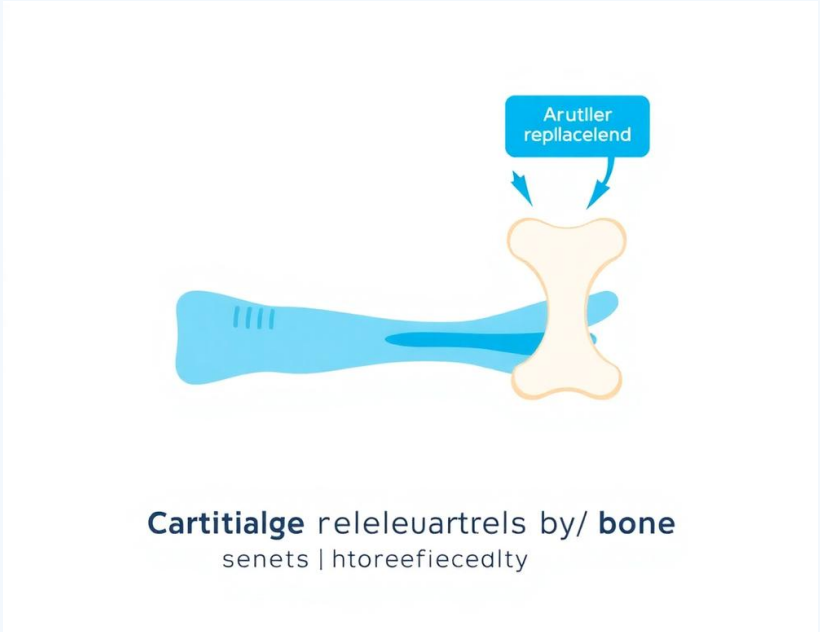
Craniofacial Bones

Formed by intramembranous ossification.

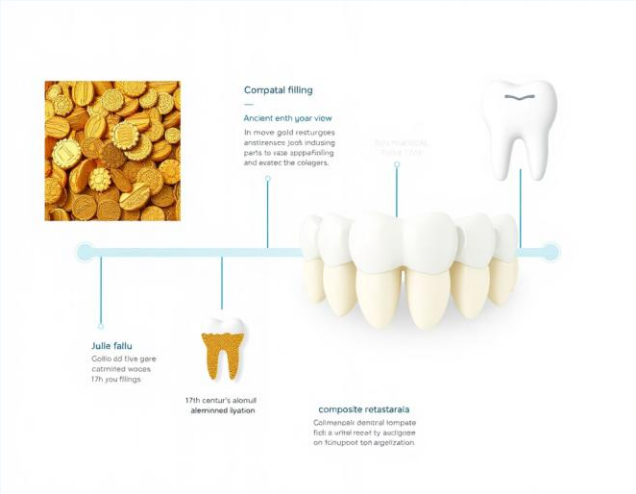


Axial Skeleton Bones

Formed via endochondral ossification.



Section 3: Restorative Materials



Restorative dental materials, used to reconstruct all or part of teeth, have played a prominent role in health care for several thousand years.

The development of dental materials has progressed more rapidly than many other areas of biomaterials.

The Harshest Environment in the Body

The oral environment subjects materials to:

High Forces

Significant and varying forces from mastication.

Fluctuating pH

Acidic and basic challenges from food and drink.

Temperature Swings

Rapid changes from hot coffee to ice cream.

Bacterial Attack

A complex and persistent biofilm.

Direct vs. Indirect Restorations

Direct Materials

The restoration is placed, shaped, and cured directly inside the prepared tooth in a single visit. Examples include amalgam and composite fillings.

Indirect Materials

The restoration is fabricated outside of the mouth in a dental lab based on an impression of the tooth. Examples include crowns, inlays, and bridges.

Range of Restorative Materials and Applications

A vast array of materials falls under the umbrella of restorative dentistry.

- Amalgams
- Composites
- Cements
- Crowns and Bridges
- Inlays
- Liners and Varnishes
- Orthodontic Materials
- Dentures
- Impression Materials

Classes of Materials Used

Metals

Silver-mercury amalgam alloys, noble metal inlays (gold), base metal alloys for partial dentures.

Ceramics

Porcelain for denture teeth, gypsum for investments and models.

Polymers

Acrylics for denture bases, alginates for impressions.

Composites

Methacrylate resins reinforced with silica particles for fillings.

The Rise of Composites

Composite materials, consisting of inorganic particulate fillers in a cross-linked polymer matrix, have largely displaced amalgams as primary restorative materials.

Reason 1: Aesthetics

Composites can be shade-matched to the natural tooth, providing superior aesthetic results.

Reason 2: Health Concerns

Public and professional concerns about the mercury content in amalgams have driven the shift.

Processing Composites: Photopolymerization

Composite restoratives are typically processed in situ. A filled resin (usually a methacrylate) is placed in the patient's mouth and irradiated with a high-intensity visible blue light.

This generates reactive species that initiate polymerization, hardening the material.

Composite Filler Particles

- **Material:** Manufactured from silica (quartz, glass, fumed or colloidal silica).
- **Size:** Range from 20 nm to 10 µm.
- **Volume Fraction:** Range from 50% to 85%.

The filler content is critical as it influences mechanical properties (stiffness, strength, fracture toughness, wear), polymerization shrinkage, and handling characteristics.

Key Challenge: Polymerization Shrinkage

Polymerization is accompanied by a significant amount of volumetric shrinkage, which generates stress at the tooth-restoration interface.

Consequences of Shrinkage Stress

1 Localized Debonding

The bond between the filling and the tooth breaks in small areas.

2 Marginal Gap Formation

A microscopic gap forms at the edge of the restoration, allowing bacterial ingress.

3 Tooth Deflection

The cusps of the tooth can be pulled inward by the shrinking material.

4 Tooth Cracking

In severe cases, the stress can lead to cracks in the remaining tooth structure.

Research: Mitigating Shrinkage Stress

Mitigation of polymerization-induced shrinkage and its associated stress is a primary area of research in dental biomaterials. Approaches explored include:

- Low-shrinkage ring-opening polymerization chemistries.
- Modification of in situ processing (e.g., 'soft-start' curing).
- Polymerization-induced phase separation.
- Thiol-ene-based polymerization.
- Allyl sulfide-based addition-fragmentation chain transfer.

Other Key Research Needs for Restoratives

Reducing Wear

Improving the material's resistance to abrasion and attrition from chewing to increase the lifespan of the restoration.

Improving Longevity of Bond

Enhancing the durability of the bond between the hydrophobic biomaterial (composite) and the hydrophilic tooth structure (dentin and enamel).

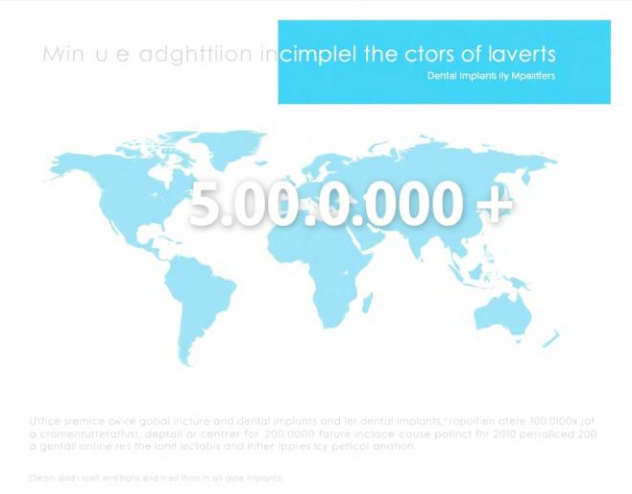
Emerging Challenges and Future Directions

- **Aging Population:** Increased need for restorations on exposed root surfaces.
- **Medically Compromised Patients:** Chronic diseases present additional challenges for material performance and healing.
- **Future Solutions:** Nanotechnology and advanced biofabrication may help overcome these challenges.

Section 4: Dental Implants

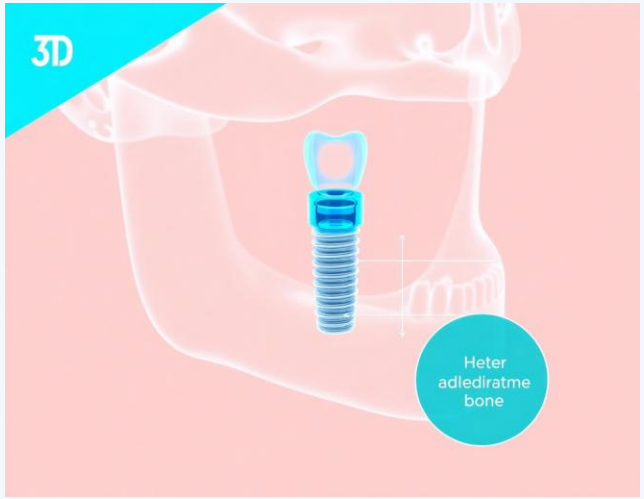
While removable dentures and fixed bridges offer effective treatments, patients who have lost substantial bone and cannot manage prostheses can vastly improve oral function through the use of dental implants.

Dental Implants by the Numbers



An estimated 5 million dental implants are inserted each year, providing long-term (15+ years) support for restorations.

The Fundamental Requirement for Success



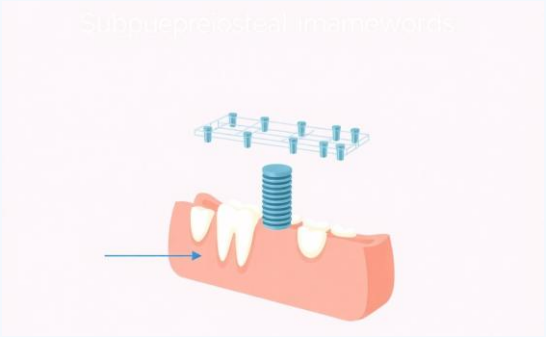
For a dental implant to be successful, there must be adequate bone to support it.

This includes sufficient bone width, height, length, contour, and density.

Classification of Dental Implants

Endosseous Implants

Embedded directly into the mandibular or maxillary bone. They project through the oral mucosa. This is the most common type.



Subperiosteal Implants

A custom framework that rests on the surface of the bone, beneath the periosteum (gum tissue).

Transosseous Implants

Penetrate through the bone, from the inferior border of the mandible upwards. Rarely used today.

Focus: Root-Form Endosseous Implants

Root-form endosseous implants are the most common type in clinical practice. The most prevalent design is the two-stage endosteal screw-type implant.

Many implant biomaterials and designs have been studied, but most applications now use these root-form designs that achieve an osseointegrated interface with bone.

Visualizing Root-Form Designs

Figure 2.5.5.1: Root-form type designs

Implants in Clinical Practice

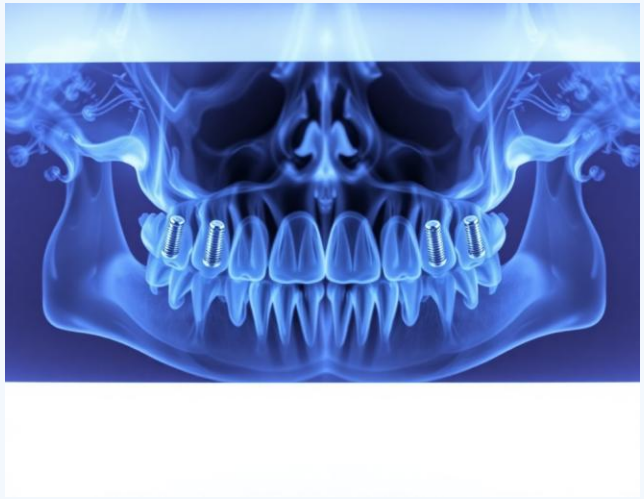


Figure 2.5.5.2: Radiograph of root-form implants

The Two-Stage Surgical Procedure

The most common approach involves a two-stage surgery:

Stage 1: Implant Placement

The implant fixture is surgically inserted into the jawbone and the gum tissue is closed over it. This allows for a controlled, undisturbed period of postsurgical healing (osseointegration).

Stage 2: Abutment and Prosthetic

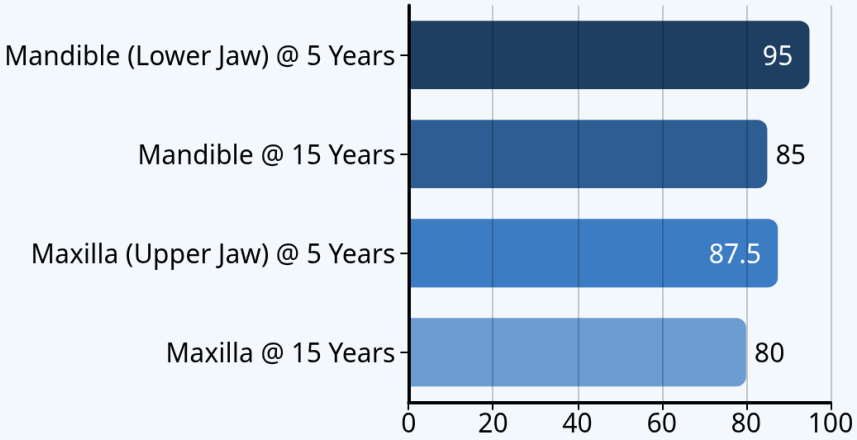
After several months of healing, the implant is uncovered, and the abutment (connecting piece) and final crown or bridge are attached.

Dominant Materials and Surfaces

The biomaterials used are now mostly titanium and its alloys, featuring a wide range of surface modifications to influence the interfacial tissue regions. These modifications include:

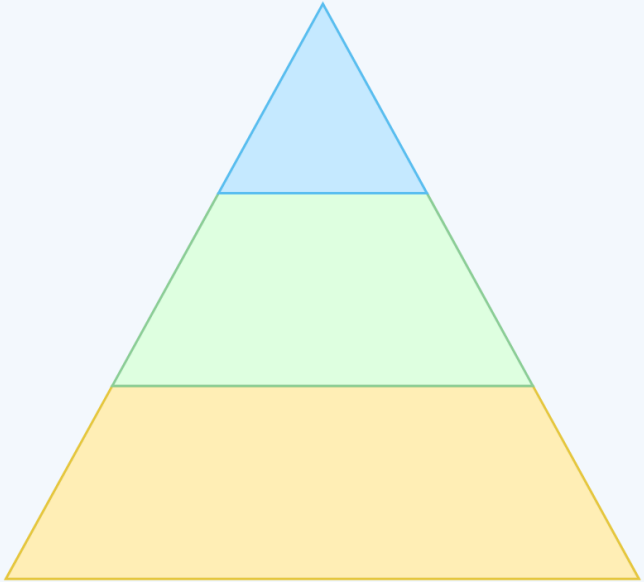
- **Compositional:** Oxides, calcium phosphates, and fluoride treatments.
- **Microtopographical:** Varying degrees of roughness to enhance bone integration.

Clinical Success Rates



Success rates for implants placed in the mandible are approximately 95% at 5 years and >85% at 15 years. For maxillary implants, which are placed in softer bone, rates are slightly lower.

Criteria for Successful Implant Function



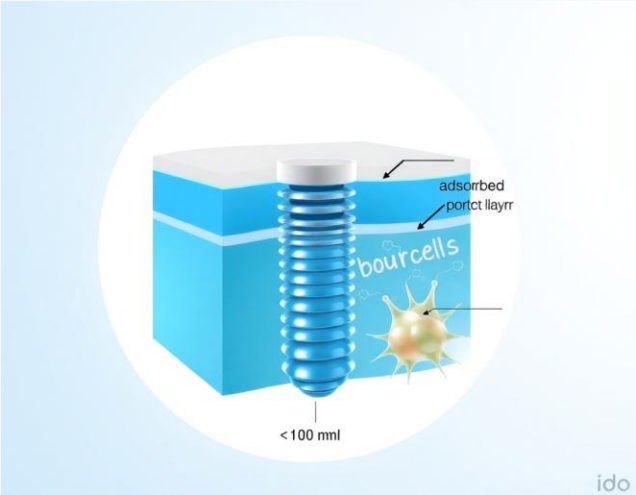
The Implant Material(s)

Healing & Remodeling of Tissues

The Interfacial Zone

A clinically successful implant is guided by the interplay of these three core factors.

The Critical Interfacial Zone



In a well-functioning, stable implant, the interfacial zone is composed of a thin (<100 µm) layer of metal oxide, proteins, and connective tissue.

The thickness and integrity of this zone are paramount for long-term success.

Interdependent Success Factors

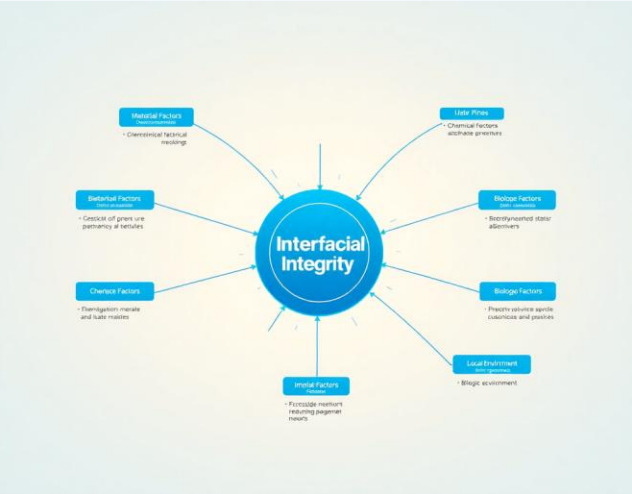


Figure 2.5.5.3: Factors Affecting Implant Success

The Concept of Osseointegration

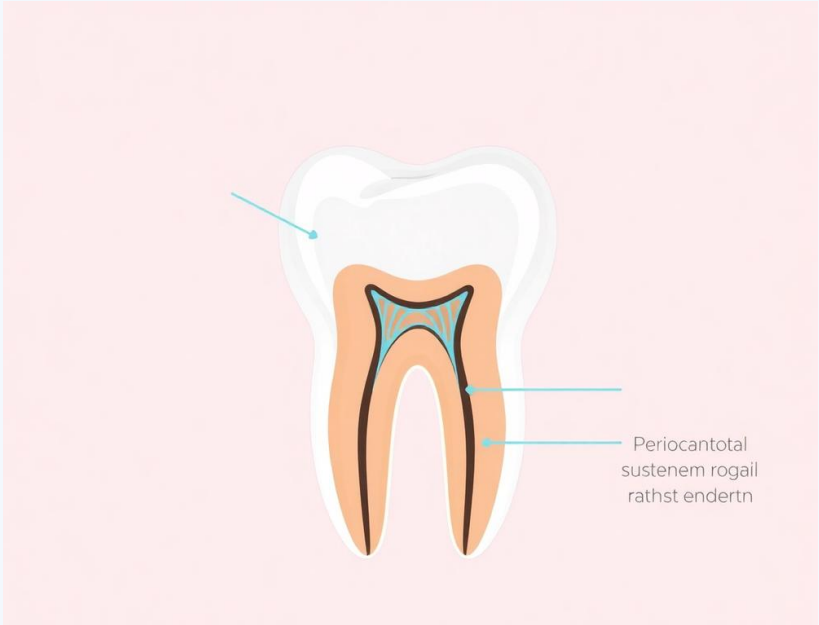
Unlike natural teeth, which are attached to bone by a shock-absorbing Periodontal Ligament (PDL), successful dental implants achieve a direct structural and functional connection with bone.

This is known as osseointegration.

Natural Tooth vs. Dental Implant

Figure 2.5.5.4: Attachment to Bone

Natural Tooth



Dental Implant

Defining Osseointegration

Osseointegration is the direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant.

This definition was originally based on light microscopy and has been refined by higher-resolution electron microscopy.

The Biological Process of Osseointegration

Fundamentally, osseointegration is the host bone's predictable response to a sterile surgical wound, leading to interfacial osteogenesis (new bone formation at the interface) and mechanical stability of the implant.

Success vs. Failure at the Interface

Success: Osseointegration

Following short-term healing (4-6 months), a stable marginal bone level is achieved and maintained.

Failure: Fibrous Encapsulation

Poorly differentiated connective tissue (scar tissue) forms at the interface, leading to mobility and implant failure.

The Importance of Stress Transfer

To function properly, an implant must carry occlusal (biting) stresses, transfer them across the interface, and transmit them to the adjacent bone. The stresses should mimic physiologic levels to maintain tissue viability.

Two Primary Design Goals for the Interface

1

Goal 1: Accelerate Stability

Stabilize the interface in as short a time postoperatively as possible to achieve osseointegration.

2

Goal 2: Maintain Stability

Ensure the interface remains stable for as long a time as possible to prevent late-term failure.

The Micromotion Threshold

'Stability' is defined as the maximum allowable displacement at the interface that will still result in osseointegration.

Motion of an implant less than 100-200 µm is considered most conducive to creating and maintaining this stable connection.

Strategies to Accelerate Healing

Because a stable interface must develop before loading, it is desirable to accelerate tissue apposition. Clinical strategies include:

- Use of surface-roughened implants
- Nanostructured surfaces
- Bioactive ceramic coatings
- Bone grafting
- Recombinant growth factors and Platelet-Rich Plasma (PRP)
- Antimicrobial coatings
- Drug-eluting coatings (e.g., bisphosphonates)

The Interface at Multiple Scales

Analysis of the interface zone at nano-, micro-, and macro-levels demonstrates the importance of controlling a multitude of factors, from implant properties to surgical method and patient maintenance.

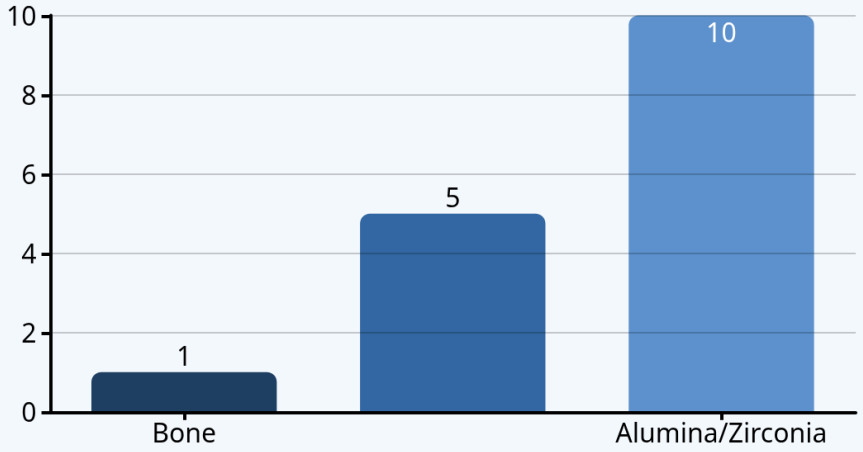
Role of Surface Roughness

Roughening the implant surface increases the surface area, which provides conditions for accelerating early healing (blood clotting, fibrin deposition, integrin binding) and allows for microscopic interdigitation with bone.

This 'mechanical lock' increases force transfer and resistance to shear at the interface.

Role of Elastic Modulus

The relative stiffness (elastic modulus) of the implant and bone affects stress distribution. A large mismatch can lead to stress shielding of the bone or high stresses at the interface.



Sub-Section: Surface Topology and Chemistry

A variety of implant surface configurations can improve the cohesiveness of the implant-tissue interface.

Alterations in surface topology can decrease relative motion and increase the transfer of occlusal loads to tissue.

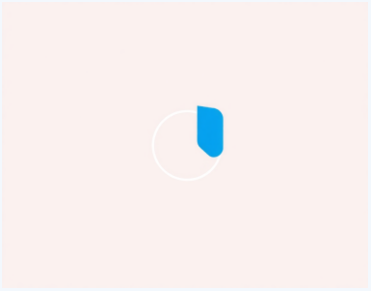
Types of Implant Surfaces

Smooth

Textured

Screw-threaded

Coated



On-growth vs. In-growth

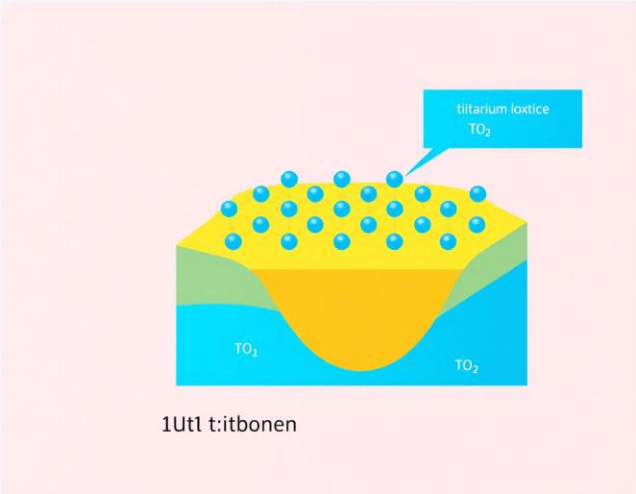
Tissue On-growth

Occurs with screw-threaded and moderately rough surfaces. Bone grows directly onto and apposes the implant surface.

Tissue In-growth

Occurs with highly porous or 3D surface layers. Bone grows into the surface features, providing stronger mechanical interlocking and higher shear strength.

Understanding Surface Chemistry



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It is critical to understand that for metal implants, the tissue interface is not with the bulk metal, but with its surface oxide layer.

This oxide's properties dictate the biological interactions.

Corrosion Resistance and Biocompatibility

Titanium-based materials are well tolerated because their passive oxide layers are extremely stable and reform instantly if scratched (repassivation).

This minimizes the release of metal ions, which can be toxic in larger concentrations.

Surface Modification Techniques

Anodization

An electrochemical process that thickens the natural oxide layer, enhancing its stability and allowing for color-coding.

Laser Treatment

Used to alter surface energy and micro-texture, and as a secondary means of sterilization.

Sub-Section: Mechanical Parameters and Implant Design

The mechanical properties of implant materials are crucial to prevent failure and ensure proper function.

Key Mechanical Properties in Implant Design

Stiffness (Modulus)

Dictates how the implant transmits stresses to the adjacent tissue. Must be balanced to avoid stress shielding.

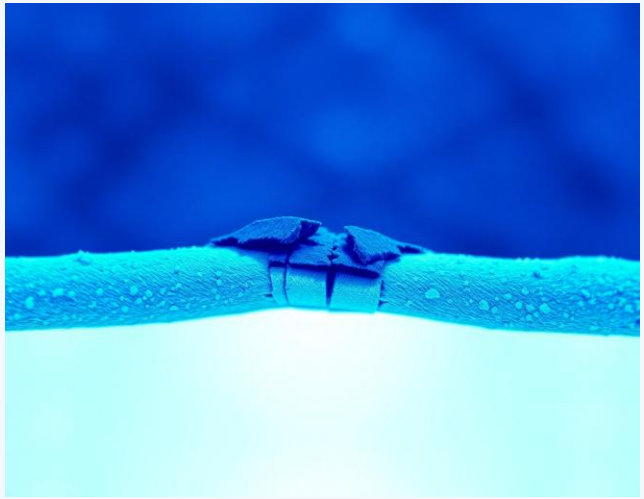
Strength (Yield, Ultimate, Fatigue)

The ability to resist deformation and fracture under load, especially repeated cyclic loads from chewing.

Fracture Toughness

A measure of the energy needed to cause fracture in the presence of a defect (like a sharp thread or surface porosity).

Fatigue Failure



Material failure of implants, generally by fatigue, does occur and is a clinically important consideration.

Fatigue properties must be a central part of implant design, as implants are subjected to millions of loading cycles over their lifetime.

Implant Geometry and Design Factors

Implant design is based on several factors, including:

- Implant geometry (length, diameter)
- Macroscopic shape (tapered, straight)
- Microscopic shape (thread design)
- How geometry affects mechanical properties and stress distribution
- Initial and long-term stability of the interface

Optimizing Implant Design: A Balancing Act

Implants can be designed to optimize different criteria, which are often in conflict:

Maximize Strength

Requires larger diameter and higher strength materials.

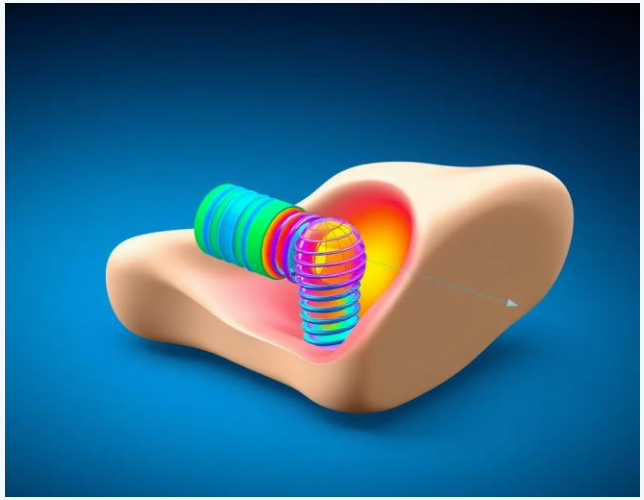
Maximize Interfacial Stability

Often relies on specific surface topographies and coatings.

Maximize Load Transfer

Requires a modulus matched to bone and good interfacial fixation.

Complex Loading Patterns



Dental implants are subjected to a complex combination of axial, shear, bending, and torsional forces in service.

The magnitude and direction of these forces must be considered in the design process.

Sub-Section: Materials Used in Dental Implants

Two primary classes of materials—metals and ceramics—are used to manufacture dental implants, either alone or in hybrid designs.

The properties of these materials are heavily influenced by their processing.

Table 2.5.5.1: Properties of Metals and Alloys

Material	Composition (w/o)	Modulus (GPa)	UTS (MPa)	Elongation (%)	Surface
Titanium	99% Ti	100	240-550	>15	Ti oxide
Titanium-aluminumvanadium	90Ti-6Al-4V	120	860-930	>8	Ti oxide
Cobalt-chromiummolybdenum	66Co-28Cr-6Mo	235	520-1170	>8	Cr oxide

Table 2.5.5.2: Properties of Inert Ceramics

Material	Modulus (GPa)	Bending Strength (MPa)	Surface
Aluminum oxide (Poly-crystalline)	370	300-550	Al2O3
Zirconium oxide (stabilized)	150-240	500-650	ZrO2
Titanium oxide (titania)	280	70-100	TiO2
Carbon	25-40	150-250	C

Table 2.5.5.3: Properties of Bioactive Ceramics

Material	Modulus (GPa)	Bending Strength (MPa)	Surface
Hydroxyapatite	10-120	15-300	Ca10(PO4)6(OH)2
Tricalcium phosphate	30-120	15-120	Ca3(PO4)2
Bioglass or Ceravital	40-140	20-350	CaPO4

Focus on Metals: Titanium

Metallic implants in modern clinical dentistry are almost exclusively manufactured from titanium and its alloys.

Strength

Derived from its hexagonal close-packed (HCP) crystal lattice structure.

Biocompatibility

Attributed to its highly stable, passive, and self-healing titanium dioxide (TiO_2) layer.

CPTi vs. Ti-6Al-4V

Commercially Pure Ti (CPTi)

Slightly more biocompatible in some studies, with tissues potentially getting in closer proximity to the surface. Lower strength.

Ti-6Al-4V Alloy

Has approximately 60% greater strength than pure titanium, but is more expensive. No discernible difference in clinical implant function has been proven.

Focus on Ceramics

Ceramic implants were introduced because of their relative biologic inertness. As fully oxidized materials, they are chemically stable and less likely to elicit an adverse biological response than metals.

Types of Ceramics in Dental Applications

"Inert" Ceramics

Includes alumina (Al_2O_3) and zirconia (ZrO_2). Used as bulk implants due to high strength and stability.

Bioactive Ceramics

Includes calcium phosphates. They elicit tissue formation, can bond with bone, and are partially soluble. Used as coatings or scaffolds.

Bioresorbable Ceramics

Have a higher degree of solubility, gradually resorbing and being replaced by new tissue. Used as bone augmentation materials.

The Concept of Bioactivity

The biocompatibility of an implant is optimal if it elicits the formation of normal tissues at its surface and establishes a contiguous, load-bearing interface.

Bioactive materials achieve this through controlled surface reactions.

Examples of Bioactive Materials

- **Bioactive Glasses:** e.g., Bioglass, Ceravital. Synthesized from mixtures of silica, phosphate, calcia, and soda.
- **Glass Ceramics:** e.g., Apatite-wollastonite glass ceramic.
- **Calcium Phosphate Ceramics:** A group of materials with varying calcium-to-phosphate ratios, with Hydroxyapatite (HA) being the most common.

Hydroxyapatite (HA) Coatings

The impetus for using synthetic HA stems from the advantage of using a material that is chemically similar to the mineral phase of natural bone, with the expectation of achieving better tissue bonding.

Advantages of Bioactive Ceramic Coatings

- Elastic properties can be tailored to be similar to bone.
- Degradation rates can be controlled via material properties (e.g., crystallinity, Ca/P ratio).
- Can function as a corrosion barrier when coated onto a metal implant.

The Importance of Processing Calcium Phosphates

Ion exchange reactions at the ceramic surface, which dictate all properties, depend heavily on processing techniques, time, temperature, and atmosphere.

Different techniques (e.g., plasma spraying, sol-gel, laser deposition) result in different structures, compositions, and dissolution rates.

Characterization of Calcium Phosphates

Material Parameter	Functional/Biological Relevance	Characterization Technique
Particle size, shape	Strength	Sifting, Stereology
Pore size, shape	Strength, Bioreactivity	Stereology, SEM
Specific surface area	Dissolution/Precipitation	Brunauer-Emmett-Teller (BET)
Phases	Dissolution, Protein Adsorption	XRD, FTIR

Section 5: Future Directions for Dental Implants

Despite excellent clinical success, failures still occur at a rate of approximately 2-5% per year. Addressing the causes of these failures is a major focus of current research.

Common Causes of Implant Failure

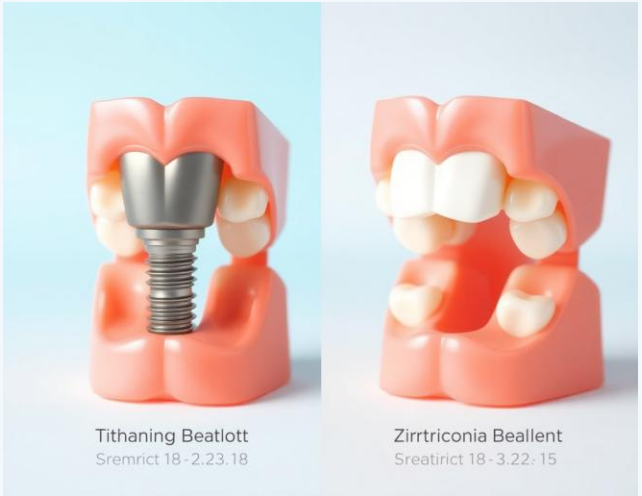
Early Loosening	Late Loosening	Bone Resorption	Infection & Inflammation	Mechanical Failure
A lack of initial osseointegration.	Loss of established osseointegration over time.	Progressive loss of supporting bone around the implant.	Peri-implantitis, an inflammatory process affecting surrounding tissues.	Fracture of the implant/abutment or delamination of coatings.

Primary Failure Mechanism: Bone Resorption

The most common failure mechanism is alveolar crest bone resorption, which leads to a decreased volume of supporting tissue and, ultimately, implant loosening.

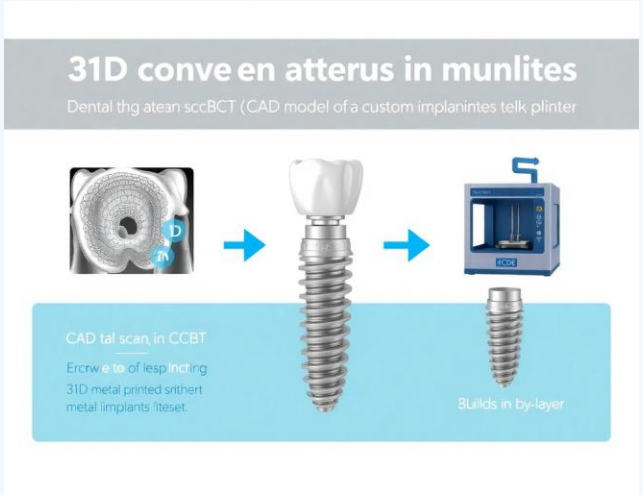
This can be mechanically mediated (stress shielding) or biologically mediated (peri-implantitis).

Biomaterials Advances: Improved Aesthetics



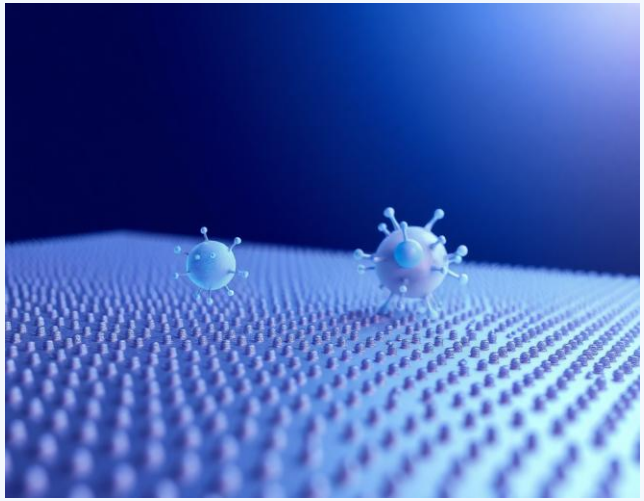
Increased use of implants made from zirconia for improved aesthetics, as they are tooth-colored and eliminate the risk of a dark metal margin showing through thin gum tissue.

Biomaterials Advances: Digital Technologies



Additive manufacturing (3D printing) of implants via digital technologies (CAD/CAM) allows for custom-fitted implants and more rapid fabrication, sometimes even allowing for fabrication before tooth extraction for immediate insertion.

Biomaterials Advances: Nanoscale Modifications



Advanced modification of implant surfaces at the nanoscale, including patterning, functionalization, and molecular grafting to better control cellular responses.

Biomaterials Advances: Antibacterial Coatings

Passive Coatings

Kill bacteria that come into direct contact with the biomaterial surface (e.g., via surface chemistry or topography).

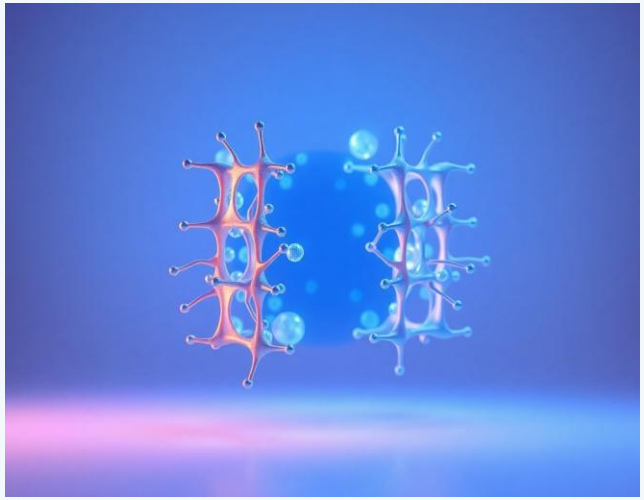
Active Coatings

Release antibacterial agents (like silver ions or antibiotics) to kill bacteria at a distance from the implant.

Biomaterials Advances: Drug-Eluting Coatings

Development of technologies for the controlled release of therapeutic agents directly from the implant surface, such as bisphosphonates (to inhibit bone resorption) or Bone Morphogenetic Proteins (BMPs) (to stimulate bone growth).

Section 6: Tissue Engineering in Dentistry



When bone stock is inadequate or lost, alternative approaches are needed to treat inflammation and/or regenerate bone.

This is the realm of tissue engineering.

Need for Tissue Engineering: Limitations of Gold Standards

Gold standard treatments for DOC tissue repair (autografts, allografts, synthetic materials) each have significant limitations and lack clinical predictability.

Limitations of Current Therapies

1 **Autografts**

Limited tissue availability, donor site morbidity and pain, difficulty shaping, failure rates as high as 30%.

2 **Allografts**

Potential for pathogen transfer, processing (irradiation, freeze-drying) can reduce structural integrity.

3 **Growth Factors**

Relies on a sufficient population of responsive host cells, which may not be available in aged or compromised patients.

4 **Synthetic Materials**

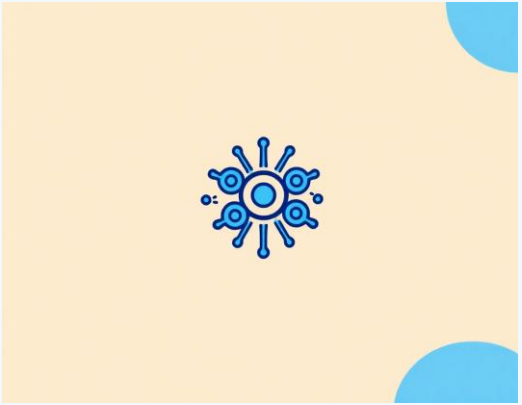
Complications include stress shielding, loosening, and mechanical breakdown over time.

The Tissue Engineering Triad

Successful tissue engineering requires the synthesis of three key components to optimize the development of DOC tissues, hybrid tissues, and their interfaces.

Scaffolds

The structural support.



Cell Sources

The 'bricks' to build the tissue.

Signals

The instructions for the cells.

Targets for Dental Tissue Engineering

- Teeth (whole or parts)
- Oral Mucosa
- Salivary Glands
- Craniofacial Bone
- Cranial Sutures
- Periodontium (ligament and bone)
- Muscle
- Temporomandibular Joint (TMJ)

General Tissue Engineering Strategies

Conduction

A biomaterial scaffold guides the growth of host cells to form new tissue. (Most common in dentistry).

Induction

Biologic agents (e.g., growth factors) induce host cells to form a specific new tissue.

Cell Transplantation

Differentiated or stem cells are transplanted, often with a scaffold, to regenerate tissue.

Design Requirements for DOC Scaffolds (1/2)

- **Biocompatibility:** Must not cause an adverse reaction.
- **Conductivity:** Guide cell attachment, proliferation, and matrix secretion.
- **Inductivity:** Ability to incorporate inductive factors to direct tissue growth.
- **Vascular Support:** Support vascular ingrowth for oxygen and nutrient transport.

Design Requirements for DOC Scaffolds (2/2)

- **Mechanical Integrity:** Support loads at the graft site.
- **Controlled Degradation:** Degrade at a predictable rate into non-toxic byproducts.
- **Processability:** Easy and cost-effective to process into complex 3D shapes.

Biomaterials Used for DOC Tissue Engineering

A wide range of synthetic and natural biomaterials are used, including:

- PLGA, PCL, PEG, Polyurethanes
- Collagen, Starch, Alginate, Silk
- Bioactive Glasses and Glass Ceramics
- Calcium Phosphate Ceramics
- Composite blends of the above materials

Enhancing Scaffold Functionality

To better mimic the native environment, material modifications are employed:

Chemical Modifications

Changes in hydrophilicity, surface functionalization, and incorporation of cell recognition peptides (e.g., RGD).

Physical Cues

Reproduction of nanoscale topology, application of mechanical stimuli, and precise control of degradation.

Biological Recognition

Designing materials that bind and release soluble factors, potentially obviating the need for direct cell/growth factor delivery.

Application: Engineering Teeth

The tooth is composed of four distinct tissues: pulp, dentin, cementum, and enamel, supported by a periodontal ligament.

This complexity makes whole-tooth engineering incredibly challenging.

The Challenge of Whole Tooth Regeneration

Unlike bone engineering, where a scaffold can draw cells from surrounding tissue, a tooth must be regenerated at a site where it no longer exists.

The engineered construct must be self-reliant, containing all the necessary cells and signals for morphogenesis and eruption.

A Bioengineered Tooth Germ

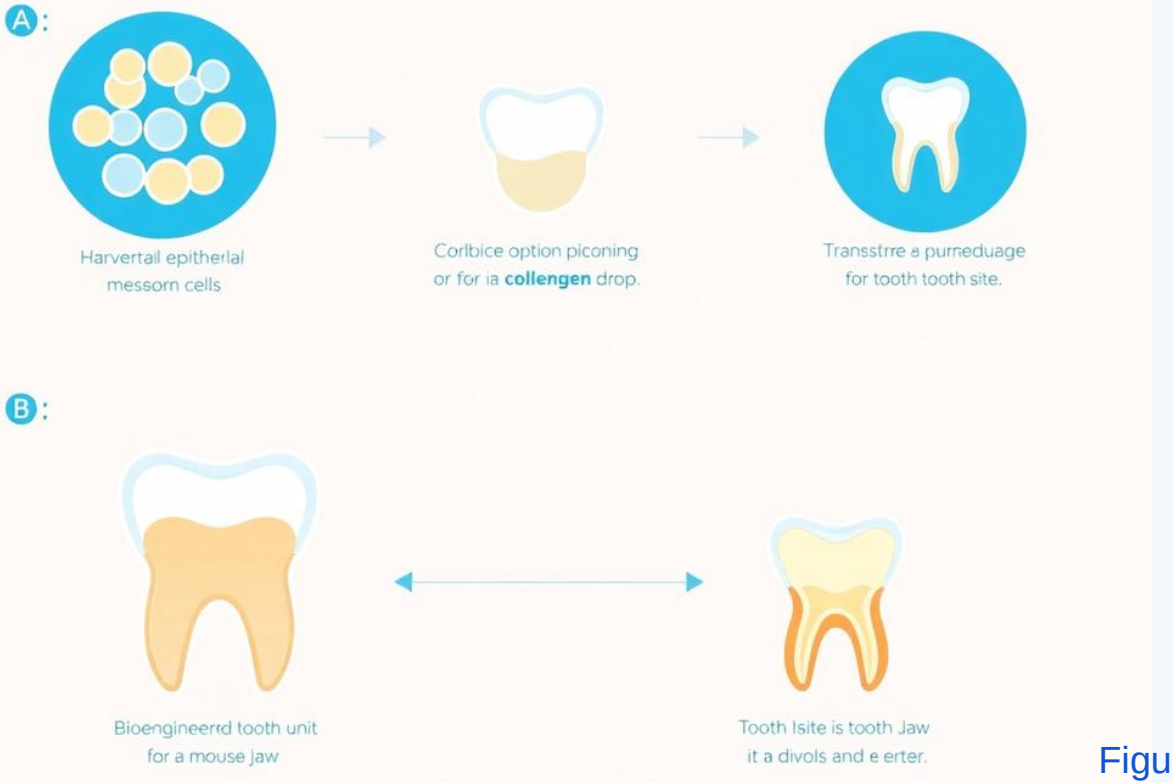


Figure 2.5.5.5: Bioengineered Tooth Unit

Dental Stem Cells

Two unique mesenchymal stem cell (MSC) populations have been isolated from teeth:

Dental Pulp Stem Cells (DPSCs)

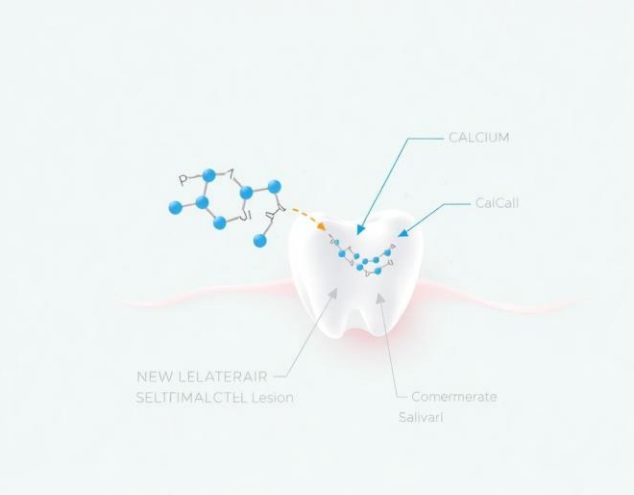
Present in the soft pulp tissue inside the tooth.

Periodontal Ligament Stem Cells (PDLSCs)

Isolated from the ligament that connects the tooth to the bone.

When transplanted on scaffolds, these cells can regenerate vascularized dentin/pulp-like complexes.

Material-Centric Approach: Enamel Remineralization



The acellular nature of enamel allows for material-centric approaches.

Self-assembling peptides have been used to promote enamel remineralization by providing a biomimetic scaffold that nucleates new hydroxyapatite crystals within early carious lesions.

Application: Temporomandibular Joint (TMJ)

Engineering strategies for the TMJ focus on regenerating the osteochondral (bone and cartilage) surfaces of the joint to overcome drawbacks of purely surgical treatments.

Engineering an Osteochondral Graft

A functional graft requires regenerating both bone and cartilage with a defined, mineralized interface.

This has been achieved using biphasic scaffolds, where different cell types are seeded onto distinct material phases.

Biphasic Scaffolds

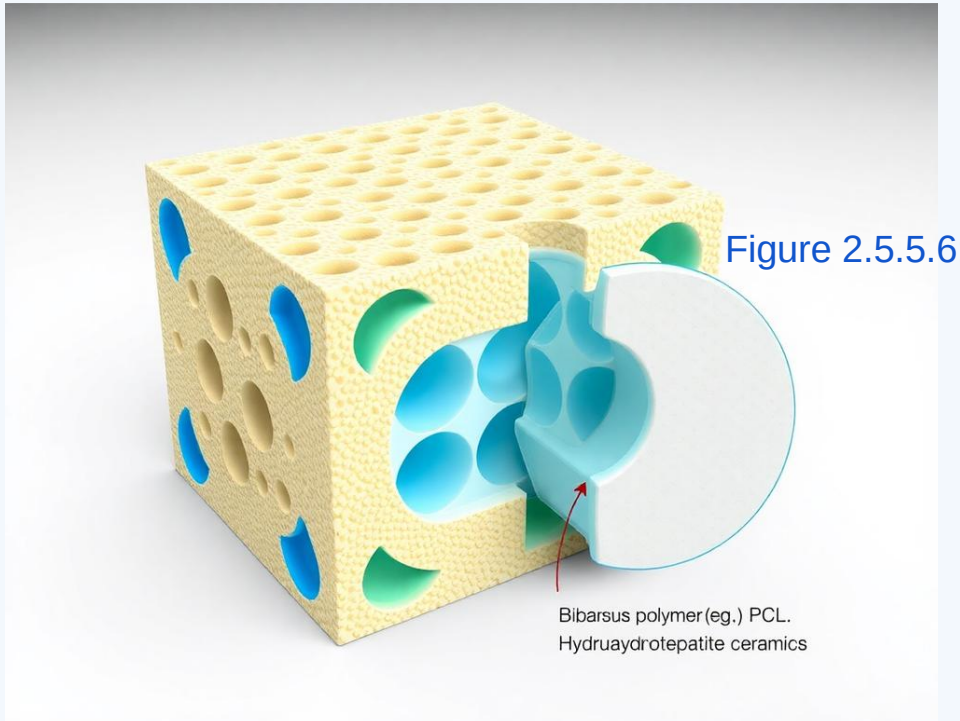


Figure 2.5.5.6: Engineered Osteochondral Graft

Application: Oral Mucosa

Oral mucosa is a specialized tissue of stratified epithelium over a supportive lamina propria.

Engineering it requires creating a full-thickness tissue with these distinct layers.

Clinical Application of Engineered Mucosa

First-in-human studies have been performed with ex vivo-produced oral mucosa equivalents (EVPOMEs).

Oral keratinocytes from a biopsy are expanded and cultured on an acellular dermal matrix, then grafted into place.

Grafting of Engineered Oral Mucosa

Figure 2.5.5.7: Clinical Views

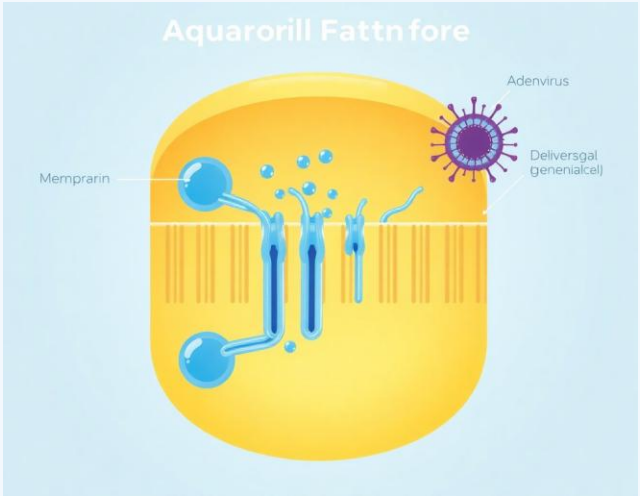
Application: Salivary Glands

Loss of salivary gland function (xerostomia) is a serious condition. Tissue engineering aims to create a substitute to restore saliva production.

Challenges in Salivary Gland Engineering

- Identifying a cell population capable of differentiation and active fluid movement.
- Optimizing scaffold material properties to form polarized epithelial ducts.
- Defining ideal culture conditions and ECM components.

Gene Therapy Approach: Aquaporins



Salivation is facilitated by water channels called aquaporins (AQPs). Isolated cells often lack AQP expression.

A recent clinical trial showed that adenoviral-mediated transfer of the AQP1 gene to irradiated salivary glands successfully increased saliva production without major side effects.

Application: Bone and Periodontium

Strategies to engineer craniofacial bone and the periodontium (the tooth-supporting structures) focus on nanomaterials and advanced signal delivery.

Patient-Specific Scaffolds for Periodontal Repair

Using 3D printing, patient-specific polycaprolactone (PCL) scaffolds can be manufactured to precisely fit a periodontal defect.

These can be designed with features to guide periodontal ligament formation and deliver growth factors.

Custom 3D-Printed Scaffold

Figure 2.5.5.8: Customized PCL Scaffold

Biochemical Signaling in Scaffolds

The Extracellular Matrix (ECM) provides adhesive ligands that direct cell function.

Scaffolds can be functionalized with peptide sequences that mimic these signals to precisely regulate cell behavior and promote tissue formation.

Growth Factor Delivery for Periodontal Regeneration

Direct delivery of recombinant growth factors has progressed to commercialization. GEM-21S, for example, consists of recombinant human Platelet-Derived Growth Factor (rhPDGF) delivered in a tricalcium phosphate (TCP) vehicle to regenerate bone in periodontal defects.

Section 7: Summary and Broader Impact

The history of biomaterials in dentistry is long and rich, and experiences from this field have brought significant value to other areas of biomaterials and medicine.

Lesson Learned: The Two-Stage Procedure

What problem was addressed?

Early examination of retrieved implants showed fibrous scar tissue at the interface, not bone.

One key factor was that implants were loaded immediately, before the bone could heal and integrate.

The Solution

This observation led directly to the development of the now-standard two-stage procedure, where implants are submerged and allowed to heal for 4-6 months before prosthetic attachment.

This concept of allowing undisturbed healing was a major paradigm shift that influenced other orthopedic therapies.

New Challenge: Reducing Wait Times

What properties were required in a material?

The 4-6 month wait time motivated the development of materials that could accelerate healing. The ideal material would be both bioactive (encouraging bone growth) and capable of delivering biological factors (like growth factors).

The Solution: Biomimetic Coatings

What material solution was developed?

Since high-temperature coating processes destroy biological agents, low-temperature 'biomimetic' processes were developed.

By immersing an implant in a simulated body fluid, a bone-like mineral layer is grown on the surface. Biological agents can be incorporated into this layer and released in a controlled manner.

The Oral Cavity as a Research Platform

The accessibility of the oral environment and the ability to create minimally invasive models make oral tissues convenient platforms for testing tissue-engineered prototypes. This has a twofold impact:

- Advances made in dentistry can be translated to other organ systems.
- Technologies developed outside of dentistry can be readily tested in oral models (e.g., the calvarial defect model).

Final Takeaway

Oral and craniofacial tissue engineering is not an isolated field.

It is an integral component of the larger field of tissue engineering and regenerative medicine, contributing key insights and benefiting from broader advances.