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Pulp therapy related materials

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Abstract: The primary objective of pulp therapy is to stimulate the remaining pulp to regenerate to maintain its vitality. Therefore maintaining the integrity and health of the teeth and their supporting tissues affected by caries, traumatic injury, or other causes especially in young permanent teeth with immature roots.
Therefore in order to preserve the tooth, dental pulp regeneration and preservation can be achieved by pulp therapy that can be classified into; Pulp Capping (Vital pulp therapy) and Whole Pulp regeneration (Non-vital therapy)

Keywords: *pulp capping,pulp regenerations,pulp capping materials,calcium hydroxide,MTA*

I- Pulp Capping:

The main goal of pulp capping is to promote the pulpal tissue to heal by revascularization and the deposition of tertiary dentin, which increases the distance between the injury and the pulp.

Vital pulp therapy is only recommended for teeth that are asymptomatic, or which exhibit only minimal inflammatory symptoms. The idea of vital-pulp therapy has been greatly enhanced with the introduction of various pulp capping materials.(2)

Pulp capping is classified into:

1) Indirect Pulp Capping: A pulp capping agent is placed over the remaining thin layer of dentin above the pulp chamber.

2) Direct Pulp Capping: A protective biomaterial (called pulp capping agent) is placed directly over the exposed pulp.

3) Pulpotomy: When dental pulp exposure is large, or the pulp is infected, all of the coronal pulp must be removed, and direct pulp capping will subsequently be performed adjacent to the root pulp. A pulp capping agent is placed over partially removed coronal pulp tissue. (2)

Requirements of ideal pulp capping materials:

1. Stimulate reparative dentin formation.

2. Maintain pulpal vitality.

3. Antibacterial effect.

4. Adhere to dentin and restorative material.

5. Resist forces during placement and the life of the restoration. 6. Radiopaque.

7. Fluoride release.(3)

The first documented pulp-capping treatment was conducted in 1756 by Pfaff, using gold foil. Since then, many agents have been recommended for direct pulp capping. (2)

1.Calcium Hydroxide:

In 1930, Hermann discovered that calcium hydroxide is effective in repairing an exposure site. Since then, calcium hydroxide has been used with clinical success for facilitating the formation of reparative dentin along with the maintenance of vital pulp, the induction of mineralization and the inhibition of bacterial growth. Calcium hydroxide has been the gold standard for pulp capping. (4)

Mechanism of action:

Ca(OH)2 release calcium (Ca) and hydroxyl (OH) ions upon dissolution.

• Calcium ions react with carbon dioxide in the tissues, forming calcium carbonate. It can also increase the action of pyrophosphatase enzyme that increases energy utilization. Therefore, stimulating DPSCs (dental pulp stem cells) differentiation and dentin-bridge formation.

• Hydroxyl ions produce high pH of approximately 12. Therefore, provides excellent antibacterial properties as it neutralizes lactic acid from bacteria and damages the bacterial cytoplasmic membrane.

The regenerative effect of Ca(OH)2 is due its alkaline PH that solubilize dentine matrix stimulating the release of pro-angiogenic growth factors as vascular endothelial growth factor (VEGF), transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) from it. These growth factors promote the migration and proliferation of (DPSCs) and periodontal ligament stem cells (PDLSCs). (5)

Three histologic zones under Ca(OH)2 are formed: -

Zone of obliteration: The pulp tissue immediately in contact with the calcium hydroxide is usually completely distorted because of the caustic effect of the drug. This zone consists of debris, dentinal fragments, hemorrhage, blood clot, and particles of calcium hydroxide. (6)

Zone of coagulation necrosis: A weaker chemical effect reaches the subjacent, more apical tissues and results in a zone of coagulation necrosis and thrombosis, also called layer of 'firm necrosis'. (6)

Zone of demarcation: A line of demarcation develops between the deepest level of the zone of coagulation necrosis and the subjacent vital pulp tissue. Exposed human dental pulp will heal with hard tissue bridging. (6)(7)

Advantages:

• Antibacterial properties

• High pH stimulates fibroblasts so promotes healing and repair. • Neutralizes low pH of acids.

• Inexpensive and easy to use.(5)

Disadvantages:

1.It has been reported that 89% of dentin bridges formed by calcium hydroxide cement contained tunnel defects. These tunnel defects fail to provide a permanent barrier and long-term biological seal against bacterial infection.

2. Dissolution which may lead to the formation of a dead space and microleakage. 3.Does not adhere to dentin or resin restoration.

4.May degrade during acid etching.

5.Associated with primary tooth resorption.(5)

2. Bonding Agents:

Dental adhesive systems were suggested for use as an indirect pulp capping material to overcome the disadvantages of calcium hydroxide as they produce superior adhesion. (3)

Disadvantages:

1. Unpolymerized monomer can cause cytotoxic effects in pulp cells 2. Absence of calcific bridge formation. (3)

Mechanism of action:

Adhesive resins could stimulate the release of pro-angiogenic factor as VEGF from the dentin matrix but decrease the release of FGF and has no effect on PDGF therefore it cannot induce the formation of an acceptable tertiary dentine bridge.(2)

3. Lasers:

Pulp capping therapy using lasers results in good prognosis for the tooth however, the sealing of exposed pulp with one of the dental materials after laser treatment is still required. Laser of different wavelengths is used. For Example: CO_2, Diode and Nd: YAG lasers.

Mechanism of action:

Sterile field is provided by the bactericidal effect of the laser. Area of coagulation is created by a superficial necrosis, with an underneath area of reversible damage, this stimulates odontoblasts to produce reparative dentin.(8)

Advantages:

1. The beam does not contact the tissue; therefore, an incision can be made without mechanical trauma to pulpal tissue.

2.Haemostatic and coagulant effect and stimulate the formation of secondary dentin.

Disadvatages: Technique sensitive and causes thermal damage to pulp in high dose. (8)

4.Zinc oxide eugenol: was introduced for direct pulp-capping.

Disadvantages: Chronic inflammation and a lack of pulp healing were observed, with no dentin bridge formation.

It was reported that eugenol is toxic, and zinc oxide eugenol resulted in high interfacial leakage.(4)

5. Resin Modified Glass Ionomer(RMGIC):

• Successful results of RMGIC as indirect pulp capping agents. As it was reported that it provides an excellent bacterial seal and fluoride release. (6)

• On the other hand not used in direct pulp capping as it irritates pulpal tissue leading to chronic inflammation and also there is failure of dentin bridge formation. (6)

6.Glucocorticoids combined with antibiotics:

In the 1970s, were frequently used in an attempt to control pulpal pain and suppress pulpal inflammation. Reports of poor wound-healing and even pulpal necrosis emerged, so steroids are no longer used for direct pulp capping. (4)

7.Growth factors, such as bone morphogenetic proteins (BMP) and transforming growth factors (TGF) induced reparative dentin formation. However,these growth factors are not adequately therapeutic, since they produce a porous osteodentin with tunnel defects. (4)

8.Extracellular matrix (ECM)

Extracellular matrix dentin molecules, for direct pulp-capping such as bone sialoprotein (BSP), matrix extracellular phosphoglycoprotein (MEPE), amelogenin and dentin phosphophoryn, have been shown to induce reparative dentin. Capping with ECM molecules is extremely promising, producing a reparative mineralized tissue with structural properties better than those produced

in the presence of calcium hydroxide. Among these, amelogenin is suggested to be most promising as a direct capping material. (4)

9.Calcium-silicate-based materials

9.1.Mineral trioxide aggregate (MTA), In the 1990s, Torabinejad and White introduced MTA which is basically a hydraulic Portland cement or calcium silicate. MTA has been used clinically with success rates similar to those achieved with calcium hydroxide.

Two types of MTA were available: White and Gray MTA. The gray version is due to the addition of iron (tetracalcium aluminoferrite). Tooth discoloration has been reported with the use of gray MTA. Therefore the use of white MTA has generally been recommended.(9)

• **The original MTA**, ProRoot MTA Gray was marketed in 1998 and was composed of 75% Type I Portland cement, 20% bismuth oxide and 5% calcium sulfate dihydrate.

The Portland cement is composed of approximately 55 wt% tricalcium silicate ($3CaO•SiO_2$), 19 wt% dicalcium silicate ($2CaO•SiO_2$),10 wt% tricalcium aluminate ($3CaO•Al_2O_3$), 7 wt% tetracalcium aluminoferrite ($4CaO•Al_2O_3•Fe_2O_3$), 2.8 wt% magnesium oxide, 2.9 wt% sulfate and 1.0 wt% free calcium oxide.

• .**ProRoot MTA White** was introduced in 2002 and differs from its predecessor in composition, *i.e.*, the elimination of tetracalcium aluminoferrite and an increase of calcium silicates. (9)

MTA without tetracalcium aluminoferrite is more popular, and many products are marketed worldwide: ProRoot MTA White, MTA Angelus White, White MTA Plus, MM-MTA, MTA, Tech BioSeal MTA.

The mechanism of action of MTA is similar to that of calcium hydroxide. The calcium hydroxide produced as a by-product of hydration of MTA is leached out and causes necrosis when in contact with the pulp. When MTA powder is mixed

with water at the time of application, calcium silicates in the powder hydrate to produce a calcium silicate hydrate gel and calcium hydroxide, as shown below:

$2[3CaO•SiO_2]+6H2O→3CaO•2SiO_2•3H_2O+3Ca(OH)2$

$2[2CaO•SiO_2]+4H2O→3CaO•2SiO_2•3H_2O+Ca(OH)2$

Thus, MTA can be described as a calcium-hydroxide releasing material and, therefore, is expected to present various properties similar to those described above for calcium hydroxide.(4)

The advantages of MTA

1. Its sealing ability, biocompatibility, bioactivity and capacity to promote mineralized tissue formation

2.MTA is suggested to be superior to calcium hydroxide due to its more uniform and thicker dentin bridge formation, less inflammatory response and less necrosis of pulpal tissue.

3.An antibacterial effect of MTA is controversial as reviewed by Parirokh and Torabinejad. MTA showed an antibacterial effect on some of the facultative bacteria but no effect on any of the strictly anaerobic bacteria. (4)

• Hydrophilic as it sets in moisture.

Disadvantages of MTA

• Expensive.

• Poor handling characteristics.

• Long setting time: Reported setting times have shown variations: (50 min, 4 h) (70 and 175 min) for the initial and final setting times, respectively. A long setting time may be inconvenient to both dentist and patient, because it requires two visits. Moreover, it may increase the risk of bacterial contamination.

• MTA cannot bond to dentin. Therefore, there is a risk of bacterial leakage, which could lead to failure of endodontically treated teeth.

• Tooth discoloration has been reported with the use of gray MTA, therefore the use of white MTA has generally been recommended in the esthetic zone.

9.2.Modified MTAs and MTA-like materials

Some modified MTAs overcoming the drawbacks of the original MTA are available, and most of them aimed to shorten setting time by modifying the composition or particle size of the powder.

In Angelus White MTA (setting time, 15 min), calcium sulfate was removed and calcium oxide was added to tricalcium silicate, dicalcium silicate, tricalcium aluminate and bismuth oxide.

In MM-MTA, calcium carbonate was added; in Tech BioSeal MTA, calcium chloride and montmorillonite were added; and the powder in MTA Plus was more finely ground.

MTA-like materials were marketed after 2006. They are not composed of Portland cement, which is manufactured from minerals of natural origin, but consist of synthetic calcium silicates as the main components and are aluminum-free. The difference in origin of calcium silicates is clearly

demonstrated in the release of metal ions from the set materials. In Angelus MTA and MM-MTA, which are based on Portland cement, a large amount of aluminum and trace amounts of arsenic, beryllium, cadmium and chromium were detected, but in DiaRoot and Bioaggregate based on synthetic calcium silicates, no metals were detected except a trace amount of aluminum.

9.2.1.BioAggregate, marketed in 2006, consists of

Tricalcium silicate

Dicalcium silicate

Tantalum pentoxide (radiopacifier)

Calcium phosphate monobasic.

Silicon oxide

Calcium phosphate reacts with part of the calcium hydroxide produced from setting (hydrating) calcium silicates, and during the reaction, hydroxyapatite and water are formed. The water thus produced contributes to the hydration reaction speed. Silicon oxide also reacts with calcium hydroxide by the so-called pozzolanic reaction ; is a measure for the reaction rate between a pozzolan [1]and Ca^{2+} or calcium hydroxide ($Ca(OH)_2$) in the presence of water and thus contributes to setting time. The setting time is within 4 h at a normal optimal powder/ liquid ratio (1 g/0.38 mL water).

[1](siliceous and aluminous materials which, in themselves, possess little or no cementitious value but which will, in finely divided form and in the presence of water, react chemically with calcium hydroxide (Ca(OH)2) at ordinary temperature to form compounds possessing cementitious properties)

9.2.2.Biodentine launched in 2009, contains tricalcium silicate, calcium carbonate and oxide and zirconium oxide (radiopacifier) in the powder, which is mixed with calcium chloride solution containing modified polycarboxylate instead of water. Both substances in the liquid contribute to shortened setting times (from 10 to 12 min). Calcium chloride accelerates the hydration reaction, and polycarboxylate reduces the amount of water required for mixing by providing proper consistency. Calcium carbonate in the powder is expected to act as a nucleation site in the hydrating mass, enhancing the hydration and leading to faster setting.

Advantages:

• Dentin bridge formation.

• Antibacterial action.

• Excellent marginal adaptability.

• Shorter setting time, better handling characteristics and higher mechanical properties compared to MTA therefore it can be considered an interesting alternative to MTA and Ca(OH)2

9.2.3. Endo Sequence Root Repair Material (ERRM):

• Recently, a new bioceramic material has been introduced to the market. It is composed of calcium silicate, monobasic calcium phosphate, zirconium oxide and tantalum oxide and fillers.

• It require no mixing because it is available as paste in syringes or in a putty form. They are composed of nano- sphere particles that can penetrate into dentinal tubules and set using their moisture.

Mechanism of action:

• ERRM promoted the vascularization, migration and differentiation of DPSCs through the release of VEGF and BMP growth factors from dentin matrix.

Advantages:

• Excellent sealing ability.

• Highly biocompatible.

• Dentin bridge formation.

• Hydrophilic and antibacterial effect. (12)

The major advantage of this material is improved handling characteristics over MTA. This novel ready-to-use bioceramic materials shows promising results in dental pulp repair application than $Ca(OH)_2$ and MTA. Further studies are needed to evaluate their long term performance in clinical uses. (12)

9.2.4. Resin-modified MTA cement

TheraCal LC is a light curing, resin-modified calcium-silicate-filled single paste, containing calcium oxide, calcium silicate particles (type III Portland cement), strontium glass, fumed silica, barium sulphate, barium zirconate and resin consisting of Bis-GMA and polyethylene glycol dimethacrylate. (10)

Advantages:

• Higher calcium releasing ability and high mechanical properties than either MTA or $Ca(OH)_2$.

Stimulates hydroxy apatite and secondary dentin bridge formation. • Light polymerization prevents the material to be washed out. Disadvantages:

Severe inflammation as unpolymerized monomers can exert toxic effects to the pulp. (10)

9.2.5. Calcium-enriched mixture (CEM):

- It has been recently introduced as a hydrophilic tooth-colored cement.
- The CEM cement powder is composed of calcium oxide, calcium sulfate, phosphorus oxide, and calcium silicate as major elements.
- CEM is alkaline cement (pH~11) that releases calcium hydroxide during and after setting. Advantages:
- This cement is biocompatible and induces formation of cementum, dentin, bone and periodontal tissues.
- Antibacterial effect comparable to Ca(OH)2 and superior to mineral trioxide aggregate (MTA) and sealing ability similar to MTA.
- Its clinical applications include pulp capping, pulpotomy and perforation repair.
- **10. Propolis:**

• It is a natural extract of honey bees from different kinds of plants. The main chemical classes present in propolis are flavonoids and phenolics. It contains some elements (zinc and iron) that are important for collagen synthesis.

Mechanism of action:

Stimulate the release of transforming growth factor (TGF) from dentin matrix which is important for the differentiation of odontoblasts.

Advantages:

• Antioxidant, antibacterial, antifungal, antiviral and anti-inflammatory. (11) Disadvatages:

Moderate pulpal inflammation with partial dentinal bridge formation.

11. Enamel matrix derivative (EMD):

• Emdogain (EMD) is enamel matrix derivative of Hertwig's epithelial root sheath during tooth development. It plays important role in enamel mineralization and periodontal tissue formation.

• The biomaterial is an injectable gel solution consisting of enamel matrix proteins (amelogenin), water and a carrier (propylene glycol alginate).

Mechanism of action:

• It was suggested as a possible pulp capping material due the presence of amelogenin in its composition which promotes odontoblast differentiation. However it was suggested that it could be preferable material for periodontium regeneration as it can stimulate the periodontal cells to release VEGF.(3)

Disadvantages: The high cost of these biomaterials, its poor sealing qualities and no effective formation of hard tissue barrier are still considerable drawbacks. (3)

II- Whole Pulp Regeneration:

Regenerative endodontics aims to replace necrotic pulp tissue with regenerated pulp-like tissue especially in young patients with immature teeth. Pulp regeneration components:

1. Stem Cells

2. Growth factors (Morphogenic Signaling Molecules)

3. Scaffolds: Scaffolds are three dimensional structures that provide matrix for cells attachement. Also can be used to deliver growth factors. Several scaffolds have already been proposed. For example, injectable hydrogels have several features that make them attractive for dental pulp tissue engineering purposes.

Pulp regeneration mechanism:

Two strategies can be applied towards dental pulp regeneration: cell transplantation and cell homing. (13)

a) Cell transplantation:

In this method, *exogenous* stem cells are loaded (seeded) onto scaffolds either incorporated with signaling molecules or not.

***b)* Cell homing:**

Scaffolds impregnated with signaling molecules are injected into root canals to induce migration, proliferation and differentiation of *endogenous* stem cells around the root apex through enlarged apical foramen. (13)

However, cell-based therapy faces many obstacles in clinical translation because complex procedures need to be followed, such as tooth extraction, pulp extirpation, in vitro cell culture, selection of stem cells, ex vivo cell expansion, storage and shipping. Also, there are other risks of immune rejection, pathogen transmission and tumorigenesis during engraftment. Despite its scientific validity, dental pulp regeneration using cell transplantation is unlikely to be economically viable or competitive with current RCT. (13)

References:

1. Morotomi T, Washio A, Kitamura C. Current and future options for dental pulp therapy. Japanese Dental Science Review. 2019;55(1):5–11.

2. D.Pathak DrS. Advances in Pulp Capping Materials: A Review. IOSR Journal of Dental and Medical Sciences. 2017;16(2):31–7.

3. Qureshi A, Soujanya E, Kumar N, Kumar P, Hivarao S. Recent advances in pulp capping materials: An overview. Journal of Clinical and Diagnostic Research. 2014;8(1):316–21.

4. Komabayashi T, Zhu Q, Eberhart R, Imai Y. Current status of direct pulp-capping materials for permanent teeth. Dental Materials Journal. 2016;35(1):1–12.

5. Baranwal R, Singh B, Dubey A, Avinash A. Review article Calcium Hydroxide in Dentistry. Journal of App. 2016;2(3):3–7.

6. Solete P, Vijaya PP. Advances in pulp capping agents. International Journal of Pharmaceutical and Clinical Research. 2014;6(4):320–3.

7. Estrela C, Holland R. Calcium hydroxide: study based on scientific evidences TT - Hidr{ó}xido de c{á}lcio: estudo baseado em evid{ê}ncias cient{í}ficas. Journal of Applied Oral Science. 2003;11(4):269–82.

8. Carmen Todea, Christina Kerezsi, Cosmin Balabuc, Micrea Calniceanu, Laura Filip. Pulp Capping - from Conventional to Laser -assisted Therapy (II). Vol. 8. 2008. p. 147–55.

9. Dawood AE, Parashos P, Wong RHK, Reynolds EC, Manton DJ. Calcium silicate-based cements: composition, properties, and clinical applications. Vol. 8, Journal of investigative and clinical dentistry. 2017.

10. Gandolfi MG, Siboni F, Prati C. Chemical-physical properties of TheraCal, a novel light-curable MTA-like material for pulp capping. International Endodontic Journal. 2012 Jun;45(6):571–9.

11. Zohereh Ahangari, Mandana Nasert, Maryam Jalili, Yasaman Mansouri, Fatemeh Mashhadiabbas. Effect of Propolis on Dentin Regeneration and the Potential Role of Dental Pulp Stem Cell in Guinea Pigs. cell journal. 2012;13(4):223–8.

12. Zhu L, Yang J, Zhang J, Lei D, Xiao L, Cheng X, et al. In vitro and in vivo evaluation of a nanoparticulate bioceramic paste for dental pulp repair. Acta Biomaterialia. 2014;10(12):5156– 68.

13. Eramo S, Natali A, Pinna R, Milia E. Dental pulp regeneration via cell homing. Vol. 51, International Endodontic Journal. Blackwell Publishing Ltd; 2018. p. 405–19.

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Smart materials

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Abstract: Smart materials technology enables us to adapt to environmental changes by activating its functions. Such materials have one or more properties can be significantly changed in a controlled manner in response to external stimuli. These properties have a beneficial application in various fields including dentistry which had revolutionary effect on it.

Keywords: Smart material; Shape memory alloy; Piezoelectric; Magnetorheological.

Smart materials are materials that have properties that may be altered in a controlled fashion by stimuli, such as stress, temperature, moisture, pH, and electric or magnetic fields. They are highly responsive and have the inherent capability to sense and react according to changes in the environment. [1, 2] Smart behavior generally occurs when a material senses some stimulus from the environment and reacts to it in a useful, reliable, reproducible, and usually reversible manner. The most important key feature of smart behavior includes its ability to return to original state even after the stimulus has been removed. These properties have a beneficial application in various fields including dentistry. [3]

Traditionally materials used in dentistry were designed to be passive and inert, to exhibit little or no interaction with body tissues and fluids. As there was no single material in dentistry that is ideal in nature and fulfills all the requirements of an ideal material, searching for an "ideal restorative material" continued and a newer generation of materials was introduced. These smart materials support the remaining tooth structure to the extent that more conservative cavity preparation can be carried out. Some of these can mimic natural tooth structures such as enamel or dentin. The use of these smart materials has revolutionized dentistry. [4]

Classification of smart materials

Smart materials are classified into four categories either:

Passive

Passive smart materials can only sense environmental conditions or stimuli without external control. [5]

Active

Active smart materials sense and react to the condition or stimuli. It has both actuators and sensors. The actuators act upon the detected signal either directly or from a central control unit. [2, 5]

Very Smart

Very smart materials can sense, react and adapt themselves to environmental conditions or stimuli with sensors. It consists of a unit, which works like the brain, with cognition, reasoning and activating capacities. [5]

Intelligent

Intelligent materials are those capable of responding or being activated to perform a function in a programmed manner. Intelligent materials can sense, react and adapt themselves to environmental conditions or stimuli without sensors. [5]

Nature of smart materials

Smart materials sense changes in the environment around them and respond in a predictable manner. In general, these properties are: [2, 5]

- Piezoelectric

Piezoelectric materials produce a voltage when stress is applied or vice versa. Structures made from these products can be made to change shape or dimensions when a voltage is applied. Likewise, a change in shape can be used to generate a voltage which can be used for the purpose of monitoring. [6]

- Shape memory

After deformation, these materials can remember their original shape and return to it when heated. e.g.:- Nickel titanium alloys. [7]

- Thermochromic

These materials change color in response to changes in temperature. E.g. Thermochromic brushes. [2]

- Photochromic

These materials change color in response to changes in light conditions. e.g.: photochromatic pits and fissure sealant (Clinpro™ Sealant (3M).) [2]

- Magnetorheological

These are fluid materials that become solid when placed in a magnetic field. [2]

- PH-sensitive

Materials which swell/collapse when the pH of the surrounding media changes.eg: - Smart composites containing amorphous calcium phosphate (ACP). [2]

- Biofilm formation

Presence of biofilm on the surface of material alters the interaction of the surface with the environment.[2]

- Ion release and recharging

The beneficial effect of fluoride release of dental materials has been the subject of much research over many years. As the products (even with high initial fluoride release) tend to rapidly lose their ability to release fluoride in significant amounts by time. However, the smart behavior of materials containing glass ionomer cement (GIC) salt phases offers some long-term solutions by the sustained re-release of fluoride after initial recharging which may be much more important than the initial burst.[2]

Smart materials in dentistry

I. Smart Memory Alloy (SMA)

The term "smart material" or "smart behavior" in the field of dentistry was probably first used in connection with Nickel Titanium (NiTi) alloys, or shape memory alloys (SMAs). Such alloys show unique properties such as super elasticity, shape memory, superior fatigue and wear resistance and relatively better biocompatibility. In 1970's, Ni-Ti was introduced in orthodontics for fabricating brackets. Wires revealing shape memory behavior at intra-oral temperature usually comprise of copper and or chromium in addition to nickel and titanium. [2, 8]

The shape memory effect (SME) was observed in the gold cadmium alloy in 1951, but this was of insignificant use. Ten years later in 1962, an equiatomic alloy of titanium and nickel was found to exhibit shape memory effect.

The SME describes the manner of a material changing shape or remembering a particular shape at a particular temperature (i.e. its transformation or memory temperature). Materials that can only demonstrate the shape change or memory effect once are known as **one-way SMAs**. However, some alloys can be skilled to show a **two-way effect** in which they remember two shapes, one below and one above the memory temperature. At the memory temperature, the alloy undergoes a solid-state phase transformation i.e. the crystal structure of the material changes resulting in a

volume or shape change and this change in structure is called a thermoelastic martensitic transformation. This occurs as the material has a martensitic microstructure below transformation temperature, which is characterized by a zig-zag arrangement of the atoms, known as twins. The martensitic structure is soft and is easily deformed by removing the twinned structure. The material has an austenitic structure above the memory temperature, which is stronger. To change from the martensitic to the austenitic shape the material is heated through the memory temperature. Cooling down reverts the alloy to the martensitic state. [2, 9] Fig.1,2

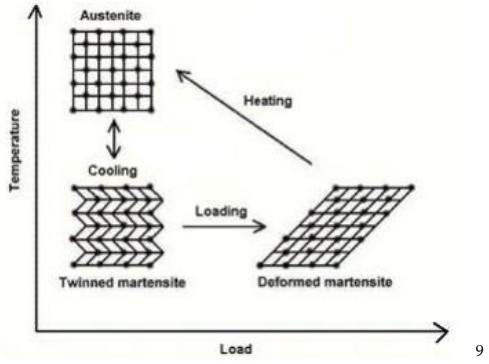

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Fig. 1. Microscopic Diagram of the Shape Memory Effect.

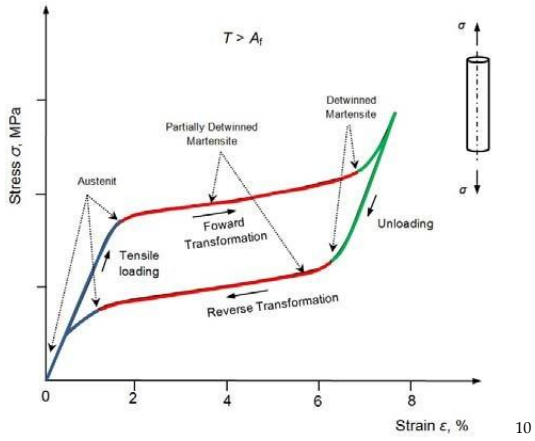

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Fig.2 Diagram of the stress-strain curve for the superelasticity shape memory alloy NiTi in the tension loading Applications

In endodontic, NiTi endodontic files offer super flexibility, durability, and torque ability as compared to the stainless-steel files used. Another important application of NiTi is in the field of orthodontics. Superelasticity of these wires along with shape memory applies continuous, gentle forces that are within physiological range over a longer period with less discomfort. Wires that exhibit shape memory behavior at mouth temperature contain copper and or chromium in addition to nickel. Other SMA devices are also being used for healing fractured bone, staples of the shape memory materials are attached to each part of the bone and these staples then apply a constant force to pull the two pieces together, as the SMA is warmed by the body temperature it tries to return to its original configuration. [2]

II. Smart resin composites

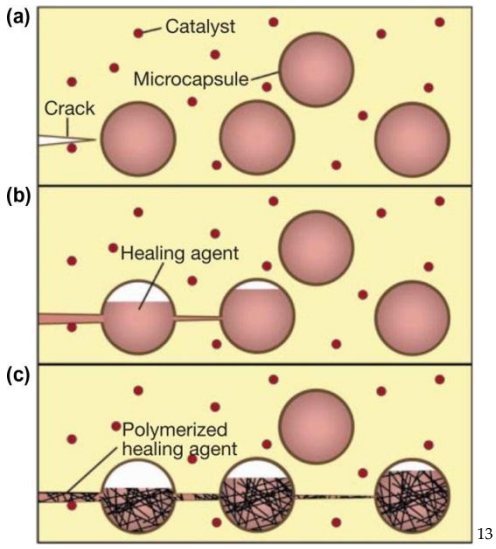
It is a light activated alkaline, nano-filled glass restorative material, which *releases calcium, fluoride and hydroxyl ions* when intraoral pH values drop below the critical pH of 5.5 and counteract the demineralization of the tooth surface and help in remineralization. The material can be adequately cured in bulk thickness up to 4mm. It is recommended for the restoration of class I and class II lesions in both primary and permanent teeth. Ex: smart dental resin composites (**Ariston** pH control) introduced by Ivoclar- Vivadent Company. [11]

Smart composites containing amorphous calcium phosphate are one of the most soluble calcium phosphate compounds of biological importance, exhibiting the most rapid conversion to crystalline hydroxyapatite (HAP). The ACP when integrated into specially designed and formulated resins to make a composite material, will have an extended time release nature to act as a source for calcium and phosphate which will be useful for preventing caries. The ACP has been evaluated as a filler phase in bioactive polymeric composites. Active restorative materials that contain ACP as

fillers may stimulate the repair of tooth structure because of releasing significant amounts of calcium and phosphate ions in a sustained manner. Then these ions can be deposited into tooth structures as apatitic mineral, which is similar to the hydroxyapatite (HAP) found naturally in teeth and bone. The ACP at neutral or high pH remains as ACP. When low pH values (at or below 5.8) occur during a carious attack, ACP converts into HAP and precipitates, thus replacing the HAP lost due to the acidic attack. So, when the pH level in the mouth drops below 5.8, these ions merge within seconds to form a gel. In less than 2 minutes, the gel becomes amorphous crystals, resulting in the release of calcium and phosphate ions. This response of ACP containing composites to pH can be described as smart. [12]

III. Self-healing composites

Materials usually have a limited life span and degrade due to different physical, chemical, and/or biological stimuli. These may include external static or dynamic forces, internal stress states, corrosion, dissolution, erosion or biodegradation. Therefore, the focus of current scientific research is the development of newer bio-inspired material systems. One of the first self-repairing or self-healing synthetic materials reported interestingly shows some similarities to resin-based dental materials. As this is an epoxy system that contains **resin filled microcapsules**, if a crack occurs in the epoxy composite material, some of the microcapsules disintegrate near the crack and they release the resin. The resin subsequently fills the crack and reacts with a catalyst that is dispersed in the matrix, resulting in a polymerization of the resin and a repair of the crack fig.3.The self-repairing mechanism based on microcapsules disintegration may have a promising future and composites repaired in that way may perform better than those repaired with macroscopic repair approaches. [13]



13

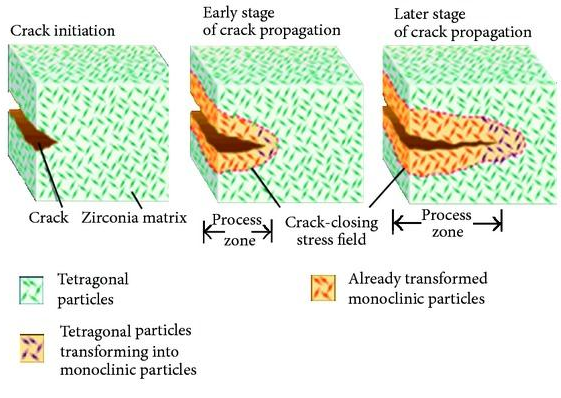
Fig.3: Mechanism of the microcapsule approach in Self-healing composite

IV. Smart ceramics

Zirconia is polycrystalline ceramics that do not contain glass. Hence, polycrystalline ceramics generally are much tougher and stronger than glass-based ceramics. In addition, zirconia exhibits phase transformation toughening increasing its mechanical properties. [1, 2]

The fracture toughness and flexural strength of zirconia are significantly higher than any other currently available ceramic. At firing temperature, zirconia is tetragonal and at room temperature monoclinic, with a unit cell of monoclinic occupying about 4.4% more volume than when tetragonal. Unchecked, this transformation was a bit unfortunate since it would lead to crumbling of the material on cooling. In the late 1980s, ceramic engineers learned to stabilize the tetragonal form at room temperature by adding small amounts (app. 3–8 mass%) of calcium and later yttrium or cerium. Although stabilized at room temperature, the tetragonal form is really only “metastable,” meaning that

trapped energy still exists within the material to drive it back to the monoclinic state. It turned out that the highly localized stress ahead of a propagating crack is sufficient to trigger grains of ceramic to transform in the vicinity of that crack tip. In this case, the 4.4% volume increase becomes beneficial hindering crack propagation. [1]
The result is that a compressive or crack closure stress is produced which slows down or stops the crack. This crystallographic transformation in response to stress makes zirconia a smart material fig.4. [1]



[1]

Fig.4 Phase transformation in Zirconia.

V. Smart impression material

These materials exhibit following characteristics:

1. They are hydrophilic to get a void-free impression.
2. They possess Shape memory so during elastic recovery it resists distortion for more accurate impression and toughness resists tearing.
3. They have a snap - set behavior those results in precise fitting restorations without distortion.
4. They cut off working and setting times by at least 33%.
5. They have low viscosity and hence high flow. E.g.: Imprint TM 3 VPS, ImpregimTM, Aquasil ultra (Dentsply). [2]

Chromatic alginates (Alginates with color indicators)
The problem observed among some of the undergraduate students is difficulty in identifying the ideal consistency of alginate material during manipulation. Various color indicators were added to the alginate impression materials to identify the different stages of manipulation. These color indicators change the color of the alginate mix as setting reaction taking place due to the change in the pH. This change in the color of the alginate mix facilitates identification of the ideal consistency to load it into the tray and make accurate impressions.[14]

VI. Smart glass ionomer cement

The scientist «Davidson» first suggested the smart behavior of GIC. It is related to the ability of a gel structure to absorb or release solvent rapidly in response to a stimulus that can be temperature, change in pH etc. GICs are described as "smart materials" with respect to their thermal behavior, since it is a desired feature, when restorative materials undergo thermally induced volumetric changes close to those of the tooth substance. [2]
Wide temperature fluctuations may occur in the oral cavity due to the intake of hot or cold food and fluids. Hence, the restorative materials placed in this environment may show thermal expansion or contraction in response to thermal stimuli. When dealing with thermally induced volumetric changes, comparison of coefficient of thermal expansion and contraction CTE values of the restorative material and the tooth substance is more important than the CTE value of the material itself. The mismatch of thermal expansion and contraction between a restoration and the tooth structure may cause stresses to develop at the interface and this may have unfavorable effects on the margins and finally lead to microleakage. [1]
For glass-ionomers, little or no change in dimension was observed when heating and cooling between 20°C and 50°C in wet conditions. In dry conditions, the materials showed a marked contraction when heated above 50°C. The explanation for this behavior is that the expected expansion **on heating** is compensated by fluid flow to the surface of the material to cause a balancing of the dimensional changes. **On cooling**, the process was reversed. In dry conditions, the rapid loss of water on heating results in the observed contraction. This behavior is similar to that of human dentine where very little dimensional change is observed on heating in wet conditions and a marked contraction is noted in

dry conditions. Both results can be explained by flow of fluids in the dentinal tubules. Hence, the glass-ionomer materials can be said to be mimicking the behavior of human dentine through a type of smart behavior. [15]

The mass loss of glass-ionomer cements (GICs) in wet conditions is significantly less than that in dry conditions. The GICs, as water-based materials, have the ability to exchange fluid with the environment. The "loosely" bound water is readily lost and regained as a result of changes in the environmental conditions (e.g., temperature). The loss of "loosely bound" water is likely to be a reversible process; that is, the water may be reabsorbed on cooling. The water gained from the environment may compensate for the contraction of the GIC matrix. Therefore, the final dimensional change of GICs in wet ambient conditions may be minimal as a net result of thermal expansion and contraction, water loss, and water gain. Hence, the reaction of GICs to their environment is active and they may be considered as having "smart" behavior. The initial water loss caused by environmental temperature change may be considered as the "trigger" to this "smart" behavior. [15]

Both the method of mixing and the viscosity of the cement have an effect on porosity. In the low viscosity material, hand mixing reduces the porosity significantly compared to mechanical mixing, either by shaking or rotation. For the viscous material, the levels of porosity are low and not significantly affected by mixing. These differences in porosity are reflected in differences in water absorption. Hence, this aspect of the smart behavior of dental cements can be controlled by the operator. [1, 15]

The other issue of the smart behavior of GIC is the **fluoride release and recharging ability**. Commonly the fluoride release is seen as a high initial fluoride release followed by a moderate reduction over a period. [16]

VII. Smart burs

These are polymeric burs that remove only infected dentin. The affected dentin, which has the ability to remineralize, remains intact. Overcutting of tooth structure, which is usually seen with conventional burs, can be avoided by the use of these smart preparation burs. The polymer cutting edges wear down on coming into contact with harder materials, such as healthy dentin and become blunt. They are open in three sizes 010, 014, and 018 and are proposed for single use**.** [2, 16]

VIII. Smart sutures

These sutures are made up of thermoplastic polymers that have both shape memory and biodegradable properties. They are applied loosely in its temporary shape and the ends of the suture are fixed. When the temperature is raised above the thermal transition temperature, the suture shrinks and tightens the knot, applying the optimum force. The thermal transition temperature is close to human body temperature and this is of clinical significance in tying a knot with proper stress in surgery. Smart sutures are made of plastic or silk threads covered with temperature sensors and microheaters, which can detect infections. E.g.: Novel MIT Polymer (Aachen, Germany). [17]

IX. Pheromone guided smart antimicrobial peptide

A new class of pathogen selective molecule called specifically (or selectively) Targeted Antimicrobial Peptides (STAMP) have been developed based on the fusion of a species-specific targeting peptide domain with a wide spectrum antimicrobial peptide domain. This pheromone-guided "smart" material peptide is targeted against the killing of ***Streptococcus mutans***, the principal microorganism responsible for dental caries. Utilizing Competence Stimulating Peptide (CSP), a pheromone produced by streptococcus mutans, can be eliminated from multi-species biofilm without affecting the nation cariogenic microorganisms. Their molecules have the potential to be developed into antibiotics that will selectively eliminate pathogens while preserving the protective benefits of a healthy oral flora. [2]

X. Smart seal obturation system

a smart seal obturation system; The C Point system (EndoTechnologies, LLC, Shrewsbury, MA, USA), is a point-and-paste root canal filling technique that consists of prefabricated, hydrophilic endodontic points and an accompanying sealer. The deformable endodontic point (C Point) is available in different tip sizes and tapers and is designed to expand laterally without expanding axially, by absorbing residual water from the instrumented canal space. Its inner core consists of a mix of two proprietary nylon polymers: Trogamid T and Trogamid CX. The polymer coating is a cross-linked copolymer of acrylonitrile and vinyl pyrrole, which are polymerized and cross-linked using allyl methacrylate and a thermal initiator. The lateral expansion of this Point occurs non-uniformly, with the expandability depending on the extent to which the hydrophilic polymer is prestressed (i.e., contact with a canal wall will reduce the

rate or extent of polymer expansion). This nonisotropic lateral expansion enhances the sealing ability of the root canal filling, thereby reducing the possibility of reinfection. [18]

XI. Smart coatings for dental implants

Researchers have developed a "smart coating" that helps surgical implants bond more closely with bone and prevents infection reducing the possibility of implant rejection. The coating creates an inner crystalline layer next to the implant and an amorphous outer layer surrounding bone. The amorphous layer dissolves over time and releases calcium and phosphate, which encourages bone growth. The bone grows into the coating resulting in improved bonding osseointegration. This bonding also makes the implant more functional, because the bonding helps the bone and the implant to share the load. The researchers have also incorporated *silver nanoparticles* throughout the coating to reduce infections. As the amorphous layer dissolves, silver incorporated into the coating is released which acts as an antimicrobial agent. This will limit the amount of antibiotics patients will need the following surgery, and will provide protection from infection at the implant site for the life of the implant. Moreover, the silver is released more quickly after surgery, when there is more risk of infection, due to the faster dissolution of the amorphous layer of the coating. The silver release will slow down while the patient is healing; therefore, it is called as smart coating. [19]

XII. Smart fibers for laser dentistry

Hollow core photonic crystal fibers (PCFs) for the delivery of high-fluence laser radiation capable of removing tooth enamel have been developed. Sequential laser radiation pulses are transmitted through a hollow-core photonic crystal fiber with a core diameter of approximately 14 micrometers and are focused on a tooth surface to cut dental tissue. The same fiber is also used to transmit emission from plasmas, which is produced by laser pulses on the tooth surface in the backward direction for detection and optical diagnostics. [2, 20]

Conclusion

In recent years there has been a huge development of materials in various fields. In dentistry, the use of smart materials promises improved reliability and long-term efficiency because of their potential to have specific functions intelligently in response to various local changes in the environment, thereby significantly improving the quality of dental treatment.

References

1- Badami, V., & Ahuja, B. (2014). Biosmart materials: breaking new ground in dentistry. TheScientificWorldJournal.
2- McCabe, J. F., Yan, Z., Al Naimi, O. T., Mahmoud, G., & Rolland, S. L. (2011). Smart materials in dentistry: Smart materials in dentistry. Australian Dental Journal.
3- Gautam, P., & Valiathan, A. (2008). Bio-Smart Dentistry: stepping into the future.Trends0Biomater Artif Organs.
4- Gupta, V. (n.d.). *Smart materials in dentistry: A review*. Ijarnd.Com. Retrieved March 21, 2022, from https://www.ijarnd.com/manuscripts/v3i6/V3I6-1159.pdf
5- Smart textiles and intelligent textiles. (2022, February 6). Textile School. https://www.textileschool.com/8307/smart-textiles-and-intelligent-textiles/2/
6- McCabe JF, Yan Z, Al Naimi OT, Mahmoud G, Rolland SL (2009). Smart materials in dentistry- future prospects, Dent Materials J
7- Wijst, van der, M. W. M. (1998). Shape control of structures and materials with shape memory alloys. Technische Universiteit Eindhoven.
8- Gautam, Valiathan A (2008). Bio-smart Dentistry: stepping into the future. Trends Biomater. Artif.Organs.
9- Rahimatpure, A. (n.d.). Smart Memory Alloys. Psu.Edu. Retrieved March 22, 2022, from https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.681.7337&rep=rep1&type=pdf
10- Rudolf, R., T., & Fercec, J., J. (2013). Force measurements on teeth using fixed orthodontic systems. Vojnotehnicki Glasnik, 61(2), 105–122. https://doi.org/10.5937/vojtehg61-2960
11- Xu, H. H. K., Weir, M. D., Sun, L., Takagi, S., & Chow, L. C. (2007). Effects of calcium phosphate nanoparticles on Ca-PO4 composite. Journal of Dental Research, 86(4), 378–383. https://doi.org/10.1177/154405910708600415.
12- Schumacher, G. E., Antonucci, J. M., O'Donnell, J. N. R., & Skrtic, D. (2007). The use of amorphous calcium phosphate composites as bioactive basing materials. Journal of the American Dental Association (1939), 138(11), 1476–1484. https://doi.org/10.14219/jada.archive.2007.0084.

13- Priyadarsini, M., Rekha Sahoo, D., & Biswal, T. (2021). A new generation self-healing composite materials. Materials Today: Proceedings, 47, 1229–1233. https://doi.org/10.1016/j.matpr.2021.06.456.
14- Alaghari, S., Velagala, S., Alla, R. K., & Av, R. (2019). Advances in alginate impression materials: a review. International Journal of Dental Materials, 01(02), 55–59. https://doi.org/10.37983/ijdm.2019.1203.
15- Yan, Z., Sidhu, S. K., Carrick, T. E., & McCabe, J. F. (2007). Response to thermal stimuli of glass ionomer cements. Dental Materials: Official Publication of the Academy of Dental Materials, 23(5), 597–600. https://doi.org/10.1016/j.dental.2006.05.001.
16- Ali Hassan, S., & Bhateja, S. (2020). Smart materials in pediatric dentistry- A review. IP Journal of Paediatrics and Nursing Science, 3(2), 31–33. https://doi.org/10.18231/j.ijpns.2020.007
17- Suture Materials in Dentistry. (n.d.). Ijisrt.Com. Retrieved March 23, 2022, from https://www.ijisrt.com/assets/upload/files/IJISRT20APR777.pdf
18- Pathivada, L., Munagala, K. K., & Dang, A. B. (n.d.). Smartseal: New Age Obturation. Oaji.Net. Retrieved March 23, 2022, from https://oaji.net/articles/2015/651-1431328988.pdf
19- Smart coating may lead to safer hip, knee and dental implants. (n.d.). Healio.Com. Retrieved March 23, 2022, from https://www.healio.com/news/orthopedics/20120331/smart-coating-may-lead-to-safer-hip-knee-and-dental-implants
20- Nimish Anand Salunkhe and Shweta Chaudhary, 2016. "Smart materials in dentistry", International Journal of Current Research, 8, (09), 37994-38002

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Pulp capping materials

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Abstract: Dental pulp-capping is done to preserve vital teeth when the pulp is exposed due to caries, trauma or instrumentation. Various materials are used as pulp-capping agent. The development of materials, techniques and knowledge of the dentin-pulp complex has gradually affecting its results positively. Nowadays, there are many direct and indirect pulp capping materials. Some, present for more than 50 years, like calcium hydroxide. Others, such as Biodentine or MTA, which are very recent, show promising results.

Keywords: Calcium hydroxide; dentinal bridge; biodentine; mineral trioxide aggregate; theracal LC; propolis; stem cells.

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Introduction

Direct and indirect pulp capping, with their different materials and clinical protocols, has been used for years to maintain the pulp health and vitality and stimulate odontoblasts to form reparative dentin. Direct pulp capping is used when the pulp is visibly exposed (vital pulp exposure), it might be either pathogenic exposure (due to caries) or accidental exposure (trauma, during tooth preparation or caries removal). Indirect pulp capping is usually used in deep cavity preparations, with or without caries remaining, which are close to the pulp but with no visible exposure. The objectives of any pulp capping procedure are to manage bacteria, arrest any residual caries progression, stimulate pulp cells to form new dentin, and provide a biocompatible and durable seal that protects the pulp from bacteria and harmful agents.[1]

Historically, the first pulp capping procedure was performed in 1756, by the Phillip pfaff, who packed a small piece of gold over an exposed vital pulp to promote healing. However, the success of the pulp capping procedure greatly depends upon the circumstances under which it is performed and the prognosis depends upon the age, type, site and size of pulp exposure. In addition to this the pulp capping material should have the following ideal properties like: [2]

- Induce reparative dentin formation.
- Maintain the pulp vitality.
- Release fluoride to prevent secondary caries.
- Bactericidal or bacteriostatic.
- Adhere to dentin.

- Adhere to restorative material.
- Resist forces during restoration placement and during the life of restoration.
- Be Sterile.
- Preferably be radiopaque.
- Provide proper bacterial seal. [3]

Pulp capping materials

1- Calcium hydroxide

In 1920 calcium hydroxide was introduced by Hermann as root canal filling material. To prove that it was a biocompatible material, between 1928 and 1930 he studied the vital pulp reaction to calcium hydroxide. Since then, calcium hydroxide has been recommended by several authors for direct pulp capping and has been considered the "gold standard" of direct pulp capping materials for several decades, against which new materials should be tested. [2]

Forms and composition

Calcium hydroxide cements are supplied in a visible light–cured system and a two-paste system. A catalyst paste containing calcium hydroxide, zinc oxide, and zinc stearate in ethylene toluene sulfonamide reacts with a base paste containing calcium tungstate, calcium phosphate, and zinc oxide in glycolsalicylate to form amorphous calcium. Visible light–cured calcium hydroxide preparations have demonstrated clinical success and may be less susceptible to hydrolysis. [5]

There is a list of well-known advantages to calcium hydroxide that have caused it to receive this acceptance. Calcium hydroxide has excellent antibacterial properties. One study found a 100% reduction in microorganisms associated with pulp infections after one-hour contact with calcium hydroxide. Most importantly, calcium hydroxide has a long term track record of clinical success as a direct pulp-capping agent in periods of up to 10 years. [3]

However, several disadvantages and limitations have been existed with the use of calcium hydroxide material such as extensive dentin formation obliterating the pulp chamber, high solubility in oral fluids, lack of adhesion, providing poor seal, low strength and degradation after acid etching. In addition, necrosis of the adjacent pulp tissue and inflammation of the contiguous tissue when calcium hydroxide is applied directly to pulp tissue. [3]

Another criticism of calcium hydroxide is the appearance of so-called "tunnel defects" in reparative dentin formed underneath calcium hydroxide pulp caps. A tunnel defect has been described as a patency from the site of the exposure through the reparative dentin to the pulp, sometimes with fibroblasts and capillaries present within the defect. However, other researchers have found that the quality of reparative dentin improves as the bridge gets thicker, and that many times, the tunnel defects are not patent with the pulp. It appears that tunnel defects are not a common finding in human studies involving direct pulp capping with calcium hydroxide. There are fewer studies that note observing tunnel defects and more studies that do not observe tunnel defects. [2, 3]

Mechanism of action

Traditionally, it has been believed that calcium hydroxide's high pH causes irritation of the pulp tissue, which stimulates repair via some unknown mechanism. In recent years, this "unknown mechanism" may have been explained by the release of bioactive molecules. It is known that a variety of proteins are incorporated into the dentin matrix during dentinogenesis. Of particular importance to the topic of pulp capping is that at least two of these proteins, Bone Morphogenic Protein (BMP) and Transforming Growth Factor-Beta One (TBF-β1), have demonstrated the ability to stimulate pulp repair. Furthermore, calcium hydroxide is known to solubilize these proteins from dentin. The release of these bioactive molecules as a significant mediator in pulp repair following pulp capping. [3]

2- Glass Ionomer (GI) / Resin-Modified Glass Ionomer (RMGI)

GI/RMGI is also cytotoxic when in direct cell contact. Glass ionomer provides an excellent bacterial seal and shows good biocompatibility when used in close approximation but not in direct contact with the pulp, fluoride release, and coefficient of thermal expansion and modulus of elasticity similar to dentin. Although there is, lack of dentin bridge formation, high solubility and slow setting rate. RMGIC as direct pulp capping agent exhibited chronic inflammation and lack of dentin bridge formation; whereas the calcium hydroxide control groups showed significantly better pulpal healing.[2, 6]

3- Adhesive systems

Adhesive systems were suggested for use as a potential direct pulp capping agent approximately 12–15 years ago. All components of adhesive systems have been shown to be cytotoxic to pulp cells, especially with increasing duration of contact with the pulp. Toxicity is seen in both multi- and single-component adhesive systems, and the unpolymerized components are more toxic than the well polymerized adhesive. [7, 2]

Some animal studies found that mechanical pulp exposures capped with adhesives generally resulted in pulp healing. A number of studies of primate, non-contaminated, mechanical pulp exposures capped with adhesive systems generally resulted in healing comparable to calcium hydroxide. However, this outcome changes when the results are examined from studies of bacteria-contaminated mechanical pulp exposures in primates. These contaminated exposures capped with adhesives resulted in poor pulp healing compared to calcium hydroxide. [7, 2]

When the results of human pulp-capping studies are reviewed, the conclusions become very different than what would have been deduced from animal studies. Calcium hydroxide provided significantly improved pulpal repair compared to adhesive systems, regardless of whether it was an etch-and-rinse or self-etch system. [7]

There are several possible explanations for these poor outcomes in human studies. First are the direct cytotoxic effects that adhesives have on pulp cells. Next is the difficulty in obtaining an adequate seal to protect against bacterial contamination. This poor seal may be due to one or more reasons. The placement of acid directly onto the mechanically exposed pulp may aggravate the bleeding process, which, in turn, makes application of the pulp capping material in a dry field very difficult. The increased moisture at the pulp cap site reduces polymerization of the adhesive. Then, resin components reduce the pulp's immune response, making it less likely that the pulp will be able to defend itself against bacterial contamination. [7]

Finally, adhesives result in chronic inflammation, even in the absence of bacteria; inflammation is a poor environment for pulp healing.

4- Mineral Trioxide Aggregate (MTA)

In recent years a new cement , mineral trioxide aggregate (MTA), developed in the 1990s by Torabinejad and his coworkers at Loma Linda University (California), has become available as a root canal repair material and for direct pulp capping. MTA is primarily calcium oxide in the form of tricalcium silicate, dicalcium silicate and tricalcium aluminate. Bismuth oxide is added for radiopacity, MTA is considered a silicate cement rather than an oxide mixture, a so its biocompatibility is due to its reaction products. The primary reaction product of MTA with water is Calcium Hydroxide, and so it is actually the formation of calcium hydroxide that provides MTA's biocompatibility. As a result, many of the advantages and potential mechanisms of action for MTA are similar to Calcium Hydroxide, including its antibacterial and biocompatibility properties, high pH, radiopacity and its ability to aid in the release of bioactive dentin matrix proteins. However, an antibacterial effect of MTA is debatable, MTA showed some of the facultative bacteria but no effect on any of the anaerobic bacteria. The antimicrobial activity of MTA may not be as strong as those of traditional Calcium Hydroxide based cements and sealers. [8]

MTA can provide more leakage-proof because of its sealing ability. MTA is suggested to be superior to Calcium Hydroxide due to its uniform and thicker dentin bridge formation, less inflammatory response and less necrosis of pulpal tissues. There are some differences between MTA and Calcium Hydroxide. First, MTA comes in two colors, white and grey. The grey version is due to the addition of iron. Another significant difference is the fact that MTA provides some seal to tooth structure. [8]

The disadvantages of MTA include long setting times approximately 2 hours and 45 minutes. Setting time of MTA Gray is shorter than that of MTA White. A long setting time may be inconvenient to both dentist and patient, because it requires direct pulp-capping with MTA in two visits: application of MTA in the first visit and seating of the permanent restoration over the sufficiently hardened MTA in the second visit. Moreover, it may increase the risk of bacterial contamination. Another disadvantage of MTA poor handling "sandy" feeling mixture produced by the coarse particles of Pro Root and water is difficult to be delivered to the required site and hard to condense adequately which can be affected by the particle size and distribution as well as by the shape of the MTA powder. Tooth discoloration has been reported with the use of gray MTA in direct pulp capping and therefore the use of white MTA has generally been recommended in the esthetic zone. However, tooth discoloration associated with white MTA was also described in case reports in endodontic treatments. Tooth color change was reported to be induced by both gray and white MTA. Several factors were reported to contribute to tooth discoloration by white MTA: contamination with blood, contact with sodium hypochlorite, the presence of light and oxygen. The possible involvement of the radio pacifier bismuth oxide in the discoloration is postulated. The reason and mechanism of tooth discoloration are not fully understood and remain to be investigated. MTA is very expensive, one gram of MTA powder costs approximately the same as 24 grams of calcium hydroxide base/ catalyst paste, making MTA much less cost effective per use. [2, 8]

5- Calcium phosphate Compound

Calcium phosphate (CP) cements have been used for repairing bone defects. They are reportedly good candidates for osseous augmentation due to their biocompatibility, moldability and osteoconductivity. Thus, there have been many dental trials investigating the use of these materials on periodontal defect. In addition, many studies have shown that CP cements stimulate pulp and can induce the formation of reparative dentin. Researchers also showed the superior physical properties of calcium phosphate cements compared to calcium hydroxide. However, CP cements were observed to have limitations, including long setting times and low compressive strength, when used alone as pulp-capping agents. [2, 9]

Recently, fast-setting α-tricalcium phosphate (TCP) based cement was developed experimentally to overcome the disadvantage of conventional CP cements. According to manufacturer, it was developed not only for endodontic use, including pulp therapy, root-end filling, and perforation repair, but also for periodontal/surgical use, such as in osseous regeneration, which has been considered a primary application of CP cements. In other words, in addition to setting time, α-TCP cement may be more advantageous in variety of clinical applications compared to MTA. [9]

The α-TCP has a similar odontogenicity to MTA both in vitro and in vivo, whereas it has a much quicker setting time. However, α-TCP showed inferior physical properties including solubility and compressive strength. The α-TCP is potentially suitable for use as an effective pulp capping material. However, long-term clinical evaluation is required with respect to the use of α-TCP. [9]

Alpha-tricalcium phosphate and Tetracalcium phosphate (4CP) set then convert to hydroxyapatite. In contrast to calcium hydroxide, tetracalcium phosphate cement induced bridge formation with no superficial tissue necrosis and significant absence of pulp inflammation. [2]

6- Biodentine

New bioactive cement was recently launched in the dental market as a dentin substitute. It shares both its indications and mode of action with calcium hydroxide, but does not have its disadvantages.[10]

It is formed of Tricalcium silicate, calcium carbonate, oxide, and zirconium oxide (radiopacifier) in the powder, which is mixed with calcium chloride solution containing modified polycarboxylate instead of water. Both substances in the liquid contribute to shorten setting times (from 10 to 12 min). Calcium chloride accelerates the hydration reaction, and polycarboxylate reduces the amount of water required for mixing by providing proper consistency, which also contributes to easy handling of the mixture. Calcium carbonate in the powder is expected to act as a nucleation site in the hydrating mass, enhancing the hydration and leading to faster setting. Biodentine sets in approximately 10-12 minutes. Bio dentine was reported to have efficacy similar to that of MTA in direct capping over mechanically exposed pulp. Complete dentinal bridge formation, an absence of inflammatory pulp response and layers of well-arranged odontoblasts and odontoblast-like cells were observed after 6 weeks. [8]

Biodentine stimulates release of transforming growth factor beta (TGF-β) from pulpal cells, stimulating reparative dentin formation in a very short period of time. Particular growth factors from the TGF-ß family have the ability to initiate odontoblast differentiation and hence produce tertiary dentine by cell signaling. [2, 8]

Another study of indirect pulp capping on rat molars concluded that Biodentine was able to stimulate (thick and dense) reactionary dentine formation, which stopped after about three months when a sufficient dentine barrier was formed. Studies conducted to test Biodentine for application as a direct pulp capping agent and for pulpotomy showed that it was well tolerated even when in direct contact with the pulp. It was even suggested that the quality of dentine bridges formed were better than those formed by calcium hydroxide alone. Used for pulp capping, the material offers certain advantages over calcium hydroxide: It is stronger mechanically, less soluble and produces tighter seals. [2]

7- TheraCal LC

Is a light cured, resin modified calcium silicate filled liner designed for use in direct and indirect pulp capping, as a protective base/liner under composites, amalgams, cements, and other base materials. TheraCal LC performs as an insulator/barrier and protectant of the dental pulpal complex. The proprietary formulation of TheraCal LC consists of tricalcium silicate particles in a hydrophilic monomer that provides significant calcium release making it a uniquely stable and durable material as a liner or base. Calcium release stimulates hydroxy apatite and secondary dentin bridge formation. The material might be very attractive for clinicians because of its ease of handling. Unlike other calcium silicate-based materials, TheraCal LC is resin-based and does not require any conditioning of the dentine surface. The material can be bonded with different types of adhesives directly after application. [2, 11]

8- Emdogain (EMD)

EMD is enamel matrix derivative secreted from Hertwig's epithelial root sheath during porcine tooth development. It is an important regulator of enamel mineralization and plays an important role during periodontal tissue formation. It stimulates the regeneration of acellular cementum, periodontal ligaments, and alveolar bone. EMD contains bone morphogenetic proteins (BMP) like molecules and BMP expressing cells. BMP like molecules in EMD promote odontoblast differentiation and reparative dentin formation. It was concluded that amount of hard tissue formed in EMD treated teeth was more than twice that of the calcium hydroxide treated control teeth. [2, 12]

9- Propolis

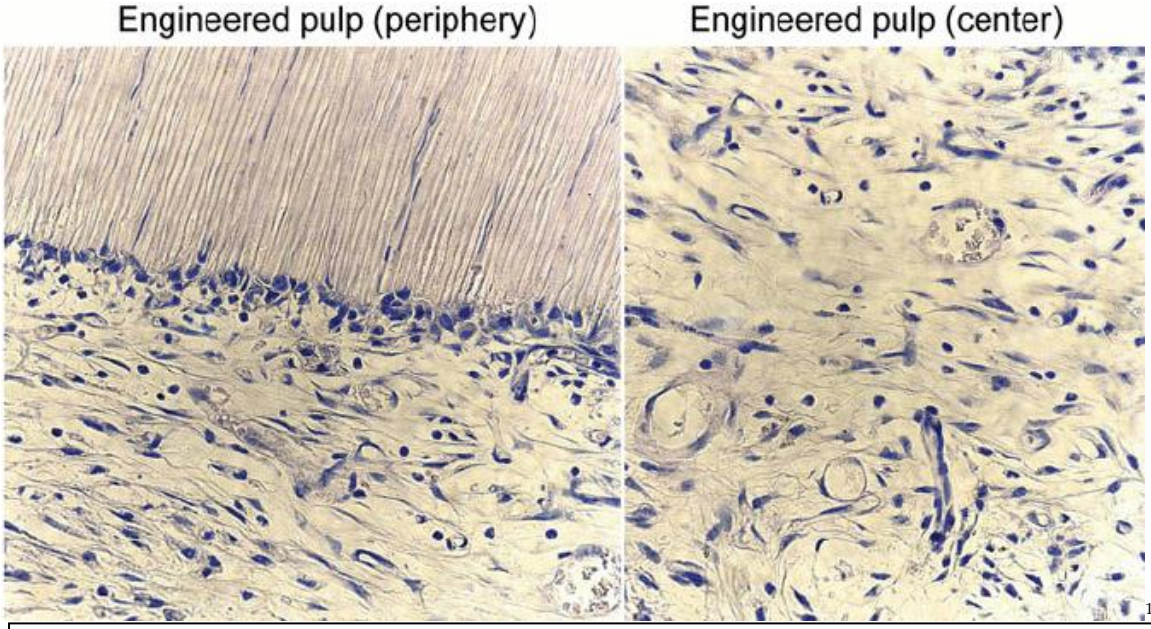
Propolis, a resinous material collected by honey bees, has been used as a traditional anti-inflammatory and anti-bacterial medicine for many centuries. Propolis is composed of 50% resin and vegetable balsam, 30% wax, 10% essential and aromatic oils, 5% pollen and 5% other various substances, including organic debris depending on the place and time of its collection. The constituents of Propolis vary widely due to climate, season and location; so its chemical formula is not stable. The most important pharmacologically active constituents in Propolis are flavonoids, which are well-known plant compounds that have antioxidant, antibacterial, antifungal, antiviral, and anti-inflammatory properties. [13]

It is used as indirect pulp capping paste when mixed with Zno powder and this showed similar effect of Zno and eugenol as secondry dentin formation. In direct capping with this paste showed no pulp degeneration and formation of protective layer. It contains flavonoids, phenolics, iron, zinc and other various aromatic compounds. propolis was compared propolis to MTA histologically in human dental pulp and showed similar bridge formation .[2, 13]

10- Dental pulp stem cells (DPSCs) and Stem cells from Human Exfoliated Deciduous Teeth (SHED)

Stem cells are unspecialized cells that continually reproduce themselves and can differentiate into specialized cells of one or more types. Stem cells can be divided into two major classes: embryonic/fetal stem cells and adult stem cells. Dental-derived stem cells are one of adult stem cells used as the cell sources for tissue engineering and regenerative medicine. Dental pulp stem cells (DPSCs) from permanent teeth are able to regenerate a dentin-pulp like complex that is composed of mineralized matrix with tubules lined with odontoblasts and fibrous tissue containing blood vessels in an arrangement similar to the dentin-pulp complex found in normal human teeth. Stem cells from human exfoliated deciduous teeth (SHED) are highly proliferative, clonogenic cells capable of differentiating into a variety of cell types including neural cells, adipocytes and odontoblasts.[14]

Nakamura S et al. (2009) used mesenchymal stem cells for clinical application in tissue engineering and regenerative medicine. In this study, they compared the proliferation of SHED, DSPCs and Bone Marrow Derived Mesenchymal Stem Cells (BMMSCs). They concluded that SHED has got significantly higher proliferation rate than that of DSPCs and BMMSCs and this could be a desirable option as a cell source for therapeutic applications, as shown in figure 1. [2, 14]



[15]

Figure 1. Dental pulp engineered with stem cells from human exfoliated deciduous teeth (SHED). SHED were seeded into tooth slice/scaffolds and transplanted into the subcutaneous space of immunodefi cient mice. After 21 days, the tooth slices were retrieved, fi xed, demineralized, and prepared for standard histology. Photomicrographs of hematoxylin/eosin- stained tissue sections (× 400) depicting the periphery and the central portion of the dental pulp-like tissue formed in the pulp chamber of these tooth slices.

Zhuang et al. also embedded Dental stem cell-derived extracellular vesicles (DSC-EVs) in the root fragment enriched with BMMSCs and observed dentine formation after 12 weeks of subcutaneously transplantation in nude mice. Besides the rodent models, DSC-EVs combined with treated dentin matrix (TDM) also presented the potential of dentin formation in a pulp exposure model of miniature pig, suggesting DSC-EVs loaded in TDM as a

promising strategy for pulp-capping therapy.Despite the obvious effects in vivo, the detailed molecular action of DSC-EVs in dentinogenesis remains unclear, calling for further mechanistic studies.[16]

References

1. Alex, G. (2018). Direct and indirect pulp capping: A brief history, material innovations, and clinical case report. Compendium of Continuing Education in Dentistry (Jamesburg, N.J.: 1995), 39(3), 182–189.
2. Priti, D & Desai, Priti & Sampurna, Dutta & Gupta, Saikat & Chatterjee, Soumyadeep & Mondol, Pritam & Sengupta, Pritam & Shromi, Roy & Choudhury,. (2019). DIRECT PULP CAPPING MATERIALS-A REVIEW. World Journal of Pharmaceutical Research. 8. 3254. 10.20959/wjpr20199-15424.
3. Qureshi, A., E, S., Nandakumar, Pratapkumar, & Sambashivarao. (2014). recent advances in pulp capping materials: an overview. Journal of Clinical and Diagnostic Research: JCDR, 8(1), 316–321. https://doi.org/10.7860/JCDR/2014/7719.3980
4. Hilton, T. J. (2010). Keys to clinical success with pulp capping: a review of the literature. Operative Dentistry, 34(5), 615–625. https://doi.org/10.2341/09-132-0
5. Nowak, A., Christensen, J. R., Mabry, T. R., Townsend, J. A., & Wells, M. H. (Eds.). (2019). Pediatric dentistry: Infancy through adolescence. Saunders.
6. Shameem, A., Muliyar, S., Thankachan, R. P., Kalliath, J. T., Mangalath, U., & Mangalath, S. (2018). Study to evaluate the efficacy of resin-modified glass lonomer cement liner as a direct pulp capping material. The Journal of Contemporary Dental Practice, 19(9), 1065–1071. https://doi.org/10.5005/jp-journals-10024-2382
7. Silva, G. A. B., Lanza, L. D., Lopes-Júnior, N., Moreira, A., & Alves, J. B. (2006). Direct pulp capping with a dentin bonding system in human teeth: a clinical and histological evaluation. Operative Dentistry, 31(3), 297–307. https://doi.org/10.2341/05-65
8. Moussa, S. A. (2018). Mineral trioxide aggregate (MTA) vs calcium hydroxide in direct pulp capping – literature review. Online Journal of Dentistry & Oral Health, 1(2). https://doi.org/10.33552/ojdoh.2018.01.000508
9. Lee, J.-B., Park, S.-J., Kim, H.-H., Kwon, Y.-S., Lee, K.-W., & Min, K.-S. (2014). Physical properties and biological/odontogenic effects of an experimentally developed fast-setting α-tricalcium phosphate-based pulp capping material. BMC Oral Health, 14(1), 87. https://doi.org/10.1186/1472-6831-14-87
10. Dammaschke, T. (n.d.). A new bioactive cement for direct pulp capping. Moderndentistrymedia.Com. Retrieved December 18, 2021, from https://www.moderndentistrymedia.com/mar_april2012/Dammascke.pdf
11. Arandi, N. Z., & Rabi, T. (2018). TheraCal LC: From biochemical and bioactive properties to clinical applications. International Journal of Dentistry, 2018, 1–6. https://doi.org/10.1155/2018/3484653
12. Najeeb, S., Khurshid, Z., Sohail Zafar, M., Zohaib, S., & Siddiqui, F. (2017). Efficacy of enamel Matrix Derivative in Vital Pulp Therapy: A review of literature. Iranian Endodontic Journal, 12(3), 269–275. https://doi.org/10.22037/iej.v12i3.12036.
13. Ahangari, Z., Naseri, M., Jalili, M., Mansouri, Y., Mashhadiabbas, F., & Torkaman, A. (2012). Effect of propolis on dentin regeneration and the potential role of dental pulp stem cell in Guinea pigs. Cell Journal, 13(4), 223–228.

14. Abdullah, M. F. (2013). DPSCs and SHED in tissue engineering and regenerative medicine. The Open Stem Cell Journal, 4(1), 1–6. https://doi.org/10.2174/1876893801304010001.
15. Casagrande, L., Cordeiro, M. M., Nör, S. A., & Nör, J. E. (2011). Dental pulp stem cells in regenerative dentistry. Odontology, 99(1), 1–7. https://doi.org/10.1007/s10266-010-0154-z.
16. Li, Y., Duan, X., Chen, Y., Liu, B., & Chen, G. (2022). Dental stem cell-derived extracellular vesicles as promising therapeutic agents in the treatment of diseases. International Journal of Oral Science, 14(1), 2. https://doi.org/10.1038/s41368-021-00152-2.

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Evaluation of retention and patient satsifaction for maxillary complete denture constructed by 3D printing technique and conventional technique

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Abstract:

Purpose: Evaluating retention and patient satisfaction for maxillary complete denture fabricated by 3D printing technique compared to conventional denture. **Material and Methods:** Subject group of ten completely edentulous patients were selected from the outpatient clinic of removable prosthodontics department, faculty of dental medicine for girls, Al-Azhar University. Each patient received maxillary and mandibular dentures fabricated by conventional technique besides maxillary denture fabricated by 3D printing technique. The ten patients were divided equally to two groups. First group patients received conventional dentures first then 3D printed ones. Second group patients received 3D printed dentures and conventional dentures later. **Results: T**his study showed that 3D printed dentures exhibited statistically significant higher retention and patient satisfaction at ($P \leq 0.05$) compared to conventional dentures. **Conclusion:** Utilizing 3D printing technique in complete denture fabrication yields better retention and patient satisfaction compared to conventional technique.

Keywords: Complete denture; 3D printed Dentures; Retention; Patient Satisfaction.

Introduction

Despite the vast abundance Despite the vast abundance of treatment methods for edentulous patients, conventional complete denture treatment still prevails (1). Nevertheless, problems may arise after insertion of complete dentures. Such problems are often complaints of insufficient retention, inadequate stability, tissue irritation, ulceration, and faulty esthetics (2).

One of the most used materials in complete dentures is Poly methyl methacrylate (PMMA) (3). Besides the great benefits such material offers, there are some downsides that restrict its use such as high polymerization shrinkage, dimensional instability, and complicated processing procedures. Such downsides in turn affects denture retention, mastication and speaking ability (4,5). Thus, needs were raised for novel techniques to overcome complete dentures downsides.

Incorporating CAD/CAM technology into complete dentures design and fabrication enhances dentures' quality and reduce lengthy laboratory work and procedures. CAD/CAM fabrication of complete dentures is attained by either

subtractive computerized numerical control (CNC) milling manufacturing, or by additive manufacturing via three-dimensional (3D) printing known as rapid prototyping (RP) (6,7).

The subtractive manufacturing utilizes end-milling of solid block materials in order to produce physical model via CNC machinery. Despite the subtractive method is effective in complete denture fabrication, it exhibits some drawbacks. Such downsides materialize in large amount of wasted material while milling. Additionally, the milling tools are exposed to high abrasion and wear. Moreover, it cannot be used in deep undercut (8).

On the other hand, additive manufacturing is a process which entails layer by layer joining to produce models relying on computerized three-dimensional data (3D). This technology was introduced in late 1980s and has been used in the medical field for production of anatomical 3D models for surgeries since 1990s (9,11).

Additive manufacturing using 3D printers has drawn attention in the field of prosthetic dentistry. Such technique showcased the ability to mold material based on CAD data influencing; the overall quality, the mechanical properties of printed parts, and the manufacturing time (12).

MATERIAL AND METHODS:

Paper scope was based on ten completely edentulous patients. The patients were selected from the outpatient clinic of removable prosthodontics department, faculty of dental medicine for girls, Al-Azhar University. Participants in this study were informed about the treatment steps, methodology, and written consent was granted accordingly. The targeted age range was from 55 to 60 years besides being free from any systemic and oral diseases. Each patient received two maxillary dentures; conventional and 3D printed, besides one mandibular conventional denture. The ten completely edentulous selected patients were divided into two equal groups, five patients each.

Group 1: Patients in this group received their conventionally fabricated denture first then were asked to take it off for 2 weeks as wash out period. Following to that they wore their rapid prototyped denture.

Group 2: Patients in this group wore their 3D printed denture first then asked to take it off for 2 weeks as wash out period. Following to that they wore their conventional denture

3D Printed Denture Construction:

To get 3D printed denture, the below sequence was undergone per patient.

Data acquisition: data obtained by scanning upper and lower master casts by extra-oral scanner. The occlusion blocks were sprayed by scanner spray then were fitted on their master cast. Following to that step the same device was used to scan the blocks.

Designing procedures: files in .STL format of master casts and jaw relation records were imported to Exocad™ software platform. The software enabled virtually simultaneous mounting and aligning. This in turn allowed further analysis and designing to be completed. Each denture had two STL files that were printed separately; one for denture base, and one for the teeth using 3D printer.

Manufacturing procedures: the designed dentures STL files were sent to the 3D printer software. The dentures were printed according to Digital Light Projection (DLP) technology using desktop 3D printer. Consequently, teeth were attached in the denture base through fitting them in recessed pockets in denture base via resin, and finally finishing was done.

Retention measurements:

Retention was measured by universal testing machine by getting denture resistance corresponding to vertical displacement force. Each denture was modified to install two small metal tubes (3 mm in diameter). The tubes were mounted few millimeters above the laterals in maxillary dentures by self-cure acrylic resin. Both distances between the right tube to the geometric center and left tube to the same center were of similar values. The exact distance for each

tube was verified by the aid of orthodontic wire. Each patient was seated in an upright position, while properly fixing his chin on a support. The device's bar was firmly connected to the denture and in accordance the attachment part of the universal machine was adjusted. The device gradually exerted steps of increasing vertical load (10mm/min) until the denture came totally out of place. The load at dislodgment point is indicated by an audible tuck sound. Also, it is characterized by an abrupt drop in force plot in the recorded computer software data. (Nexyge- MT-4.6; Lloyd Instruments). The same test was repeated five times to obtain five records.

Patient's satisfaction:

Patient satisfaction was evaluated for both conventional and 3D printed dentures after 1 and 3 months follow up through a validated questionnaire. That questionnaire was given to the patients in Arabic to obtain relevant data for assessment. It entailed five domains: functional complaints, overall masticatory ability, masticatory ability for different types of food, effect on mental and daily life and overall denture satisfaction. Evaluation of patient satisfaction took place by scoring system and visual analog scale (VAS) in which patients provided their answers as a mark on a scale from 0 to 10 cm (low/worst to high/best).

RESULTS:

Retention: Two-way repeated measures ANOVA results reflected that the two variables (denture type regardless of time, and time regardless of denture type) are independent. Regarding effect of different interactions on retention, it was found that at base line, after one as well as three months; 3D printed dentures showed statistically significantly higher mean retention than conventional denture (P-value = 0.028, Effect size = 0.432), (P-value = 0.026, Effect size = 0.442) and (P-value = 0.017, Effect size = 0.489). With both denture types, there was a statistically significant change in mean retention values by time (P-value <0.001, Effect size = 0.947) and (P-value <0.001, Effect size = 0.89). Pair-wise comparisons between follow up times revealed that there was a statistically significant increase in mean retention values after one month as well as from one to three months.

Table 1. The mean, standard deviation (SD) values and results of two-way repeated measures ANOVA test for comparison between retention values with different interactions of variables

Time	**3D Printed**		**Conventional**		***P*-value (Between dentures)**	**Effect size *(Partial eta squared)***
	Mean	**SD**	**Mean**	**SD**		
Base line	20 ^{C}	3.2	15.5 ^{C}	4.3	0.028*	0.432
1 month	22.5 ^{B}	3.2	18 ^{B}	3.9	0.026*	0.442
3 months	24.3 ^{A}	3.8	20 ^{A}	3.8	0.017*	0.489
***P*-value (Between times)**	<0.001*		<0.001*			
Effect size *(Partial eta squared)*	0.947		0.89			

*: Significant at P ≤ 0.05, Different superscripts in the same column indicate statistically significant change by time.

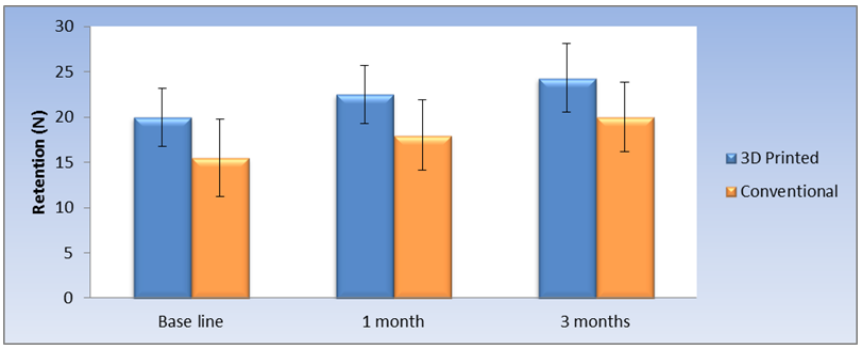

Figure 1-Bar chart representing mean and standard deviation values for retention with different interactions of variables

Patient Satisfaction: Patient Satisfaction surveyed after one month exhibited no statistically significant difference between each item of satisfaction scores with the two denture types. Nevertheless, 3D printed dentures showed statistically significantly higher median overall satisfaction score than conventional denture (P-value = 0.039, Effect size = 4.737).

Patient satisfaction conducted after three month showed no statistically significant difference between each item of satisfaction scores with the two denture types, however; 3D printed denture showed statistically significantly higher median overall satisfaction score than conventional denture (P-value = 0.042, Effect size = 4.355).

Table 2. Descriptive statistics and results of Wilcoxon signed-rank test for comparison between patient satisfaction scores with the two denture types after one month

Item	Time	3D Printed		Conventional		*P*-value	Effect size *(d)*
		Mean (SD)	Median (Range)	Mean (SD)	Median (Range)		
Functional complaints	1 Month	1.44 (0.25)	1.29 (1.21-1.79)	1.64 (0.32)	1.5 (1.29-2.07)	0.500	0.632
Overall masticatory ability		1.09 (0.36)	1 (0.86-1.71)	1.83 (0.54)	1.86 (1-2.43)	0.078	2.556
Masticatory ability with food types		1.1 (0.14)	1 (1-1.25)	1.3 (0.33)	1.25 (1-1.75)	0.157	1.633
Effect on daily life		1.7 (0.14)	1.75 (1.5-1.88)	1.63 (0.32)	1.5 (1.38-2.13)	0.581	0.509
Overall satisfaction		8 (0.2)	7.86 (7.86-8.29)	5.83 (0.19)	5.71 (5.71-6.14)	0.039*	4.737
Functional complaints	3 Month	1.23 (0.2)	1.21 (1.07-1.57)	1.54 (0.36)	1.5 (1.07-2)	0.279	1.109
Overall masticatory ability		1.06 (0.37)	0.86 (0.86-1.71)	1.77 (0.52)	1.71 (1-2.43)	0.104	2.116
Masticatory ability with food types		1.1 (0.14)	1 (1-1.25)	1.3 (0.33)	1.25 (1-1.75)	0.102	2.138
Effect on daily life		1.58 (0.11)	1.5 (1.5-1.75)	1.55 (0.23)	1.5 (1.25-1.88)	0.705	0.343
Overall satisfaction		8.34 (0.16)	8.29 (8.14-8.57)	6.37 (0.3)	6.43 (6-6.71)	0.042*	4.355

*: Significant at P ≤ 0.05.

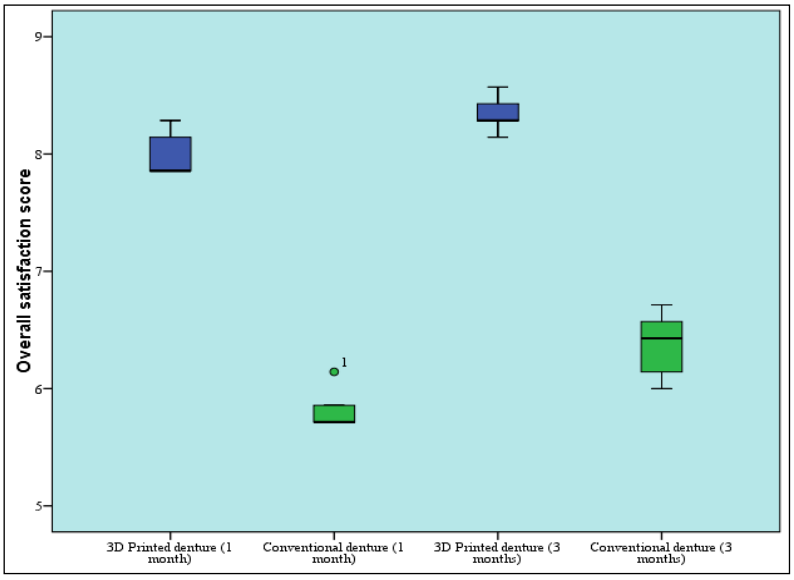

Figure 2 Box plot representing median and range values for overall satisfaction scores of the two denture types (Circle represents outlier).

DISCUSSION:

In this study retention and patient satisfaction for two different manufacturing techniques of complete dentures, printed and conventional, were compared. Retention is an inherent factor that greatly influences patient satisfaction. Nonetheless, patient satisfaction is considered as an important outcome that enables better evaluation of success of any prothesis in terms of retention, stability, function, esthetics, and psychological comfort. Thus, both were recorded together (13).

Several studies have proven that the dentures fabricated from conventional processing techniques suffer from dimensional changes due to polymerization shrinkage and release of internal stresses. That resulting distortion compromises retention besides support and stability of the denture, which lead to adverse consequences on the patient's satisfaction. This in turn substantiated the need for advanced techniques in fabrication of complete dentures. (14-16).

The result of this study showed superiority in terms retention of the 3D printed dentures over the conventional dentures. This is could be attributed to utilized denture construction technique. This technique was attained by additive manufacturing methods that created the object by successive layering of photosensitive resin, then UV light polymerizing it. This technique was used because it allows material conservation and exhibits the ability to print complex geometries with reasonable dimensional accuracy. The dimensional changes of each layer are compensated for by addition of the successive resin layer (17).

In accordance with the findings of the study, other recent studies indicated that 3D printed dentures exhibited better retention compared to conventional dentures. The main reason was that 3D printed dentures revealed less shrinkage and distortion, along with consistent better adaptation compared to conventional dentures. (17-19).

The prolonged success of prosthesis is pivoted on the fit accuracy incurred between denture base and mucosal tissue. A recent study that used surface matching software focused on accuracy of the denture revealed comparative feedback. The study evaluated denture bases manufactured by three methods: injection molding, milling, and rapid prototyping. The findings depicted that highest deformation was in the conventionally made dentures, whilst least deformation was associated with rapid prototyped dentures.

Regarding patient satisfaction, 3D printed dentures showed enhanced overall satisfaction with respect to conventional dentures. This aligned with former research concluding improved surface quality of printed dentures along with better

patient satisfaction (20,21). Additionally, a systemic review reflected that digitally fabricated dentures had more positive impact rather than conventionally fabricated dentures (22).

CONCLUSION:

With respect to constraints of the subject study, it was concluded that 3D printed dentures exhibit better retention and patient satisfaction. However, further studies need to be conducted.

References

1. Lee DJ,Saponaro P. Management of Edentulous Patients. Dental Clinics of North Am.2019;63:249-61.
2. Sharma A, Singh R, Sharma R, Dhanda A, Neha, Thakur V. Post insertion problems in complete denture: A review. IP Ann Prosthodont Restor Dent. 2020; 6:189-193.
3. Zafar MS. Prosthodontic Applications of Polymethyl Methacrylate (PMMA): An Update. Polymers (Basel). 2020.12:2299.
4. Vallejo-Labdara M, Ocampo BL. Comparison of the Polymerization Shrinkage of Eclipse Resin for Prostheses with Conventional Acrylic Resins. Int. J. Odontostomat 2019;3;279-86.
5. Steinmassl O, Dumfahrt H, Grunert I, AncaSteinmassl P. CAD/CAM Produces Dentures with Improved Fit. Springer. Clin Oral Investig; 2018; 22:2829-35.
6. Nadim Z B,Hamad S. AlRumaih, Brian J. Goodacre, Charles J. Goodacre. Current Techniques in CAD/CAM Denture Fabrication. Gen Dent.2016; 64: 23-8.
7. Yoon SN, Oh KC, Lee SJ, Han JS, Yoon HI. Tissue surface adaptation of CAD-CAM maxillary and mandibular complete denture bases manufactured by digital light processing: A clinical study. J Prosthet Dent. 2020;124:682-9.
8. Dikova T, Dzhendov D, Simov M, Bozukova IK, Angelova S, Pavlova D, et al. Modern Trends In The Development Of The Technologies For Production Of Dental Constructions. J of IMAB.2015; 21: 974-81.
9. Almufleh B, Emami E, Alageel O, de Melo F, Seng F, Caron E, et al. Patient satisfaction with laser-sintered removable partial dentures: A crossover pilot clinical trial. J Prosthet Dent. 2017; 119:560-7.
10. Barzanchi A, Li KC, Al-Amleh B, Lyons K, Waddell JN. Additive technology: update on current materials and applications in dentistry. J Prosthodont.2017; 26: 156-63.
11. Bilgin MS, Baytaroglu EN, Erdem A, Dilber E. A review of computer –aided design/computer –aided manufacture techniques for removable denture fabrication. Eur J Dent. 2016; 10: 286-91.
12. Tasaka, A., Matsunaga, S., Odaka, K., Ishizaki, K., Ueda, T., Abe, S., Yoshinari, M., Yamashita, S., & Sakurai, K. Accuracy and retention of denture base fabricated by heat curing and additive manufacturing. Journal of prosthodontic research.2019;63:85–9.
13. Kavita K, Iqubal, M.A., Singh R., Singh S., Nazeer J, Singh R.Factors affecting patient satisfaction among patients undergone removable prosthodontic rehabilitationJ Family Med Prim Care.2020 ;9: 3544–8.
14. Chintalacheruvu VK, Balraj RU, Putchala LS, Pachalla S. Evaluation of Three Different Processing Techniques in the Fabrication of Complete Dentures. J Int Soc Prev Community Dent. 2017;7:18-23.

15. Savirmath A, Mishra V. A Comparative Evaluation of the Linear Dimensional Changes of Two Different Commercially Available Heat Cure Acrylic Resins during Three Different Cooling Regimens. J Clin Diagn Res. 2016;10:50-4.
16. Steinmassl O, Dumfahrt H, Grunert I, Steinmassl PA. CAD/CAM produces dentures with improved fit. Clin Oral Investig. 2018;22:2829-35.
17. Revilla-León M, Özcan M. Additive Manufacturing Technologies Used for Processing Polymers: Current Status and Potential Application in Prosthetic Dentistry. J Prosthodont. 2019;28:146-158.
18. Kattadiyil MT,Jekki R, Goodaere CJ,Baba NZ.comparison of the treatment outcomes in digital and conventional complete removable dental prosthesis fabrications in a predoctoral setting.2015;114:818-25.
19. Chalapathi Kumar VH, Surapaneni H, Ravikiran V, Chandra BS, Balusu S, ReddyVN. Retention of denture bases fabricated by three different processing techniques—an in vivo study. J Int Soc Prev Community Dent 2016;6:245–50.
20. Ahmad MN, Wahid MK, Maidin NA, Ab Rahman MH, Osman MH, Alis-Elias IF. A complete denture by rapid prototyping with reverse engineering approach. Int J Mech Mechatronics Eng. 2019;19:50-7.
21. Kattadiyil MT, AlHelal A: An update on computer-engineered complete dentures: a systematic review on clinical outcomes. J Prosthet Dent 2017;117:478-85.
22. Clark WA, Brazile B, Matthews D, Solares J, De Kok IJ. A Comparison of Conventionally Versus Digitally Fabricated Denture Outcomes in a University Dental Clinic. J Prosthodont. 2021;30:47-50.

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Introduction to Materials–Tissue Interface

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Abstract: The introduction of a foreign material into living tissue intentionally as in biomedical applications (implants, prostheses, drugs) or unintentionally as when minerals or fibers are inhaled results in the creation of interfaces between the material and the surrounding tissue. The material surface properties and molecular processes at such interface play a major role.

Keywords: Interface; surface; dental implant; bone cement; dental composites; adhesives; sealers.

Introduction

The introduction of a foreign material into living tissue ***intentionally*** as in biomedical applications (implants, prostheses, drugs) or ***unintentionally*** as when minerals or fibers are inhaled results in the creation of interfaces between the material and the surrounding tissue. The material surface properties and molecular processes at such interface play a major role. [(1)]

For kinetic and thermodynamic reasons, ***surfaces*** are different from the corresponding bulk of the material, and contain reactive (unsaturated) bonds, which in turn lead to the formation of surface layers (e.g., surface oxides on metals). Encountering with biological environment leads to further surface reactions, ***adsorption of water, ions, and bio-molecules***. The exact nature of the adsorbed coating in turn influences the behavior of ***cells*** approaching the material surface, and hence the tissue response. [(1, 2)]

II- General Guide Lines

1- Main factors affecting Materials –Tissue interface

Factors greatly affect the materials–tissue interface include material surface properties and processes at such interface.

a) Material Surface Properties

The surface of a material is a termination of an extended; three dimensional structure. Thus, generally represents an increase in energy due to unsaturated bonds (the surface energy). If there is a reactive environment at the surface, the bonds react to form new bonds and compounds, to ***lower its surface energy***. [(1)]

If the reacted surface is placed in another new environment, it is likely to react again to lower further the energy of the system. There is thus a ***built-in thermodynamic driving force*** for reactions. Only in ***two exceptional cases***

no reactions occur: either when the separated material and tissue systems have the lowest thermodynamic state, or when kinetic barriers prevent all possible reactions [3].

An ***example*** here is titanium, which is used for dental implants and in orthopedic devices. When fresh titanium is exposed to air it reacts rapidly with atmospheric oxygen to form a surface oxide which is typically a few nanometers thick. The oxide stoichiometry is approximately TiO_2. The surface is never perfectly clean TiO_2, for the TiO_2 terminated surface tends to bind molecules or atoms from the surroundings as a mono-molecular layer. Even ***inert surfaces*** such as gold or diamond have a tendency to lower their surface energy by suitable terminations on the ***atomic scale***. For example, diamond may terminate by C-H bonds at the surface. [1]

At the tissue-material interface, surfaces properties such as ***chemical composition***, ***wettability***, and ***topography*** play a determinant role in the biological interactions, particularly the ***microstructure*** and ***surface roughness***. Thus, surface preparation and characterization, on the atomic scale, are vital ingredients in any research effort to improve our understanding of the material-tissue interaction and the processes occurring there. It is possible to analyze the outermost atomic layer(s) of a material with a sensitivity of down to 0.1 to 1% of a monolayer. [1, 5]

b) Processes at the Material-Tissue Interface

The ***chemical constituents*** and ***pH***, for example, of the biological environment influence the interaction at the surface. The material surface, in relation to the tissue, is a foreign chemical species that has reactive sites which can either be the main constituents of the surface or impurities incorporated in it. Reactions between a bio-molecule and the material surface may lead to a temporary or permanent bond formation, which are either weak , van der Waals or hydrogen bonding type, or stronger ionic or covalent bonds.[1]

The molecular events at the material-tissue interface involve ***small molecules***, like water, which can dissociate to OH groups or bind to the surface by hydrogen bonds. The molecular events also involve ***larger molecules*** like proteins, which sometimes denature. This hydration and protein layer is dynamic and surface specific since different surfaces will develop very different coatings in the same tissue, because of their different chemical properties. [1, 2]

Eventually the larger structures like ***cells***, which have lower mobility, will reach the surface with its organic over-layer. Since both the cell membrane with its coating of bio-molecules and the material surface are dynamic, they can exchange proteins, ions, and other substances, and form a complex and dynamic interface. Depending on the nature of the material surface and its organic coating, cells react differently to different biomaterials. The cells may experience the surface as a serious perturbation and react violently inducing an inflammatory response; if the surface is experienced as "tissue-like," no reactions or only mild ones may occur.

If the material is a metal, ***degradation*** by corrosion may result in release of metal ions from the oxidized metal surface into solution, which may then migrate throughout the biological system, potentially producing negative systemic effects such as allergic reactions. This has been demonstrated in animal experiments, and in humans, with metal ions such as Ni, Cr, Al, and V. [1]

Biodegradable materials constitute an extreme and intentional case of this event, where the whole material eventually is dissolved. In the other extreme, like bone anchored devices, the requirement is a stable, yet fully

tissue-integrated device, which may require an initial or continuous microscopic remodeling of the surface, but at a rate that has a negligible effect on the macroscopic dimensions of the implant.[5]

The surface may be attacked by the tissue by an ***oxidative process*** if the oxide layer, instead of remaining passive, becomes thicker via anion or cation transport through the oxide layer. This can occur in the presence of oxygen radicals and peroxy species, or certain complex forming ions in the biological environment, or catalyzing species that accelerate oxidization. If oxide growth occurs in vivo, as has been demonstrated experimentally, it may be accompanied by ***inclusion of ions*** present in the bio-liquid. Thus, the surface of the material, and its interface with the tissue, may be very dynamic and may undergo continuous remodeling. [1]

2-Ten Key Questions [1]

Ten key questions for better understanding of Materials –Tissue interface:

1. How does the ***chemical composition*** of the surface influence the biological response? What is the role of ***surface contamination***?
2. How important is the ***microstructure*** and ***topography*** of the surface?
3. Which bio-molecules are adsorbed in the first ***monomolecular layer*** on the biomaterial surface? Which molecules are bound in ***the successive layer***s and how are they bound to each other?
4. How are ***water*** and hydrated ions structured at the interface and how do they bind to the surface? How does water bonding influence protein bonding, etc.?
5. What ***type of bonding*** keeps the bio-molecules to that surface? How strong are the bonds? Which part(s) of the adsorbed bio-molecules is (are) involved in the bonding?
6. Is the ***conformation of these bio-molecules*** changed and if so, is the conformational change reversible or irreversible?
7. Is there a ***continuous exchange***, over time, of the molecules adsorbed at the surface, and what are the time scales for such exchange?
8. How ***close can cells come*** to the surface? Is there always a layer of extracellular components that separate cells from the surface?
9. How does the ***surface influence*** cell differentiation and activity?
10. How is information communicated between cells and biomaterial surfaces ***in vivo***?

3-Research Program

A research program addressing these issues involves ***adsorption studies of water and proteins***, with a variety of spectroscopic methods of atomic resolution, microscopic methods to obtain the bonding, orientation, and structure of water and proteins on the surface, etc. ***Cell level interaction studies*** are necessary, as well as real ***in vivo*** experiments (animals, humans). There is always a demand for new and improved experimental methods.

III- Dental Examples

1-Dental Implants

Implants are commonly used in dental surgery for restoring teeth.

One of the challenges in implantology is to achieve and maintain the ***osseointegration*** as well as the ***epithelial junction*** of the gingiva with implants. An intimate junction of the gingival tissue with the neck of dental implants may prevent bacteria colorizations which cause peri-implantitis while direct bone bonding may ensure a biomechanical anchoring of the artificial dental root.[5]

The first step of the osseointegration of implants is called ***primary stability*** and is related to the mechanical anchorage, design of implants, and bone structure. This primary interlock decreases with time at the benefit of the ***secondary anchorage***, which is characterized by a biological bonding at the interface between bone tissues and implant surface. ***Between*** the primary mechanical and secondary biological anchorage, a decrease of implant stability could be observed. [6]

Many studies have attempted to enhance the osseointegration of implants by ***various surface modifications***. The aim is to provide implants with surface biological properties for the adsorption of proteins, the adhesion and differentiation of cells, and tissue integration. However, the control of these surface properties at the protein and cell levels, thus in the nanometer range, remains a challenge for researchers and dental implants manufacturers.

Nanotechnologies may produce surfaces with controlled topography and chemistry that would help understanding biological interactions and developing novel implant surfaces with predictable tissue-integrative properties [6, 7]. Various surface treatments such as lithography, ionic implantation, anodization, and plasma treatments may be applied to the surfaces of dental implants to produce controlled features at the nanometer scale. These surfaces may then be screened by using high throughput biological assays *in vitro*. For instance, specific protein adsorption, cell adhesion, and differentiation of stem cells should be studied in relation to the surface properties. This approach may define the ideal surface for a specific biological response. Following *in vitro* screening, nanostructured surfaces may then be tested in animal models[4].

a) Interactions of Surface Dental Implants with Blood

During surgery, blood vessels are injured and, thus, dental implant surfaces interact with blood components. Various plasma proteins get adsorbed on the material surface within a minute, depending on the surface properties of the material [8]. A hydrophilic surface is better for blood coagulation than a hydrophobic surface. Consequently, dental implants manufacturers have developed high hydrophilic and rough implant surfaces for better osseointegration [9]. Adsorption of proteins such as fibronectin, vitronectin on surface of dental implants could promote cell adhesion by ***cell-binding RGD domain*** (arg-gly-asp). This RGD sequence interacts with integrin present on the cell membrane [10]. Interactions between cell membrane integrins and proteins coated onto implant surface play a key role in adhesion of many cells types. After proteins absorption, the osseointegration is characterized by platelets adhesion and fibrin clots formation at the injured blood vessels site.[4]

There is a controversy about the role of platelet-rich plasma on the osseointegration. It has been shown that implants in contact with platelet-rich plasma (PRP) with a platelet concentration of approximately1,000,000 pro-

tein/μL have a positive effect on osteointegration. At lower concentrations of PRP, the effect was not optimal, while higher concentrations resulted in a paradoxically inhibitory effect of bone regeneration. Other studies were not in agreement with this PRP beneficial effect on the osseointegration of dental implants. [11]

The assessment of bioactivity of surface-treated dental implants should be tested *in vitro* using biological fluids containing blood components [12].

b) Interactions between Surfaces and Mesenchymal Stem Cells

Following blood clotting around dental implants, several cells interact with surfaces for tissue healing. Mesenchymal stem cells (MSCs) attracted to the injured site by chemotactic factors have a determinant role in peri implant tissue healing.

b-i) Origin of Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are stem cells derived from somatic tissue which can be differentiated into mesenchymal lineages such as bone, cartilage, fat, and skin. In addition, MSCs are present in blood at low concentrations serving as a sort of internal repair system. Mesenchymal stem cells are distinguished from other cell types by two important characteristics. ***First***, they are unspecialized cells able to renew themselves through cell division, sometimes after long periods of inactivity. ***Second***, under certain physiologic or experimental conditions, they can be induced to become tissue- or organ-specific cells with special functions. Thus, MSCs have high proliferative and multipotent capacity leading to differentiated cells under the guidance of various cues or niches. [4]

b-ii) Migration, Adhesion, and Proliferation

Cell migration, adhesion, and proliferation on implant surfaces are a prerequisite to initiate the tissue regeneration. Authors have shown that some factors present in tissues and secreted during the inflammatory phase are able to attract MSCs to the injured site [13, 14]. MSCs migration and proliferation were stimulated by many growth factors including PDGF [15,16], EGF [16,17], VEGF [18], TGF-β [15, 19], and BMP-2 and BMP-4 [15,18]. These factors are certainly released in the injured sites by cells involved in tissue healing. Furthermore, plasma clot serves as storage to fibrin molecules and releases system for a variety of bioactive factors including growth factors that attract and differentiate MSCs into specific lineages [20-22].

After MSC recruitment in the injured site, cells adhere on the local extracellular matrix as well as on the implant surface beginning an extensive proliferation in order to build up new tissue. Again, surface modifications of implants in the nanometer range condition the biological responses. [4]

b-iii)Differentiation

MSCs are stimulated by ***some specific factors*** to differentiate into the adequate cell line. Under the influence of these factors, MSCs switch to osteoblastic cells in contact to bone tissue while they differentiate into fibroblastic lineage in the gingival tissue region. These two differentiation pathways are in concurrence around dental implants. In some cases, implants are encapsulated by fibrous tissue due to the proliferation and differentiation of MSCs into fibroblastic cells causing implant failure [23]. However, fibroblasts adhesion and proliferation have been shown to be lower on nanoscale implant surface. Special membranes could be used in such cases for guided-tissue-regeneration. [24-26].

Titanium and zirconia are the most widely used dental implant materials.The goal of dental implants is to achieve ***osseointegration*** or ***biointegration*** where ceramic coatings promote chemical integration of the implant with the bone [27, 28]. Animal studies with histological, radio- graphical and mechanical investigations [29-31], cell culture and clinical cases have been widely reviewed in literature in dental implant researches[32-33].

2- Dental Composite/ Adhesives

The fast progress in dental adhesive technology has extensively influenced modern restorative dentistry. Although decayed/fractured teeth can be reconstructed minimal invasively and nearly invisibly using adhesive technology, the clinical longevity of composite restorations is today still too short [35, 36]. Despite the enormous advances made in adhesive technology during the last 50 years, the bonded interface remains the main challenge of an adhesive filling [37, 38]. Modern adhesive approaches can be divided into (1) etch&rinse, (2) self-etch (or etch&dry), and (3) self-adhesive approach [39].

a- Etch&rinse

The multi-step etch&rinse approach involves a phosphoric acid-etch step that at enamel produces deep etch-pits in the hydroxyapatite (HAp)-rich substrate, and at dentin demineralizes up to a depth of a few micrometers to expose a HAp-deprived collagen mesh. The next step involves either a separate priming step followed by the application/curing of a combined primer/adhesive resin following a simplified 2-step procedure, or a separate primer and adhesive resin step following a 3-step procedure. The final objective is to micro-mechanically interlock upon diffusion and *in situ* polymerization of monomers into the enamel etch-pits, the opened dentin tubules and the exposed collagen network, the latter forming the well-documented hybrid layer. Without doubt, the micro-mechanical interlocking of tiny resin tags within the acid-etched enamel surface is still today the best achievable bond to enamel [39]. It not only effectively seals the restoration margins on the long term, but also protects the more vulnerable bond to dentin against degradation [40].

On the contrary, etching dentin is a rather aggressive procedure as it dissolves and removes (through rinsing) the natural protection of collagen, thereby producing a resin–collagen complex that is vulnerable to degradation upon water sorption, possibly enhanced by the documented enzymatic degradation process [41-43]. As the most intimate and stable intermolecular interaction possible, primary chemical interaction between resin and the mainly organic substance remaining at acid-etched dentin would definitely contribute to the bond durability, but is however lacking [44,45]. This deficient chemical interaction should most likely be regarded as the major shortcoming of today's etch&rinse approach. Nevertheless, traditional 3-step etch&rinse adhesives are still today regarded as 'gold-standard' [46].

b- Self-etch

The self-etch approach can be further subdivided into a 'strong' (pH < 1), an 'intermediately strong' (pH≈1.5), a 'mild' (pH≈2), and an 'ultra-mild' (pH≥2.5) self-etch approach depending on the self-etching or demineralization intensity [47]. Self-etching only dissolves the smear layer, but does not remove the dissolved calcium phosphates, as there is no rinse phase. The more intense the self-etching, the more calcium phosphates are dissolved and embedded within the interfacial transition zone [48]. Such resin-encapsulated calcium phosphates within the exposed collagen mesh are however rather soluble and may explain the lower laboratory and clinical bonding performance of strong self-etch adhesives, in particular to dentin [49]. At enamel, they however perform in general much better due to this more aggressive self-etching [50]. The less intense the self-etching, the more

bur-smear may interfere with the eventual bonding performance [51, 52]. In particular 'mild' (pH≈2) self-etch adhesives appear to deal reasonably well with bur-smear, producing a submicron hybrid layer with substantial HAp-crystals still protecting the collagen fibrils.

Functional monomers, in particular like 10-***MDP*** (10-methacryloyloxydecyl dihydrogen phosphate), have been proven to interact with this residual HAp through primary ionic binding [53, 54]. The resultant two fold micro-mechanical and chemical bonding mechanism closely resembles that of glass-ionomers [55-59]. However, chemical bonding potential on its own is insufficient; the formed ionic bonds should also be stable in an aqueous environment. Chemical bonding promoted by 10-MDP appeared not only more effective, but also more stable in water than that provided by other functional monomers like 4-MET (4-methacryloyloxyethyl trimellitic acid) and phenyl-P (2-methacryloyloxyethyl phenyl phosphoric acid), in this order [54].

The dissolution rate of the respective calcium salts of these three monomers, as measured by AAS (or atomic absorption spectroscopy), was inversely related to their chemical bonding potential revealed by XPS: the more intense the chemical bonding potential, the less the resultant calcium salt could be dissolved. This finding was further explained in the 'AD-concept' or the adhesion–decalcification concept that dictates if molecules will either adhere to or decalcify mineralized tissues [60, 61].

Two-step self-etch adhesives involve the application of a separate, more hydrophobic adhesive resin after the hydrophilic self-etch primer. This makes the interface more hydrophobic and thus better seals it to the direct benefit of bond durability. Finally, the most simple- and fast-to-use 1-step (self-etch) adhesives generally come with some sacrifice in bonding performance. This lower bonding efficiency has been thoroughly documented in laboratory research, and must be ascribed to, among others, to a lower polymerization conversion and thus inferior mechanical properties, enhanced water sorption through osmosis from the host dentin, potential phase-separation effects when the adhesive solution is

lowin or free of HEMA(2-hydroxyethyl methacrylate), filler debonding

within the adhesive resin through hydrolysis of the silane coupling, potential smear interference for ultra-mild self-etch adhesives, and reduced shelf life in particular with regard to one-component formulations [62-67].

c- Self-adhesive

Glass-ionomers and resin-modified glass-ionomers are 'selfadhesive' through submicron hybridization, combined with well-proven primary ionic interaction of polyalkenoic acid with calcium within HAp. Polyalkenoic acid possesses abundant functional carboxylic groups that 'grab' HAp simultaneously at different and remote sites. Other 'self-adhesive' materials are the so-called self-adhesive luting composites that have been introduced some years ago [68-70]. They are often mistakenly termed as 'self-etching', while they interact only very superficially with dentin without clear signs of demineralization. Finally, it is in the line of expectations that such self-adhesive luting composites will soon lead to the development of self-adhesive flowable and later full restorative composites.

While adhesive–enamel/dentin interfacial characterization using scanning and even more reliably using transmission electron microscopy (potentially supplemented with chemical interfacial analysis) definitely reveals a deeper insight in the underlying mechanisms of adhesion, the actual bonding effectiveness of today's adhesive approaches should be measured using a mechanical bond-strength test.

It was shown that the shade of the composite has an influence on its cytotoxicity and that this cytotoxicity is also influenced by the light curing unit used. It was observed that composites of the darker shade had a higher cytotoxicity, which varied with the light curing unit employed.

As the longevity of an adhesive composite restoration is mainly affected by leakage of oral fluids along the interface between restorative material and tooth substrate [71, 72], probably more clinically relevant than bond-strength studies is to evaluate the capacity of an adhesive to maintain the tooth-restoration transition sealed. It is especially thought

to predict better the clinical performance of adhesives with regard to the occurrence of postoperative sensitivity and/or secondary caries [72]. This included micro-leakage, marginal adaptation/gap formation, bacterial leakage permeability, nano-leakage and 3D-leakage. Acoustic emission and Micro-CT have been used for non-destructive examination of interfacial debonding [73].

Bond durability can be measured using bond strength test (macro or micro test, basically depending upon the size of the bond area), measured in 'shear', 'tensile', or using a 'push-out' protocol. Despite the importance of laboratory studies attempting to predict clinical performance of biomaterials, clinical trials remain the ultimate way to collect scientific evidence on the clinical effectiveness of a restorative treatment [74, 75]. Clinical effectiveness of adhesives should best be determined using Class-V clinical trials.

3- Tissue engineering

As a multi-disciplinary field, tissue engineering integrates materials science with regenerative medicine by applying the principles of engineering and biology to clinical issues. A typical tissue engineering strategy can be separated into three components: a ***scaffold*** [an artificial extracellular matrix (ECM)], ***cells***, and ***biological factors***. The scaffold serves as a template for tissue regeneration and plays a pivotal role in cell adhesion, proliferation, differentiation, and new tissue formation in three dimensions (3D). [76]

With the advancement of developmental biology and nanotechnology, recent research on scaffolding has more focused on the design and synthesis of functionalized scaffolds that can elicit desirable cell/material interactions to guide cell behaviour and enhance new tissue formation. [77]

Generally, bioactive agents can be incorporated onto functionalized scaffolds through bulk or surface modification. In the bulk modification process, bioactive agents are coupled with functional polymers prior to scaffold fabrication. For example, the RGD peptide was first chemically attached to the lysine residue of poly[(L-lactic acid)-*co*-(L-lysine)] before scaffold preparation. The RGD peptide, therefore, was distributed both on the surface and in the bulk of the poly[(L-lactic acid)-*co*-(L-lysine)] scaffold. Since cell/material interactions take place on scaffold surfaces, the bioactive molecules encapsulated inside the scaffold will not be able to interact with cells. Therefore, bulk modification is not an efficient way to incorporate bioactive agents. Furthermore, bulk modification often alters the mechanical and processing properties of the scaffold. In contrast, surface modification only presents bioactive agents on a scaffold surface; therefore, it can overcome the above limitations. In fact, this strategy has become increasingly attractive to prepare functional scaffolds. [77]

Functionalizing the scaffold with carboxylic acid groups has shown promise by making the surface more hydrophilic. Fibroblasts seeded on carboxylic acid modified PGA, PLGA, and PLLA scaffolds were spread over a larger area and had higher adhesion and proliferation rates compared to unmodified scaffolds. Incorporation of

hydroxyapatite (HA) into scaffolds has been shown to significantly increase osteoblast adhesion and proliferation compared to pure PLLA scaffolds. [77]

A more reliable method to functionalize scaffolds is to use bioactive molecules derived from natural ECM proteins. For instance, ***gelatin***, a denatured form of collagen, was used to modify the surfaces of 3D PLLA scaffolds[86, 87]. The presence of gelatin greatly increased the adherence, proliferation, and spreading of MC3T3-E1 cells and more collagen fibers and other cell secretions were deposited on the surface-modified scaffolds than on the control scaffolds. More specific than gelatin, ***peptide fragments*** have been used to tailor cell adhesion and growth. The RGD peptide is ubiquitous in the ECM and promotes cell adhesion by acting as a binding site for integrins. PCL films modified with RGD served to promote the attachment and spreading of mesenchymal stem cells (MSCs). RGD may increase focal adhesion kinase (FAK) phosphorylation for integrin-based signal transduction, which could play a role in cell proliferation and viability. [77]

In addition to adhesion and proliferation, functionalized scaffolds can be used to direct cell differentiation. The incorporation of HA on gelatin scaffolds was used to study the differentiation of MC3T3-E1 preosteoblasts into osteoblasts. Cells were seeded on gelatin scaffolds with and without HA for 4 weeks and two osteogenic markers [bone sialoprotein and osteocalcin] were examined. Results showed that levels of BSP and OCN were five and two times higher, respectively, in the gelatin-HA scaffolds compared to the gelatin scaffolds. The use of HA thus not only enhances the mechanical strength of the scaffold, but it also plays a role in cell differentiation and tissue formation. [77]

The most widely used method to induce cell differentiation is the ***delivery of growth factors*** from scaffolds. A variety of methods have been developed to incorporate growth factors into scaffolds. For example, recombinant human bone morphogenic protein 7 (rhBMP-7) was encapsulated in PLGA microspheres using a double emulsion technique, and the microspheres were incorporated onto the surface of a nano-fibrous PLLA scaffold. The biomimetic PLLA scaffolds incorporated with rhBMP-7 microspheres were found to significantly enhance bone formation. After 6 weeks of subcutaneous implantation in Sprague-Dawley rats, the scaffolds with rhBMP-7 microspheres showed significantly more bone formation than scaffolds with rhBMP-7 simply adsorbed on the surface. This study illustrates the important role that growth factors can play in a tissue engineering strategy. [77]

While the most common method is to use growth factors to induce differentiation and tissue neogenesis, small molecules are also capable of guiding cell fate through cell/matrix interactions. Recent work has shown that the fate of human MSCs could be changed when they were seeded on ***hydrogels with various functional groups***. Carboxylic acid groups, mimicking cartilage glycosaminoglycans, increased the expression of aggrecan, an indicator of chondrogenic differentiation. Phosphate groups, important for mineralized tissue formation, increased expression levels of CBFA1, a marker for osteogenic differentiation. Finally, *t*-butyl groups, mimicking lipid filled adipocytes, increased expression of peroxisome proliferating antigen receptor gamma (PPARG), a measure of adipogenic differentiation. The ability of small molecules to induce differentiation shows potential as an easier, cheaper, and safer way to guide the fate of stem cells, yet more work needs to be done to validate their efficacy when compared to the use of growth factors. [77]

4- Pulp Therapy Related Materials

a- Pulpotomy Dressing Agent

Pulpotomy is a vital pulp therapy indicated for deciduous teeth with exposed pulp and reversible pulpitis. ***MTA*** is believed to preserve pulp vitality by disinfecting, sealing and inducing the formation of a calcific barrier over the radicular pulp tissue due to its high pH. This is in contrast with the superficial fixation (*i.e.* in the histological sense) of healthy radicular tissue with ***formocresol*** in conventional pulpotomy. Clinical studies over 24–42 months have indicated a high success rate for pulpotomy using MTA (67–98.5%), comparable with formocresol (77–83%) and ferric sulfate (73%), but not with ***calcium hydroxide*** (46%). The apparent contradiction here may be due to the relatively rapid dissolution of the latter while the high pH over, and thus cytological activity of, MTA is maintained.

The incidence of ***post-operative internal root resorption*** was lowest for MTA. In contrast to MTA, and in addition to concerns arising from the toxicity and genotoxicity of formocresol, both formocresol and ferric sulfate were found to irritate and cause comparatively substantial inflammatory responses of the pulp in animal studies. Although MTA can induce initial inflammation of rat dental pulp cells *via* its effect on the nuclear factor-kappa B signaling system, a subsequent anti-inflammatory effect due to down-regulation of the expression of certain inflammatory mediators is also observed.

b- Pulp-capping agent

Combined histological and immune-histochemical analyses in human and animal studies have demonstrated reparative dentin formation by odontoblast-like cells. These have originated from the differentiation of progenitors which proliferated and pooled at the site of the capping agent. These materials appear to work to preserve exposed pulp vitality in permanent teeth by promoting the formation of dentin bridges. ***MTA*** induced reparative dentinogenesis was found to be more consistent and prominent compared with direct pulp-capping with ***$Ca(OH)_2$***. [77]

MTA can provoke the formation of reparative dentin by odontoblast-like cells originating from the differentiation of progenitors which proliferated and pooled at the site of MTA capping. "Ion dissolution" (Al, Ca, K, Na) from MTA has been said to 'solubilize' the extracellular matrix components of dentin, including non-collagenous protein, glycosaminoglycans, transforming growth factor (TGF-β1) and adrenomedullin, that may mediate cellular activity in dentinogenesis. However, none of these components, especially not Al, could have that property, which is more likely due to hydrolysis arising from the high surface pH produced by the excess $Ca(OH)_2$, that is, the process is one of base-catalysed hydrolysis. Even so, enzyme-linked immunosorbent assay (ELISA) has evidently demonstrated the stimulatory effect of MTA on the production of bone morphogenetic protein (BMP-2) and TGF- β1 by fibroblasts of human periodontium. Similarly, MTA provoked mineralization of rat dental pulp cells, accompanied by a remarkable increase in the production of BMP-2. However, beyond the observations themselves, no mechanism for these effects was identified, and especially it is not clear whether these are direct effects of the MTA or indirect *via* hydrolysis products. [77]

c- Open-Apex Sealing Materials

Sealing of necrotic immature permanent teeth with open apices using ***MTA*** is considered to be a viable treatment alternative to the conventional use of both ***$Ca(OH)_2$***-assisted apexification and resin-, zinc oxide-, glass ionomer- or amalgam-based root-end endodontic surgical retrograde filling of open apical foramina, accompanied by canal obturation with gutta percha. This is the case whether the MTA is used in orthograde filling over sterile radicular blood clot (revascularization) or residual vital apical radicular tissue (apexogenesis); in the direct

formation of a plug as an artificial apical barrier (apexification) or complete orthograde obturation; or even in simple retrograde root-end filling. (77)

d- Endodontic sealers

The sealers are responsible for the principal functions of the final root filling: sealing off of the root canal system, entombment of remaining bacteria and the filling of irregularities in the prepared canal. A variety of sealing materials with different specifications is currently available, such as, calcium hydoroxide-, zinx-oxide-eugenole-, glass ionomer-, and resin-based. (78)

The extrusion of sealing agents over the apical constriction is, however, a phenomenon, frequently observed in clinical routine. Although the area of contact is small, there is always concern about untoward reactions by the tissue to the filling material. Biologically unfavorable materials, while not necessarily causing overt clinical symptoms, may affect the healing processes in the periapical tissues and delay or prevent resolution of lesions. Materials used for root canal Sealing materials should not exert an irritating effect on the peri-radicular tissue and complications relating to persistence of sealing agents in the peri-apical tissue could result in endodontic failure. The knowledge of the inflammatory response pattern to the employed material is crucial in order to assess the clinical consequence of a potential material over extrusion. (78)

5- Desensitization Agents

Dentin hypersensitivity (DH) is one of the most commonly occurring clinical dental conditions, and up to 69% of the UK population has reported experiencing some form of tooth sensitivity. Although the ***etiology*** of DH is multi-factorial and not yet fully understood, it is attributed to the general increase in exposed root surfaces of the teeth from periodontal disease, toothbrush abrasion or cyclic loading fatigue of the thin enamel near the cemento-enamel junction. The currently accepted ***theory*** for a DH mechanism is the hydrodynamic theory , which proposes that external stimuli such as cold, hot, tactile or osmotic pressure, when applied to exposed dentin, cause fluid movement within the dentinal tubules. This fluid movement stimulates mechanoreceptors near the base of the tubule trigger a pain response. (79)

Open tubules allow fluid flow through the tubules, which results in pressure changes that excite the nerve endings in the dental pulp. This is consistent with the observation that when DH is treated with a ***tubule-occluding agent,*** this will result in a reduction in DH. Occlusion of exposed dentinal tubules is therefore a common approach for treating DH. (79)

Existing resin-composite restorative materials and adhesives are essentially inert space fillings for lost tooth structure. Currently available dental materials can be used to repair or replace lost or diseased tissue but they do not regenerate it. Furthermore, resin-composite materials and their associated dentin bonding agents are formulated with reactive chemical species. If the materials are optimally polymerized on placement then they are widely considered to be sufficiently safe, in accordance with the European Medical Device Directive and ISO Standards. However, recent research has drawn attention to the potential adverse consequences of inadequate cure of such materials. Therefore, if such potential hazards could be avoided in future formulations, that would be beneficial. (79)

Strontium chloride is the active ingredient in the original Sensodyne® dentifrice (GlaxoSmithKline, London, UK) and was the first tubule occluding agent incorporated into a dentifrice; later products also contained strontium acetate. ***Fluoride*** was first proposed as a desensitizing agent in 1941 and has subsequently been used in dentifrices, gels, mouth rinses and varnishes. Recently, a ***bioactive glass*** (NovaMin®, developed by NovaMin Technology Inc., Alachua, FL, USA) based on the original 45S5 Bioglass® (US Biomaterials Corp., Jacksonville, FL, USA) composition has been incorporated as a remineralising ingredient in dentifrice formulations for treating DH by precipitating ***hydroxycarbonate apatite*** *(HCA) onto the tooth surface and subsequentl*y occluding the dentinal tubules. However, concerns have been expressed over the long-term durability of HCA in the mouth, and formation of fluorapatite (FAp) rather than HCA is preferable, as it is more resistant to acid attack and would therefore dissolve less readily when teeth are exposed to acidic conditions. [79]

It was recently shown that ***fluoride-containing bioactive glasses*** form FAp rather than HCA in physiological solutions. Here a series of bioactive glasses (SiO_2–P_2O_5–CaO–CaF_2–SrO–SrF_2–ZnO–Na_2O–K_2O) were produced, which form FAp in physiological solutions, release strontium and fluoride for caries prevention, zinc for bactericidal properties and potassium, which is currently used as a desensitizing agent in dentifrices. [79]

Tooth surface loss may be due to ***erosion*** and a frequent reason for DS. The deposition of enamel-like materials that substitute for lost tooth structure is therefore an important research area. Restorative materials that exhibit even greater biomimetic design features could play a valuable role in this regard. A recently introduced technique of guided formation of an enamel-like fluorapatite layer on a mineral substrate has the potential to enable remineralization of superficial enamel defects and/or exposed dentin. The technique, biomimetic mineralization system utilizes the diffusion of calcium ions from solution into a glycerine enriched gelatine gel that contains phosphate and fluoride ions. When the conditioned gel is in direct contact with the exposed tooth surface, within 8 h, a firmly adhering mineral layer is formed on the tooth surface. [80]

6- Drug Delivery Systems

A wide range of drug delivery systems has been applied to accommodate the needs of regenerating oral tissues. Cells that are responsible for tissue regeneration may be either delivered via biomaterial carriers or recruited in vivo by signaling molecules. [81]

Drug delivery by controlled release provides several critical advantages because bioactive factors are transported to the desirable milieu in biocompatible carriers, released in a controlled manner and may locally regulate multiple processes of cell chemotaxis, attachment, proliferation, differentiation, and morphogenesis. In the absence of drug delivery and controlled release, bioactive factors may undergo rapid diffusion and denature shortly after in vivo delivery, and often fail to induce the intended effects on target cells and tissues. Although control released drugs or bioactive factors may also diffuse and denature, the continuous dosing provides sustained effects where subsequent doses act on cells that have already been sensitized by previous growth factor exposure. The bio-resorbable drug delivery systems should degrade into products that can be eliminated from the body through natural pathways or, even better, which are involved normally in metabolic pathways. [82]

Example: For treatment of ***periodontal disease***, there is a need for an optimal local drug delivery system since the widespread systemic administration of antibiotics might cause undesired side effects or favor the development of resistances. The use of antibacterial biomaterials becomes increasingly important in medical and dental science. Especially in the field of conservative dentistry, the elimination of bacteria and plaque is foundational for effective treatment. [83]

For instance, the conventional treatment of ***periodontitis*** by scaling and root planning is advantageously accompanied by the adjuvant administration of antibiotics. Antibacterial drug compounds can be applied by systemic or local administration. Compared to systemic drug delivery the local administration of drugs in periodontology is considered to be more effective, since the pathogen-specific drug can be placed directly in the periodontal pocket achieving effective concentrations. In addition the risk of undesired side effects caused by high systemic doses or resistance development can be reduced. (83)

For effective elimination of pathogenic bacteria, the antibiotic agent has to be available in the periodontal pocket in adequate concentrations for a sufficiently long period of time. It is therefore necessary to use local delivery systems that control the release of their agents and guarantee lasting drug concentrations in the pocket in spite of high sulcular fluid rates. (83)

Non-resorbable drug carrier systems is time consuming and their removal is required this incurs the risk of tissue damage. Thus, many resorbable drug delivery systems were developed during recent decades, such as drug loaded hydroxypropylcellulose films, which were first described by Noguchi et al. in 1984, or drug carrying gels such as Elyzol® (Dumex GmbH, Bad Vilbel, Germany) dental gel, based on melted glycerol mono-oleate. However, also for these systems, the periodontal milieu often poses the major problem that the required period of drug exposure (7–10 days) cannot be achieved. Also in the field of periodontal surgery – as in the transplantation of a mucous membrane– resorbability of the scaffold material is important to avoid inflammatory effects and surgical removal. Polylactide fibers containing the antibiotic metronidazole were also generated. (83)

7- Denture-Related Mucosa

Adherent and healthy mucosa tissues covering the residual ridge and palate are very important criteria for the clinical success of wearing full dentures. Wearing full dentures applies mechanical stress to the epithelium and connective tissue. These forces may affect the integrity of these tissues and the organization of extracellular matrix components. Full dentures may also create a favorable environment for yeast development like *Candida* on the oral mucosa. (84)

Denture-related stomatitis (DRS) is an inflammatory process affecting the oral mucosa of denture-bearing tissues. The prevalence of denture stomatitis is around 30% in patients with complete prostheses. The pathogenesis of denture stomatitis is still unclear, but a combination of trauma/stress, *Candida* infection, poor denture hygiene and wearing dentures 24 h a day have all been suggested as etiologic factors. (84)

Histological section through ***healthy mucosa*** of hard palate never covered by full denture shows the presence of keratin and classical srata in the epithelium and keratinocytes near the basement membrane. The interface between the basement membrane and the underlying connective tissue exhibited a regular limit. On the other hand, histological section of palatal mucosa showing ***denture stomatitis*** indicated a total absence of keratin, no clear division of the stata, the junction between the epithelium and the underlying connective tissue was not clearly visible. Scattered inflammatory cells were seen in the connective tissue. (84)

A good anatomical fit for the full denture and control of yeast are currently the most relevant strategies to prevent the occurrence of denture related stomatitis. (84)

8- Bone Cements

Cements based on calcium phosphates, calcium carbonates or calcium sulphates, attracted much attention as biomaterials due to their excellent biocompatibility and bone repair properties. These cements do not have to be delivered in a prefabricated form, and this is a remarkable advantage of this type of material over conventional bioceramics. Most of the injectable calcium phosphates used evolve to an apatitic calcium phosphate during the setting reaction. Physicochemical properties of these materials, such as setting time, porosity and mechanical behaviour, depend on the cement formulation and the presence of additives. These cements are able to harden *in situ*, are biocompatible and may be slowly resorbed. During this gradual process, the newly formed bone grows and replaces the cement. Some aspects that must be still improved are related to their mechanical toughness, setting time, application techniques on the osseous defect and the final biological properties. Research is under way to get shorter setting times, even in contact with blood, and to improve mechanical toughness. [85]

References

1. Kasemo B, Lausmaa J. Material-tissue Interfaces: The Role of Surface Properties and Processes. Environ Health Perspect 1994; 10:41-45.
2. Teoh SH. Engineering Materials for Biomedical Applications. World Scientific Publishing Co. 2004: 2.9-2.11.
3. Kasemo B, Lausmaa J. The biomaterial-tissue interface and its analogues in surface science and technology. In: The Bone- Biomaterials Interface. Davies JE ed, University of Toronto Press, 1991; 19-32.
4. Lavenus S, Louarn G, Layrolle P. Nanotechnology and Dental Implants. International Journal of Biomaterials. 2010, ID 915327; 1-9. doi:10.1155/2010/915327
5. Rozé J, Babu S, Saffarzadeh A, Gayet-Delacroix M, Hoornaert A, Layrolle P. Correlating implant stability to bone structure. Clinical Oral Implants Research. 2009; 20:1140–1145.
6. Le Guéhennec L, Soueidan A, Layrolle P, Amouriq Y. Surface treatments of titanium dental implants for rapid osseointegration. Dental Materials. 2007; 23:844–854.
7. Lavenus S, Ricquier J-C, Louarn G, Layrolle P. Cell interaction with nanopatterned surface of implants. Nanomedicine. 2010; 5:937–947.
8. Miller R, Guo Z, Vogler EA, Siedlecki CA. Plasma coagulation response to surfaces with nanoscale chemical heterogeneity. Biomaterials. 2006; 27:208–215.
9. Sawase T, Jimbo R, Baba K, Shibata Y, Ikeda T, Atsuta M. Photo-induced hydrophilicity enhances initial cell behavior and early bone apposition. Clinical Oral Implants Research. 2008; 19:491–496.
10. Balasundaram G, Sato M, Webster TJ. Using hydroxyapatite nanoparticles and decreased crystallinity to promote osteoblast adhesion similar to functionalizing with RGD. Biomaterials. 2006; 27:2798–2805.
11. Weibrich G, Hansen T, Kleis W, Buch R, Hitzler WE. Effect of platelet concentration in platelet-rich plasma on peri-implant bone regeneration. Bone. 2004; 34:665–671.
12. Le Guéhennec L, Soueidan A, Layrolle P, Amouriq Y. Surface treatments of titanium dental implants for rapid osseointegration. Dental Materials. 2007; 23:844–854.
13. Agis H, Kandler B, Fischer MB, Watzek G, Gruber R. Activated platelets increase fibrinolysis of mesenchymal progenitor cells. Journal of Orthopaedic Research. 2009; 27:972–980.
14. Vogel JP, Szalay K, Geiger F, Kramer M, Richter W, Kasten P. Platelet-rich plasma improves expansion of human mesenchymal stem cells and retains differentiation capacity and in vivo bone formation in calcium phosphate ceramics. Platelets. 2006; 17:462–469.

15. Mishima Y, Lotz M. Chemotaxis of human articular chondrocytes and mesenchymal stem cells. Journal of Orthopaedic Research. 2008; 26:1407–1412.
16. Ozaki Y, Nishimura M, Sekiya K. Comprehensive analysis of chemotactic factors for bone marrow mesenchymal stem cells. Stem Cells and Development. 2007; 16:119–129.
17. Kuznetsov SA, Friedenstein AJ, Robey PG. Factors required for bone marrow stromal fibroblast colony formation in vitro. British Journal of Haematology. 1997; 97:561–570.
18. Fiedler J, Leucht F, Waltenberger J, Dehio C, Brenner RE. VEGF-A and PlGF-1 stimulate chemotactic migration of human mesenchymal progenitor cells. Biochemical and Biophysical Research Communications. 2005;334(2):561–568.
19. Jian H, Shen X, Liu I, Semenov M, He XI, Wang XF. Smad3-dependent nuclear translocation of β-catenin is required for TGF-β1-induced proliferation of bone marrow-derived adult human mesenchymal stem cells. Genes and Development. 2006;20:666–674.
20. Catelas I, Dwyer JF, Helgerson S. Controlled release of bioactive transforming growth factor beta-1 from fibrin gels in vitro. Tissue Engineering C. 2008; 14:119–128.
21. Wong C, Inman E, Spaethe R, Helgerson S. Fibrin-based biomaterials to deliver human growth factors. Thrombosis and Haemostasis. 2003; 89:573–582.
22. Mosesson MW. Fibrinogen and fibrin structure and functions. Journal of Thrombosis and Haemostasis. 2005; 3:1894–1904.
23. Hobkirk JA. Progress in implant research. International Dental Journal. 1983; 33:341–349.
24. Eisenbarth E, Meyle J, Nachtigall W, Breme J. Influence of the surface structure of titanium materials on the adhesion of fibroblasts. Biomaterials. 1996; 17:1399–1403.
25. Cohen A, Liu-Synder P, Storey D, Webster TJ. Decreased fibroblast and increased osteoblast functions on ionic plasma deposited nanostructured Ti coatings. Nanoscale Research Letters. 2007; 2:385–390.
26. Miller D, Vance R, Thapa A, Webster T, Haberstroch K. Comparaison of fibroblast and vascular cell adhesion to nano structured poly(lactic co glycolic acid) films. Applied Bionics and Biochemics. 2005; 2:1–7.
27. Powers JM and Sakaguchi RL. Craig's Restorative Dental Material, Twelfth Edition. Mosby, 2006; 556-565.
28. Anusavice KJ. Phillips' Science of Dental Materials, Eleventh Edition, Saunders, 2003; 760-780.
29. Sennerby L, Dasmah A, Larsson B, Iverhed M. Bone tissue responses to surface-modified zirconia implants: A histomorphometric and removal torque study in the rabbit. Clinical Implant Dentistry and Related Research, 2005; S13-S20.
30. Gahlert M, Gudehus T, Eich¬horn S, Steinhauser E, Kniha H, Erhardt W. Biomechanical and histomorphometric com¬parison between zirconia implants with varying surface textures and a titanium implant in the maxilla of miniature pigs. Clin Oral Implants Res 2007; 662- 668.
31. Langhoff JD, Voelter K, Scharnweber D, Schnabelrauch M, Schlottig F, Hefti T, Kalchofner K, Nuss K, Von-Rechenberg B. Comparison of chemically and pharmaceutically modified titanium and zirconia implant surfaces in dentistry: a study in sheep. Int. J. Oral Maxillofac. Surg. 2008; 1125–1132.
32. Oliva J. One-year follow-up of first consecutive 100 zirconia dental implants in humans: A comparison of 2 different rough surfaces. International Journal of Oral & Maxillofacial Implants 2007; 430-435.
33. Pirker W, Kocher A. Immedi¬ate, non-submerged, root-analogue zirconia implant in single tooth replacement. Int J Oral Maxillofac Surg 2008; 293-295.

34. Kohal, RJ, Klaus GA. Zirconia Implant-Crown System. Int J Periodontics Restorative Dent 2004; 47–153.
35. Manhart J, Chen H, Hamm G, Hickel R. Buonocore memorial lecture. Review of the clinical survival of direct and indirect restorations in posterior teeth of the permanent dentition. Oper Dent 2004; 29:481–508.
36. Peumans M, Kanumilli P, De Munck J, Van Landuyt K, Lambrechts P, Van Meerbeek B. Clinical effectiveness of contemporary adhesives: a systematic review of current clinical trials. Dent Mater 2005; 21:864–81.
37. De Munck J, Van Landuyt K, Peumans M, Poitevin A, Lambrechts P, Braem M. A critical review of the durability of adhesion to tooth tissue: methods and results. J Dent Res 2005; 84:118–32.
38. Breschi L, Mazzoni A, Ruggeri A, Cadenaro M, Di Lenarda R, Dorigo ES. Dental adhesion review: aging and stability of the bonded interface. Dent Mater 2008; 24:90–101.
39. Van Meerbeek B, De Munck J, Yoshida Y, Inoue S, Vargas M, Vijay P. Buonocore memorial lecture: adhesion to enamel and dentin: current status and future challenges. Oper Dent 2003; 28:215–35.
40. De Munck J, Van Meerbeek B, Yoshida Y, Inoue S, Vargas M, Suzuki K. Four-year water degradation of total-etch adhesives bonded to dentin. J Dent Res 2003; 82:136–40.
41. Pashley DH, Tay FR, Yiu C, Hashimoto M, Breschi L, Carvalho RM. Collagen degradation by host-derived enzymes during aging. J Dent Res 2004; 83:216–21.
42. Hebling J, Pashley DH, Toderhane L, Tay FR. Chlorhexidine arrests subclinical degradation of dentin hybrid layers in vivo. J Dent Res 2005; 84:741–6.
43. De Munck J, Van den Steen PE, Mine A, Van Landuyt KL, Poitevin A, Opdenakker G. Inhibition of enzymatic degradation of adhesive–dentin interfaces. J Dent Res 2009; 88:1101–6.
44. Xu J, Stangel I, Butler IS, Gilson DF. An FT-Raman spectroscopic investigation of dentin and collagen surfaces modified by 2-hydroxyethylmethacrylate. J Dent Res 1997; 76:596–601.
45. Nishiyama N, Suzuki K, Komatsu K, Yasuda S, Nemoto K. A study on the adsorption characteristics of HEMA to dentinal collagen. J Dent Res 2002; 81:469–71.
46. Van Meerbeek B, Peumans M, Poitevin A, Mine A, Van Ende A, Neves A, De Munck J. Relationship between bond-strength tests and clinical outcomesdental materials 2010;26: e100–e121.
47. De Munck J. An in vitro and in vivo study on the durability of biomaterial–tooth bonds. PhD dissertation, KULeuven; 2004.
48. Inoue S, Van Meerbeek B, Vargas M, Yoshida Y, Lambrechts P, Vanherle G. Adhesion mechanism of self-etch adhesives. In: Tagami J, Toledano M, Prati C, editors. Advanced adhesive dentistry. Granada international symposium 1999. Cirimido, Grafiche Erredue; 2000. p. 131–48.
49. Brackett WW, Covey DA, St Germain Jr HA. One-year clinical performance of a self-etching adhesive in class V resin composites cured by two methods. Oper Dent 2002; 27:218–22.
50. Perdigo J, Lopes MM, Gomes G. In vitro bonding performance of self-etch adhesives. II. Ultramorphological evaluation. Oper Dent 2008; 33:534–49.
51. Ermis RB, De Munck J, Cardoso MV, Coutinho E, Van Landuyt KL, Poitevin A. Bond strength of self-etch adhesives to dentin prepared with three different diamond burs. Dent Mater 2008; 24:978–85.
52. Cardoso MV, Coutinho E, Ermis RB, Poitevin A, Van Landuyt K, De Munck J. Influence of dentin cavity surface finishing on micro-tensile bond strength of adhesives. Dent Mater 2008; 24:492–501.

53. Van Meerbeek B, Yoshida Y, Van Landuyt K, Perdigão J, De Munck J, Lambrechts P. In: Summitt JB, Robbins JW, Hilton TJ, Schwartz RS, editors. Fundamentals of operative dentistry. A contemporary approach. 3rd ed. Chicago: Quintessence Publishing; 2006. p. 183–260.
54. Yoshida Y, Nagakane K, Fukuda R, Nakayama Y, Okazaki M,Shintani H. Comparative study on adhesive performance of functional monomers. J Dent Res 2004; 83:454–8.
55. Yoshida Y, Van Meerbeek B, Nakayama Y, Snauwaert J, Hellemans L, Lambrechts P. Evidence of chemical bonding at biomaterial–hard tissue interfaces. J Dent Res 2000;79:709–14.
56. Fukuda R, Yoshida Y, Nakayama Y, Okazaki M, Inoue S, Sano H. Bonding efficacy of polyalkenoic acids to hydroxyapatite, enamel and dentin. Biomaterials 2003; 24:1861–7.
57. Yiu CK, Tay FR, King NM, Pashley DH, Sidhu SK, Neo JC. Interaction of glass-ionomer cements with moist dentin. J Dent Res 2004; 83:283–9.
58. Tay FR, Sidhu SK, Watson TF, Pashley DH. Water-dependent interfacial transition zone in resin-modified glass-ionomer cement/dentin interfaces. J Dent Res 2004; 83:644–9.
59. Coutinho E, Van Landuyt K, De Munck J, Poitevin A, Yoshida Y, Inoue S. Development of a self-etch adhesive for resin-modified glass ionomers. J Dent Res 2006; 85:349–53.
60. Yoshida Y, Van Meerbeek B, Nakayama Y, Yoshioka M, Snauwaert J, Abe Y. Adhesion to and decalcification of hydroxyapatite by carboxylic acids. J Dent Res 2001; 80:1565–9.
61. Yoshioka M, Yoshida Y, Inoue S, Lambrechts P, Vanherle G, Nomura Y. Adhesion/decalcification mechanisms of acid interactions with human hard tissues. J Biomed Mater Res 2002; 59:56–62.
62. Tay FR, Pashley DH. Have dentin adhesives become too hydrophilic? J Can Dent Assoc 2003; 69:726–31.
63. Tay FR, Frankenberger R, Krejci I, Bouillaguet S, Pashley DH, Carvalho RM. Single-bottle adhesives behave as permeable membranes after polymerization. I. In vivo evidence. J Dent 2004;32:611–21.
64. Yiu CK, Hiraishi N, Chersoni S, Breschi L, Ferrari M, Prati C. Single-bottle adhesives behave as permeable membranes after polymerisation. II. Differential permeability reduction with an oxalate desensitiser. J Dent 2006; 34:106–16.
65. Van Landuyt KL. Optimization of the chemical composition of dental adhesives. Towards a simplified and durable, universal enamel/dentin adhesive. PhD dissertation, KULeuven; 2008.
66. Van Landuyt K, Mine A, De Munck J, Jaecques S, Peumans M, Lambrechts P. Are one-step adhesives easier to use and better performing? Multi-factorial assessment of contemporary one-step self-etch adhesives. J Adhes Dent 2008; 11:175–90.
67. Van Landuyt KL, De Munck J, Mine A, Peumans M, Lambrechts P, Van Meerbeek B. Predominant failure underneath hybrid-layer with mild self-etch adhesives after aging. In: CED-IADR. 2009 [Abstract #31].
68. Hikita K, Van Meerbeek B, De Munck J, Ikeda T, Van Landuyt K, Maida T, et al. Bonding effectiveness of adhesive luting agents to enamel and dentin. Dent Mater 2007; 23:71–80.
69. Radovic I, Monticelli F, Goracci C, Vulicevic ZR, Ferrari M. Self-adhesive resin cements: a literature review. J Adhes Dent 2008;10:251–8.
70. Monticelli F, Osorio R, Mazzitelli C, Ferrari M, Toledano M. Limited decalcification/diffusion of self-adhesive cements into dentin. J Dent Res 2008; 87:974–9.
71. Raskin A, D'Hoore W, Gonthier S, Degrange M, Déjou J. Reliability of in vitro microleakage tests: a literature review. J Adhes Dent 2001; 3:295–308.

72. Almeida JB, Platt JA, Oshida Y, Moore BK, Cochran MA, Eckert GJ. Three different methods to evaluate microleakage of packable composites in Class II restorations. Oper Dent 2003; 28:453–60.
73. Li H, Li J, Yun X, Liu X, Fok AS-L. Non-destructive examination of interfacial debonding using acoustic emission. Dental Materials 2011; 27: 964–971.
74. Van Meerbeek B, Peumans M, Verschueren M, Gladys S,Braem M, Lambrechts P. Clinical status of ten dentin adhesive systems. J Dent Res 1994; 73:1690–702.
75. Van Meerbeek B, Perdigo J, Lambrechts P, Vanherle G. The clinical performance of adhesives. J Dent 1998; 26:1–20.
76. Liu X, Holzwarth JM, Ma PX. Functionalized Synthetic Biodegradable Polymer Scaffolds for Tissue Engineering Macromol. Biosci. 2012, DOI: 10.1002/mabi.201100466
77. Darvell BW, Wu RCT. "MTA"—An Hydraulic Silicate Cement: Review update and setting reaction. Dental Materials 2011;127; 407–422.
78. Ghanaati S, Willershausen I, Barbeck M, Unger RE, Joergens M, Sader RA, Kirkpatrick CJ, Willershausen B. Tissue reaction to sealing materials: different view at biocompatibility European Journal of Medical Research 2010, 15:483 doi:10.1186/2047-783X-15-11-483
79. Lyncha E, Brauerb DS, Karpukhinab N, Gillama DG, Hill RG. Multi-component bioactive glasses of varying fluoride content for treating dentin hypersensitivity. Dental Materials 2012;28:168–178.
80. Guentscha A, Seidler K, Nietzscheb S, Heftic AF, Preshawd PM, Wattse DC,f, Jandtf KD, Siguscha BW. Biomimetic mineralization: Long-term observations in patients with dentin sensitivity. Dental Materials 2012; 28:457–464.
81. Edlund U, Albertsson AC. Degradable Polymer Microspheres for Controlled Drug Delivery Advances in Polymer Science, Springer-Verlag Berlin Heidelberg 2002;157: 68-91.
82. Moioli EK, Clark PA, Xin X, Lal S, Mao JJ. Matrices and scaffolds for drug delivery in dental, oral and craniofacial tissue engineering. Advanced Drug Delivery Reviews 2007;59:308–324
83. Reise M, Wyrwab R, Müllerb U, Zylinskia M,NVolpela A, Schnabelrauchb M, Bergb A, Jandtc KD, Watts DC, Siguscha BW. Release of metronidazole from electrospun poly(l-lactide-co-d/l-lactide) fibers for local periodontitis treatment. Dental Materials 2012; 28: 179–188.
84. Le Bars P, Soueidan A. Distribution Patterns of E-Cadherin, Type VII Collagen and Fibronectin in Denture-Related Stomatitis: A Preliminary Stud. The Open Dentistry Journal, 2012; 6: 14-22
85. Vallet-Regí M, Ruiz-Hernández E. Bioceramics: From Bone Regeneration to Cancer Nanomedicine. Adv. Mater. 2011, 23, 5177–5218.