BIOCOMPATABILITY BLUES IN RESTORATIVE DENTISTRY

Abstract

In the process of manufacturing of any biomaterial, biocompatibility consideration is equally important to strength, aesthetics, and functional attributes of the material. Biocompatibility is an interdisciplinary field that incorporates information from a variety of disciplines, including material science, biochemistry, bioengineering, molecular biology, tissue engineering, and others. By definition, "Biocompatibility is the ability of a material to elicit an appropriate biological response in a given application in the body". When a substance is implanted in the body, an interface is formed that must be able to retain both biological and structural stability for the course of the implanted device's existence in the body. This stability is a high requirement because the interface is dynamic with constant interactions which may cause the body to alter the material or the material to cause changes in the body. Discussing about the interactions caused by the interface, in oral cavity four different types of interactions are possible, namely, between the material and oral cavity, with the dental pulp through the dentinal tubules, with the periodontium and between the material and the periapical bone. Concerns about biocompatibility of materials are shared by other medical specialties including dentistry. This chapter briefs about the basic concepts of biocompatibility and it's relevance to dentistry along with the tests used for evaluating biocompatibility of the materials, comparison among them with their advantages and disadvantages.

Keywords: biomaterial, biocompatibility, ANSI/ADA Specification, Liners.

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I. INTRODUCTION

In the process of manufacturing of any biomaterial, biocompatibility consideration is equally important to strength, aesthetics, and functional attributes of the material. Biocompatibility is an interdisciplinary field that incorporates information from a variety of disciplines, including material science, biochemistry, bioengineering, molecular biology, tissue engineering, and others. By definition, “Biocompatibility is the ability of a material to elicit an appropriate biological response in a given application in the body”. When a substance is implanted in the body, an interface is formed that must be able to retain both biological and structural stability for the course of the implanted device's existence in the body. This stability is a high requirement because the interface is dynamic with constant interactions which may cause the body to alter the material or the material to cause changes in the body. Discussing about the interactions caused by the interface, in oral cavity four different types of interactions are possible, namely, between the material and oral cavity, with the dental pulp through the dentinal tubules, with the periodontium and between the material and the periapical bone. Concerns about biocompatibility of materials are shared by other medical specialties including dentistry. This chapter briefs about the basic concepts of biocompatibility and it’s relevance to dentistry along with the tests used for evaluating biocompatibility of the materials, comparison among them with their advantages and disadvantages. The last part of the chapter is dedicated to discussing the biocompatibility of the various materials used in dentistry.

Factors affecting biocompatibility of a material are mentioned as follows:

- The chemical nature of its components
- The physical nature of the components
- The types and locations of patient tissues that will be exposed to the device
- The duration of the exposure
- The surface characteristics of the material
- The amount and nature of substances released from the material

II. EFFECTS IN THE BODY

1. **Side Effects** adverse effects of a biomaterial are described as those additional effects that, apart from the intended primary function, are also inherent to this biomaterial but are undesired. The term "adverse effect" is used interchangeably.

2. **Toxicity** Toxicity of a substance refers to its capacity to harm a biological system through chemical mechanisms. In more complex organisms such as animals and humans, local toxicity, which refers to adverse reactions occurring at the site of application, is distinguished from systemic toxicity, where adverse reactions manifest in a region distant from the application site. In the field of dentistry, local reactions mainly occur in the pulp, periapical periodontium, and the gingiva/oral mucosa.

3. **Immunotoxicity** Immunotoxicity of a substance pertains to detrimental impacts on the structure and operation of the immune system, affecting important cells like monocytes. These effects can hinder the host's defense mechanisms, such as protection against infections, or lead to tissue damage, often through chronic inflammation.
   Health effects can be subdivided into the following:

- **Systemic Toxicity:** Any biomaterial can have biological impacts if it is positioned next to a naturally occurring tissue in the body. The compounds that are released from the material and the body's reactions to those substances regulate these effects. The application site and the effect may be in various places in the event of systemic toxicity. Some of the sources by which they enter the body are as follows: (1) consumption and absorption; (2) vapor inhalation (3) leakage from the apex of the tooth, and (4) absorption via the mucosa of the mouth. Four key aspects affect the ultimate systemic reaction: (1) the substance's concentration; (2) the duration of exposure; (3) the substance's rate of excretion; and (4) the organ of relevance or the site of exposure. Reviewing the scientific literature, however, clearly shows that there is rarely evidence linking dental material exposure to long-term systemic health problems.

- **Local Reactions:** Local responses are a regular occurrence in dentistry, and determining the cause of these reactions is crucial to developing effective treatment plans. The pulp tissue, the periodontium, the root apex, or adjacent oral tissues like the tongue or buccal mucosa may all experience local impacts. Furthermore, because the periodontal ligament is next to the pocket or attachment area—which is often a spot where biofilms and ions, atoms, or molecules of chemicals discharged from the cervical region of dental restorations that might extend into this area accumulate—it is an important tissue. Necrosis or inflammation could be the reaction. Furthermore, if there is a disruption in cell metabolism, pro-inflammatory mediators may be released. The ability of drugs to be delivered to these areas, their concentrations, and exposure times—which can vary from seconds to years—all affect these local effects.

- **Allergy:** If the organism has already become sensitive to a substance, it may cause an allergic reaction. There are four distinct categories of allergic reactions. Type IV is connected to cells, whereas types I, II, and III are mediated by antibodies (IgE, IgG). In dental materials, type I (rapid reaction) and type IV (delayed reaction) are most frequently encountered. Certain items, including latex, can directly trigger allergies by triggering the body's defense mechanisms. We categorize these as Type I, Type II, or Type III reactions. Dental materials can result in more distant extraoral reactions, such those brought on by touch, or localized intraoral allergic reactions.

  Additionally, a cross-sensitivity is indicated if a patient develops sensitivities to compounds that are related chemically. Such conditions should be known to a dentist before choosing a dental material. Palladium and nickel, for instance, belong to the same major group in the periodic table. Palladium allergies are common in patients with nickel allergies.

- **Other Reactions:** These include teratogenic, mutagenic, and carcinogenic consequences. The DNA in the human genome can be altered by substances released from materials (genotoxicity). Numerous methods exist in cells to reverse genotoxic damage. Alternately, planned cell death (apoptosis) can prevent the transmission of certain abnormalities to a cell's subsequent generation. However, this consequence is known as mutagenicity if these genetic damages are passed on to the following generation. For compounds that directly attack DNA, mutagenicity can be used as a potential predictor of carcinogenic potential. The aforementioned health risks

associated with this group are typically more theoretical in respect to dental materials because, as of yet, no such clinically documented damages have been associated with the use of dental materials.

III. MEASUREMENT OF BIOCOMPATIBILITY

The main goal of biocompatibility tests is to protect the clinical staff and lab technicians who will be handling the materials as well as the dental patients who will be treated with them. Testing for biocompatibility is related to risk assessment because no dental biomaterial is completely devoid of the possibility of adverse reactions. A material's biocompatibility cannot be determined by a single test but rather by a combination of different evaluation methods. Different types of tests are mentioned in the fig. 1. The first tests (phases I and II) are inexpensive, easy to complete, and fast. The material only progresses from simpler in vitro tests to the more complicated in vivo tests after completing the initial test. Animals or humans can be used in usage tests (clinical trials). In that they provide the final determination of whether a material is biocompatible or not, these usage tests are gold standard tests. One has to remember that assessing biocompatibility of materials using invitro assays and extrapolating the same in-vivo, anticipating the same results in oral tissues still remains debatable.

1. **Invitro Tests:** These examinations are conducted externally placing a substance, or a substance's component, in contact with an enzyme, a cell, or another isolated biological system. When there is no barrier between the material and the cell system, the contact is called direct. When there is a barrier of some kind between the material and the cell system, the contact is called indirect. One can further categorize direct testing into two groups: ones where the substance is directly incorporated with the cells, and others where a material extract comes into touch with the cells.

   Invitro Measures-
   - cytotoxicity or cell growth
   - some metabolic or other cell function
   - effect on the genetic material in a cell (mutagenesis assays

   Advantages: comparatively rapid, usually less expensive than use or animal testing, standardizable, appropriate for large-scale screening, and closely regulated to answer certain scientific concerns.

   Disadvantages: Questionable relevance to the material's ultimate in vivo use has already been mentioned.

   - **Cytotoxicity Tests:** The potential effect a chemical may have on cell survival is a clear indicator of biocompatibility, which is measured using the term "cytotoxicity." The series of molecular events that disrupt macromolecular synthesis and clearly cause structural, functional, and cellular damage is referred to as "cytotoxicity." It evaluates the amount of cell loss brought on by a substance by counting the number of cells or comparing their growth before and after exposure.

- **Membrane Permeability:** Because membrane permeability is comparable to or very close to cell death, membrane permeability assays are used to quantify cytotoxicity by measuring the ease with which a dye can flow through a cell membrane.
- **Cell Metabolism/ Cell Function:** Certain in vitro biocompatibility studies evaluate the cytotoxic reaction by measuring the biosynthetic or enzymatic activities of the cells. The MTT test (MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide]), NBT (nitroblue tetrazolium), XTT [2,3-Bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide salt], and WST (a water-soluble tetrazolium) are among the frequently used enzymatic tests for cytotoxicity. These colorimetric assays are based on various tetrazolium salts.
- **Indirect Tests:** Since in vivo use frequently results in no direct contact between cells and materials, a number of in vitro barrier tests have been created to replicate in vivo circumstances. These tests include the Millipore filter assay, which involves growing a monolayer of cells on a filter that is turned over so that test materials are placed on the filter and leachable diffusion products are allowed to interact with the cells, and the agar overlay method, which uses agar to form a barrier between the cells and the material.
- **Mutagenesis Assay:** It evaluates how a biomaterial affects the genetic makeup of a cell. The most popular and only short-term mutagenesis test that is thought to have been fully validated is the Ames test. The Styles' cell transformation test is an additional mutagenesis test. An alternative to the bacterial tests (Ames test), which might not be applicable to mammalian systems, is provided by this test on mammalian cells.

2. **Animal Tests:** Biocompatibility testing on animals typically use mammals like guinea pigs, rats, mice, or hamsters. as opposed to usage testing, where the substance is not given to the animal in relation to its intended use.

   Advantages: Comparing in vitro experiments with animal tests reveals more detailed and potentially important biological responses.

   Disadvantages: Difficult to understand and manage costly, time-consuming, and frequently involving serious ethical issues.

   - **Mucous Membrane Irritation Test:** ascertains whether a substance irritates the skin or mucous membranes that have been abraded.
   - **Skin Sensitisation Test:** To check for the development of skin hypersensitivity reactions, materials are injected intradermally. Adhesive patches containing the test substance are then applied as a secondary therapy.
   - **Implantation Tests:** Examine materials that will come into contact with bone or subcutaneous tissue.

   According to OECD Guideline, the following two guinea pig testing techniques are suggested - maximization test and Buehler test.

   - **Maximization Test:** The substance under inquiry and Freud's Complete Adjuvans (FCA) are first intradermally administered into the test subject in order to complete

the maximization test. Seven days later, the same chemical is applied topically for two days at the same site. Its objective is to boost FCA's immunological effect and hence raise the test's sensitivity. An further area of skin is treated with the test chemical after this fourteen-day induction period, and the proper reaction is assessed.

- **Buehler Test:** The procedure is same as that of the maximization except the application of FCA. It is considered safer test to maximization test.
- Other tests like the mouse local lymph node assay (LLNA) and mouse ear swelling test (MEST) are becoming increasingly significant.

3. **Usage Tests:** Animals or human study subjects may be used in usage tests. They differ from other animal experiments in that the substance must be exposed to conditions corresponding to its intended clinical application. Usage testing typically involve larger animals, such as dogs, mini-swine, or monkeys, whose oral environments are similar to those of humans. The usage test is referred to as a clinical trial if it involves using humans. The primary targets of usage testing in dentistry are gingival or mucosal tissues, periodontium, and dental pulp.

   Advantage: Relevance: These tests are the gold standard since they provide the definitive response on a material's potential for biocompatibility and clinical utility.

   Disadvantages: Extremely expensive, over extended periods of time, raise numerous ethical and frequently legal issues, are incredibly challenging to correctly manage, and could potentially damage test subjects.

   - **Dental Pulp Irritation Tests:** Materials to be tested on the dental pulp are put into healthy, intact teeth with class 5 cavity preparations. The teeth are removed and sectioned for microscopic examination when the investigation is finished. Next, the degree of tissue necrosis and inflammatory responses are ranked.

   - **Mucosal and Gingival Tests:** Placing the materials in cavity preparations with subgingival extensions allows for the assessment of the tissue response to materials that come into direct contact with the mucosa and gingiva. According to the quantity of mononuclear inflammatory cells, the material's impact on gingival tissues is detected, and reactions are classified as mild, moderate, or severe. This type of study is challenging because gingival tissue frequently has some level of preexisting inflammation brought on by the presence of bacterial plaque, the roughness of the restorative material's surface, open or overhanging borders, and the over- or under-contouring of the restoration.

IV. STANDARDS REGULATING BIOCOMPATIBILITY

The American Dental Association (ADA) made its initial attempts to create standards for dental materials in 1926. Unfortunately, the technological advancement of dental materials has evolved more compared to the biological compatibility recommendations and conditions of materials.

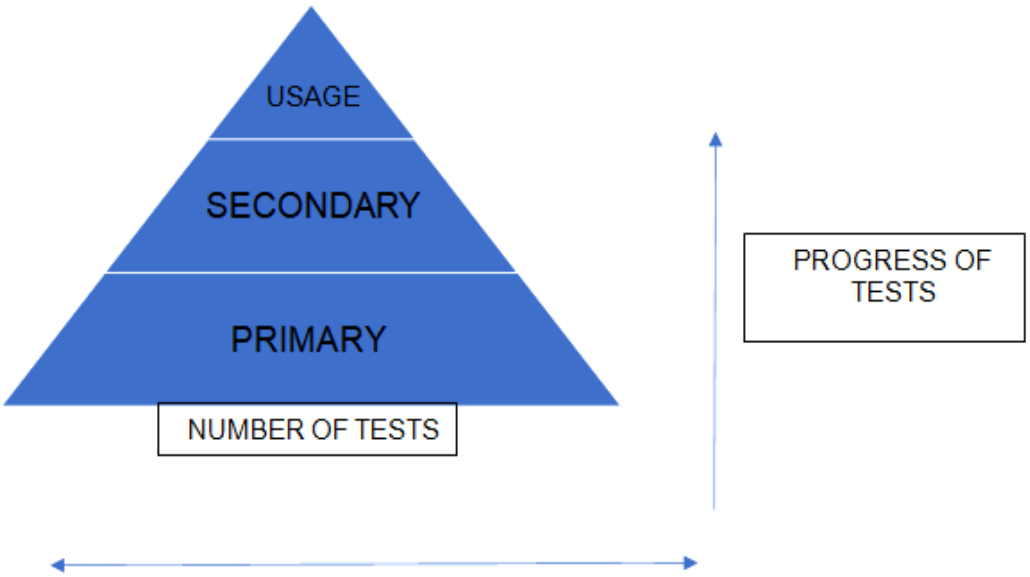
This is due to the following factors:

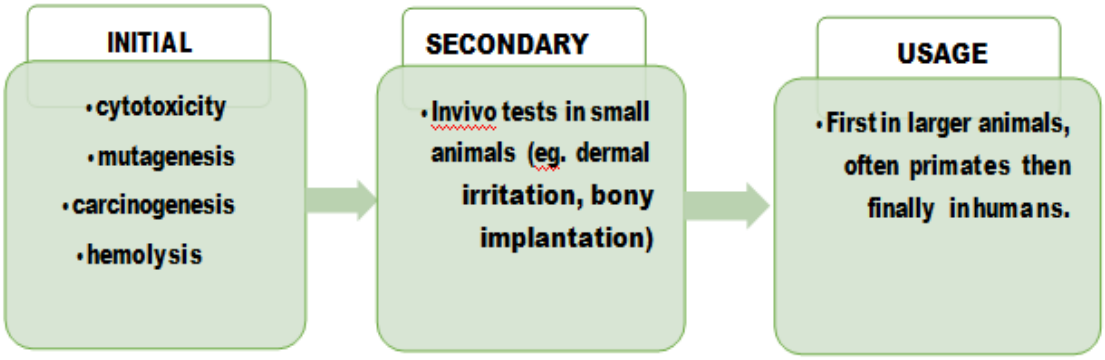
- Rapid advancements in cellular and molecular biology
- A wide range of tests available to evaluate the biocompatibility of materials
- A lack of standardization of these tests.

One of the earliest attempts to give a universal test for all materials was the 1933 research by Dixon and Rickert, which evaluated the toxicity of most dental materials then in use by implanting the materials into pockets in subdermal tissue. After sterilizing, small, standard-sized particles of gold, amalgam, guttapercha, silicates, and copper amalgam were placed into uniformly sized compartments into skeletal muscle tissue. Biopsy specimens were inspected under a microscope six months later. Other preliminary attempts to standardize methods were made on connective tissue by Mitchell (1959) and on tooth pulp by Massler (1958).

Specification No. 41 for Recommended Standard Practices for Biological Evaluation of Dental Materials was approved in 1972 by the ADA Council on Dental Materials, Instruments, and Equipment (now the Council on Scientific Affairs). This document advocated the use of **sequential testing of materials and standardized testing** procedures in order to reduce the variety of materials that would require clinical testing. This document was modified in 2005 to its current version after an addendum was added in 1982.

1. ANSI/ADA Specification 41:





The 2005 ANSI/ADA (American National Standards Institute/American Dental Association) specification describes three types of tests: use, secondary, and initial tests

2. **ISO 10993:** Several organizations launched global initiatives to create standards for biomedical materials and technologies in the 1980s. A number of international working groups were established to draft standard ISO 10993, which was published in 1992. These groups included scientists from the ISO and ANSI. ISO 7405:2008, "Preclinical evaluation of biocompatibility of medical devices used in dentistry— Test methods for dental materials," is the product of revisions made to this document's dental sections. The most recent ISO standard for evaluating the biocompatibility of dental materials is this one.

V. BIOCOMPATIBILITY OF RESTORATIVE DENTAL MATERIALS

1. Restorative Materials:

- **Amalgam:** Amalgam fillings, which are commonly referred to as silver filling, are one of the first materials used for restoring teeth. Since many years, there has been debate concerning the biocompatibility of amalgam, which is a byproduct of the interaction between liquid mercury and silver and other metals. It is well known that mercury can be found in an inorganic form (methyl mercury), as a metal, or in one of two charge states. It is well known that methyl mercury is extremely hazardous when present. Methyl mercury (free mercury) has caused hazardous effects like contact dermatitis in the hat business, in environmental catastrophes, and when seafood is consumed. The body is capable of absorbing mercury vapor easily. Mercury vapor inhalation can harm the kidneys, brain, and other key organs. It enters the lungs through inhalation and travels to the brain via the blood. If eaten, the metallic form of mercury present in an amalgam reaction is difficult for the digestive system to absorb. Due to the chemical reaction that unites it with the other metals in the amalgam to create an alloy, it is entirely combined with them.

  Tests on cell cultures have shown that the free Hg in amalgams is harmful. Copper (Cu) added to amalgams causes toxicity in cultured cells; yet, after being incubated for 24 hours, so-called low-Cu amalgams (i.e., 2-5% Cu) do not even impede cell development. Implant studies show that low-Cu amalgams are well tolerated, while so-called high-Cu amalgams (20–40% Cu) cause severe reactions when they come into direct contact with tissue.

Cavity Type	Response for Amalgam
Shallow, deep lined cavities	Minimal response, no irreversible damage
Deep unlined cavities (>0.5-1mm remaining dentin thickness)	Pain

Research has shown that mercury from amalgams in humans and canines does not reach the pulp. The conceptual terms state that rather than dissolving, mercury seeps back into the amalgams and carries on reacting with the alloy cores that haven't yet reacted with it. "Amalgam tattoo": a harmless darkening of the mucosa brought on by amalgam particles lodged in the tissue. Any pulpal reaction to amalgams seems to be relatively short-lived and solely related to the amalgams' physical insertion, notably the condensation pressure. Some people even want amalgam fillings removed because they continue to be concerned about their presence. However, it might be more harmful than beneficial to remove the filling for no other dental-related reason. This is because drilling existing fillings would cause more mercury vapor to be produced and would cause the patient to inadvertently inhale more mercury vapor. There is no proof of any mercury poisoning from dental amalgam to the patient based on available evidence, according to studies examined by the US Public Health Service and the Food and Drug Administration, with the exception of cases of allergy. Although amalgam appears to be safe for use in the mouth, dental practitioners who are exposed to it on a regular basis may have concerns. A recent study showed that those who handle amalgam while working in a dental setting have higher amounts of mercury in their blood. Implementing adequate regulatory safety precautions, such as donning protective masks and gloves, could help prevent increasing mercury levels in dentists' blood. It can be concluded that amalgam remains a viable option for restorations since it seems to be a biocompatible material that does not cause harm to the human body. The increased exposure to electromagnetic fields brought on by everyday objects like Wi-Fi routers, computers, mobile devices, and MRIs also raises a fresh question about the safety of amalgam fillings. Further future research is required on this aspect for continued usage of amalgams.

- **Glass Ionomer Ceme:** Glass ionomer cements were initially introduced by Wilson and Kent, and since 1969, they have been used in dentistry. Glass ionomer has been employed as a restorative material, base, liner, and cement (luting agent). Ionomers that are freshly synthesized have a small cytotoxic effect, however screening experiments show that this effect diminishes over time. In vitro cytotoxicity is caused by the fluoride release from these compounds. The inability of high molecular-sized polyacrylic acid to diffuse into dentine has been related to the overall pulpal biocompatibility of glass ionomer materials. According to histological analyses, any inflammatory infiltration from an ionomer is either negligible or absent after four weeks, and pulp reactions to these cements appear to be generally mild based on usage testing. Following the insertion of glass ionomers into cervical cavities, pulpal hyperalgesia has been reported for brief intervals (days). The enhanced dentin permeability following acid etching is most likely the cause of this phenomenon. In any case, it has been demonstrated that glass ionomer, used as a direct pulp capping agent, is not well tolerated when applied directly to living pulp tissue.

- **Zinc Oxide Eugenol:** Research done in vitro and in vivo has shown that eugenol (4-allyl-2-methoxyphenol, C10H12O2) released from Zn oxide (ZnO) eugenol cements (ZOE) fixes cells, inhibits cell respiration, and reduces nerve transmission upon direct contact. Eugenol exhibits effects that are dose-dependent, and diffusion through dentin considerably dilutes eugenol. Although eugenol is irritating to connective tissues, its sealing properties and antimicrobial activity appear to hasten pulpal repair.

- **Zinc Phosphate Cement:** Zn phosphate Zn3(PO4)2, cement has strong to moderate cytotoxic effects, which gradually lessen because of Zn ion leaching and a low pH, hence protecting the pulp, according to in vitro screening trials. During implantation investigations, Zn3(PO4)2 cements were injected into the rat dental pulp. The localized necrosis that resulted confirmed the cement's cytotoxic effects on pulp tissue. Within three days of usage tests, deep-cavity preparations showed moderate to severe localized pulpal injury; this is probably because of the initial low pH (pH 4.2 in three minutes). However, the hardened cement's pH approaches neutrality after 48 hours. It is recommended to add a protective layer of dentine-bonding agent, ZOE, cavity varnish, or Ca(OH)2 under Zn3(PO4)2 cement in deep cavities.

- **Zinc Polycarboxylate Cements:** Freshly-set and fully-set cement cytotoxicity has been linked to a lower pH, Zn and fluoride ion release into the cell culture media, and short-term tissue culture experiments. Additionally, tissue culture assays suggest that polyacrylic acid doses greater than 1% are cytotoxic. However, testing on bone implants and subcutaneous tissue conducted over a year did not reveal these cements' long-term cytotoxicity. As a result, additional mechanisms, like buffering and protein binding of these chemicals, may eventually neutralize these effects in vivo. These cements are only recommended for use in cavity preparations where the dentine is intact, due to their low dentine production reparative properties.

- **Liners:** Cavity liners made of Ca(OH)2 are available in variety of forms, including modified versions that contain ZnO, titanium dioxide (TiO2), and certain resins, as well as saline suspensions with a high alkaline pH (>12). Ca(OH)2 in suspension has a high pH, which causes severe cytotoxicity in screening assays. When pulp tissue is exposed to these extremely alkaline aqueous pulp-capping compounds, the immediate reaction is necrosis to a depth of 1 mm. Any hemorrhagic exudates of the superficial pulp are also helped to coagulate by the alkaline pH. Neutrophils invade the subnecrotic region shortly after necrosis develops. Only a minor inflammatory reaction is left after 5-8 weeks. The necrotic zone experiences dystrophic calcification within weeks to months, which then appears to be a stimulant for dentine bridge development. A number of in vivo investigations using various resin-modified glass ionomer cements as liners had no pulp damage reported as well. Hard-setting cements like Ca(OH)2 have been utilized as bases or liners because of their antibacterial qualities, thermal isolation, and biocompatibility with the pulp tissue.

- **Bleaching agents:** These solutions are usually available as gels that patients or dentists can apply to their teeth at home. The peroxide in these products is either hydrogen peroxide or carbamide. Depending on the material's formulation, the agents may remain from a few minutes to many hours in contact with the teeth. Peroxides can quickly (within minutes) and in high enough quantities to be cytotoxic cross the

dentin, according to in vitro research. The amount of peroxide in the bleaching chemical has a big impact on how hazardous it is to cells. Even more research has revealed that peroxides can quickly penetrate healthy enamel to get to the pulp in a matter of minutes. Bleaching has been shown to have harmful pulpal effects in in vivo investigations, and the majority of research concur that there is cause for concern over the prolonged use of these treatments on teeth. Although the exact cause of these reactions is unknown, using these medications frequently results in tooth sensitivity, according to clinical research. If the agent is not used properly, bleaching agents will also chemically burn the gingiva.

- **Etchants:** The mineral acid H3PO4 (PHOSPHORIC ACID) is highly corrosive and fairly powerful; it may burn the soft tissues severely if it came into touch with the gingiva or lip. Etchants that leak onto tissues from the teeth should therefore be completely cleaned with water. Hydrofluoric acid, on the other hand, is toxic and has a potent corrosive impact on living tissues, hence it should only be used extra orally.

- **Bonding agents:** Several bonding substances have been created and are used in dentin while restoring a tooth. The biocompatibility of these bonding systems has been the subject of numerous research. If evaluated in vitro alone, several of these chemicals are harmful to cells. To decrease cytotoxicity, the manufacturer recommends applying to dentin and rinsing with water in between applications of additional reagents. The components of the bonding agents, however, may permeate the dentin up to 0.5 mm, according to longer-term in vitro investigations, and significantly restrict cellular metabolism for up to 4 weeks after application. In tissue culture, the hydrophilic resin hydroxyethyl methacrylate (HEMA), which is present in a number of bonding systems, is at least 100 times less cytotoxic than Bis-GMA. However, studies employing long-term in vitro systems have demonstrated that when exposure times are raised to 4 to 6 weeks, detrimental effects of resins occur at considerably lower doses (by a factor of 100 or more). The presence of a dentin barrier considerably lessens the cytotoxic effects of many resin components. The "smear layer" is a 1-2 lm layer of organic and inorganic material that covers the dentine surface that remains after being cut, such as during a cavity preparation.In addition to covering the dentine's surface, the smear layer is also deposited inside the tubules, resulting in dentinal plugs that appear impenetrable when examined under an electron microscope. The amount of debris significantly reduces the tubular fluid flow. This smear layer is essential for the adhesion and biocompatibility of restorative materials. But there is some evidence that HEMA is toxic in vivo if the cavity preparation's floor has very thin dentin (0.1 mm). Nevertheless, it has been demonstrated that HEMA increases the expression of growth factors in cells that resemble mouse odontoblasts. Several studies have demonstrated the in vitro cytotoxicity of the most widely used resins in bonding agents, such as Bis-GMA, triethylene glycol dimethacrylate, urethane dimethacrylate (UDMA), and others. Dentin bonding agents containing HEMA and other resins may work in concert to produce cytotoxic effects in vitro.

- **Resin Based Materials:** For dental restorations, resin-based composites (RBC) have been used as cements and restorative materials. Because they incorporate both organic and inorganic components, they are referred to as resin composite materials.

These materials are made up of additives, initiators, fillers, monomers, and accelerators that are mixed together via a curing reaction of some kind.

These fillings could include substances like Bisphenol A (BPA) that become toxic when released as monomers. BPA is used to synthesis a number of the monomers that make up RBC, such as BPA-glycidyl methacrylate (BisGMA). When RBC material is being created, BPA residues are often left behind. One member of the xenoestrogen class is BPA. Chemicals known to be endocrine disruptors and to impede regular hormone function are called xenoestrogens. The E-screen assay is one technique that is frequently used to evaluate xenoestrogenic activity. The growth response of breast cancer cells, which are susceptible to certain estrogenic substances, is what this in vitro test is based on.

The mean degree of conversion (DC) for each of the composites was between 60 and 70%. Depending on the type of composite, the total monomer release varied significantly. The composite that resembled paste had the least amount of monomer elution. This can be attributed to the fact that it initially contains less resin. It is also applied in layers, allowing for better healing. Lower DC and more monomer release were obtained with four mm bulk placement. Evidently, complete polymerization of the material is less successful when curing through a thicker layer of composite material. As a result, greater amounts of toxic monomers are released.

It's interesting to note that dental professionals are more likely to experience asthma attacks and other respiratory problems, while a specific explanation is unknown. This observed phenomenon might be caused by composite dust particles that were released into the atmosphere. It is necessary to take further steps to limit the inhalation of composite dust. To lessen the exposure to harmful composite dust, perhaps improved safety masks should be used.

Chemically cured and light-cured resins that have recently been set often induce mild cytotoxic reactions in cultured cells when exposed for 24 to 72 hours in vitro. Research indicates that light-cured resins generally exhibit lower cytotoxicity compared to chemically cured systems. Nevertheless, the extent of this effect largely relies on the specific resin system used and the efficiency of the curing light. When placed in cavities with around 0.5 mm of remaining dentin, both chemically and light-activated resin composites resulted in a mild to moderate pulpal inflammatory response after 3 days. However, when a protective liner or bonding agent is applied, the pulp's reaction to resin composite materials is minimal. The long-term consequences of directly placing resins on pulpal tissue remain uncertain.

Allergic reactions stemming from resin-based materials, including resin composites, impact both patients and dental professionals who handle such substances. Limited information is available regarding the in-vivo effects of composite components released into soft tissues. Although clinical research in this area is relatively scarce, some indications suggest that methacrylate-based composite constituents may substantially raise the risk of hypersensitivity reactions. Conversely, allergic responses related to acrylic resins have been associated with contact dermatitis, indicating a potential risk.

- **Ceramics:** Apart from potential wear on opposing teeth and/or existing restorations, indirect ceramic restorative materials, also referred to as dental porcelains, are generally considered to have no significant biological impact. In comparison to other restorative materials, dental ceramics are believed to exhibit a relatively low incidence of biological side effects. Nonetheless, as indicated by Roulet et al., ceramics are not associated with any long-term consequences.

  Zirconia (also known as zirconium dioxide, ZrO2) is an incredibly dense, inert, and hard material that is also quite biocompatible. ZrO2 is currently employed for a variety of applications, including as root canal posts to strengthen non-vital teeth.

2. Endodontic Materials:

- **Sodium Hypochlorite:** Sodium hypochlorite (NaClO) is the most commonly utilized irrigation fluid for root canal preparation due to its pulp dissolution and potent antimicrobial properties. However, at high concentrations, NaClO can be highly toxic and may cause tissue irritation upon contact. Reports suggest that a safe concentration to use is 0.025% NaClO, as it exhibits bactericidal effects without adverse tissue reactions. In vitro studies have shown that even a concentration as low as 1:1000 in saline can lead to complete hemolysis of red blood cells. To strike a balance between effective antibacterial action and minimal tissue irritation, it may be reasonable to consider using 0.5–1% NaClO for endodontic irrigation, as it maintains a pH level close to neutral.The majority of problems associated with the use of NaClO seem to be caused by its unintentional injection beyond the root apex, which may result in strong tissue reactions characterized by pain, edema, and bleeding. It has been observed that NaClO might cause hypersensitivity reactions, paraesthesia, and secondary infections in some cases.

- **EDTA:** The chemo mechanical enlargement of root canals is enhanced, the smear layer is removed, and the dentinal walls are cleaned and disinfected using EDTA frequently in endodontic therapy. When EDTA leaks into the periapical tissues during root canal preparation, this may decrease macrophage activity and change how the periapical lesions respond to inflammation.

- **Calcium Hydroxide Medicament:** In vivo studies have shown that Ca(OH)2 intracanal dressings effectively removes the majority of bacteria from infected root canals 7 days, 4 weeks, and 3 months afterwards. Ca(OH)2 intruded to the periapical area seems to be well tolerated and is thereafter reabsorbed.

- **Gutta Percha:** 80% of gutta-percha is made up of ZnO, which is what gives gutta-percha its radiopaque quality (60–70%). The added complication of heat generation during obturation, which could be harmful to periodontal tissues, is imposed by warm gutta-percha procedures. Due to the substances added to the base material, especially Zn, it has been claimed that some commercially available gutta-percha points are highly cytotoxic. This is because Zn may leak into the surrounding soft tissues, which is thought to be the critical level at which irreversible damage to the periodontal tissues can occur. Pure gutta-percha can be considered fully biocompatible, as no

effect on the frequency of chromosomal aberrations in in vitro experiments has been seen.

- **Chlorhexidine:** Human keratinocytes and fibroblasts were used in the wet disc assay to investigate the cytotoxicity of the antiseptic CHX and other antimicrobial compounds as well as their microbic impact.The CHX that was tested was consistently effective against six strains of frequent microorganisms found in burns, however it was unsuitable for clinical usage due to its significant cytotoxicity. Therapeutic mouth rinses used to treat gingivitis contain CHX digluconate as one of the active components.

- **Mineral Trioxide Aggregate:** For the past ten years, mineral trioxide aggregate (MTA) has gained popularity as a root-end filler. Portland cement has the potential to be employed as a less expensive root-end-filling material in dentistry practice because it was found in one study to contain the same chemical components as Mineral Trioxide Aggregate (MTA). Furthermore, it has been established that Portland cement and MTA are equally biocompatible.

- **Chitosan:** A macromolecule called chitosan is generated when D-glucosamine, which comes from the deacetylation of chitin found in the shells of marine crustaceans, particularly crabs and prawns, is repeated. It is a fiber that is indigestible and chemically comparable to cellulose. Chitosan is a natural polysaccharide that is non-toxic, biocompatible, and biodegradable and has been shown to have antibacterial properties.

3. Other Materials:

- **Latex Allergy:** Natural rubber latex is a substance that can be found in a variety of dental supplies, including gloves, rubber dams, and toys that kids utilize during dental procedures including pacifiers, nursing bottles, and balloons. Individuals that exhibit latex hypersensitivity fall into either type IV or type I categories. Latex exposure has been linked to dermatitis, swelling, redness, and irritation.

VI. CONCLUSION

The manufacturer is in charge of guaranteeing the safety of its products when used in accordance with instructions, but the healthcare professionals should validate that all necessary testing has been carried out. Dentists should be aware that no material is completely free of potential adverse effects. It should be clear that dental professionals cannot select restorative materials for their patients by just using a guidebook method. Instead, they must ensure that any possible risks are reduced by using their best clinical judgment, which is supported by scientific data, their own dental experience, and, when appropriate, statements from patients, their doctors, and prior dentists. The patient should be told of the advantages and disadvantages of the suggested treatment as well as any potential alternatives after the practitioner has made a treatment decision. The patient must thereafter give consent for the suggested treatment in order for medical and legal requirements to be addressed.

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