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Original Research

Biocompatible Issues Related to Restorative Dental Material - I (Regulations, Interfaces, Measuring Tests)

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ABSTRACT:
The commercial market of dental materials has widened during the last few decades with the introduction of modern computer assisted diagnosis and computer assisted machining (CADCAM) and three dimensional printing. New restorative materials are being introduced with claims of many advantages over their predecessors. These materials are governed by standard regulations that have been laid down by various national and international organizations. Researchers are investigating these materials to either support the claim of the manufacturers or to prove it otherwise. In the light of new introduction of dental materials it is mandatory to review various factors that are associated with the biocompatibility of a material. This review article therefore aims to provide a clinically applied overview of newly introduced materials in the light of existing biocompatibity standards.In its introductory part, the article reviews various regulations, biological interfaces, biocompatibility measurements and adverse effects. Keywords: Biocompatibility, dental cements, dental alloys, dental regulations, adverse effects

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INTRODUCTION

For more than 2000 yrs, attempts have been made to improve life quality of dental patients with the use of various new materials and devices. Evidence suggests that bridges were built with materials such as animal and human teeth extracted in 400 B.C.[1] In prehistoric times, the roots of natural teeth were used for retaining crowns and such practices are just two centuries old.[2] The concept of ethical treatment of patients was emphasized by Hippocrates during the 460-370 B.C. era.[3] Few of the 1st review articles published on evaluation of a biologic response to dental materials, were those of Autian & his colleagues in 1971.[4] Biocompatibility can include the negative impact of a material on tissues and physiologic systems depending on how it is defined. The material may be negatively affected by the physiological environment, or both. At times, one material placed in the oral cavity may come into contact with other previously present material and may initiate a response. These occur in either the metallic restorations or endodontic obturation procedures.[5, 6] The products of material degradation caused by physiological exposure have a negative impact on tissue. Concepts of hermetic seal implicates a fluid impervious bacteria-tight seal.[6] The ability of a material to live in harmony with its surroundings is called biocompatibility.7 The biocompatible material should have the capacity to trigger a physiological response in a specific body application.8

Existing regulatory bodies and standards: Global regulating standards measuring biocompatibility of materials include Food and Drug Administration (FDA), American National Standards Institute (ANSI), International Organization for Standardization (ISO), American Dental Association (ADA).[9-11] The first efforts of the ADA to establish guidelines for dental materials came in 1926 when scientists at the National Bureau of Standards, now the National Institute of Science and Technology, developed specifications for dental amalgam.[10] In 1972 the ADA Council on dental materials instruments and equipment approved Specification number 41 for recommended standard practices for biological evaluation of dental materials.[12] The unregulated mercury content in the amalgam at that time exceeded beyond the biocompatible limits of the body. High content of mercury mainly organic and

vapour form resulted in nervous and neurologic damage.[13] Testing programs for dental materials are based on specifications by national or international standards organisations, such as American national standard institute (ANSI) /ADA specification (41) and international standard organisation (ISO) (10993).[14,15] Further revision of the dental components of this document resulted in the publication of ISO (7405:1997).[10, 16] In 1982, an addendum was made to this document, including an update of the Ames test for mutagenic activity.[10] There are no true inert materials i.e. when material placed in the living tissue, interaction with complex biological system will occur and therefore will result in some sort of biological response. It is an ongoing process i.e. it is a dynamic process.

Dynamicity of oral cavity: Response of body to the material can change over time as the body may change during disease or ageing, or material may change due to corrosion/fatigue/loads placed on the material. Most of these changes are directly or indirectly attributed to occlusion of the restoration since most of the masticatory loads are generated by the powerful musculature associated with the stomatognathic complex. The contact of tooth with each other in complex occlusal rehabilitations ensures biocompatible and a durable response from the material used for replacing or restoring a tooth.[17] Occlusal rehabilitations require not only efficient and competent designs but also one that is biocompatible to surrounding tissues and temperomandibular joint in terms of mechanics.[18] A restorative material may change and bring changes in the occlusion therefore the interaction between host, material and function will continue over time. The interaction will depend not only on local factors but also the systemic factors of an individual.[19] Medical conditions that decrease salivary secretion will alter the bioenvironment of the restoration and bring changes in the way material responds.[20] Oral hygiene is a local factor and altes the microbes according to the status maintained. Like color therefore, biocompatibility is not the property only of a material, but of a material interacting with its environment. A material's color depends on the character of light source, how light interacts with the material and how the observer interprets reflected light.[21] Similarly biocompatibility is a property of a material interacting with its environment. It is mandatory to follow the principles of biocompatiblity when materials are concerned.

In the last two decades there has been a plethora of materials that have been introduced in dentistry and most of them are digitally manufactured and processed. The introduction of computer aided diagnosis and computer aided manufacturing (CADCAM) has flushed the market with new restorative materials and designs. Researchers have been kept busy to understand the advantages and disadvantages of these newly introduced materials which is why it becomes significant to review the current materials. Therefore this review was aimed to provide a comprehensive overview of the newly introduced materials in the light of biocompatibity standards that have been previously established. The objective of reviwing is to compare the selective properties that are associated with biocompatibility. Literature search was conducted in relation to the historical and present day context of biocompatibility of dental materials. Four different medical and dental electronic databases were scrutinized utilizing multiple scientific terminology related to material biocompatibility. Relevant papers were screened in references and abstracts were thoroughly read. In total 48 articles were isolated that fulfilled the aims and objectives of the study. Individual case reports, reviews, systematic reviews and original research articles were included in the final phase. The review is considered to be presented in two parts to maximize the evidence collected.

Relevance of biocompatibility to a dentist: The placement of dental restoration onto a tooth creates an interface between the material and the tissues adjacent to the material. In dentistry these interfaces may be between materials and pulp via dentine, the periodontium, periapical bone or the oral cavity in general.[23,24] Wherever an interface exists, it is active and dynamic involving two way interactions that allow tissue to influence the material and the material to influence the tissue. The activity of these interfaces depends on location of material, its duration in the body, the properties of material and health of the host.[6,9,24,25] Various aspects of oral anatomy influences the biocompatibility of a dental material namely tooth anatomy, periodontal attachment, periapical environment.[26] Although enamel is permeable to some substances, such as the peroxides in bleaching agents, it is generally not permeable to material components, bacteria, or bacterial products.[27] However, it is used to advantage with bonding agents and therefore provides micromechanical retention with resin composites.[28] Composite nature of dentine allows bonding to occur because acids may selectively dissolve the mineralized matrix but not the collagenous network, therefore most dentin bonding agents attempt to penetrate the undissolved collagen matrix.[29] These tubules are about 0.5µm in diameter near enamel and increases to 2.5µm near pulp.[26,29] Density of tubules is about 20,000/mm^2 near enamel and >50,000/mm^2 near pulp.[29] Therefore, if the enamel is violated by caries, other pathology or by a dentist, dentinal tubules may serve as conduits by which material components, bacteria or bacterial components may reach and affect the pulp of the tooth. As the diameter near pulp is more, there is greater risk of allowing substances to reach the pulpal tissues when deeper dental restorations are placed. When dentist cuts the dentin, a smear layer of dentinal debris covers the dentin and inhibits diffusion of products through the

tubules to some extent.[30] This layer can be removed by acid etching, which also demineralizes the openings of the tubules and establishes continuity with pulpal fluid to facilitate the diffusion of molecules, both natural and from materials into and out of the pulp. Pupal side of dentin is lined by odontoblasts that formed the dentin during the tooth development and maintain and form new dentin as the tooth ages or when triggered by noxious stimuli. Aging, nutritional and hormonal influences mucosal as well as reactions from hard tissues like dentin.[31] Biological response does not remain same throughout life, it changes according to the stimulus and the capability of the defense mechanism of the body. [31] Moderately deep cavity preparation will damage odontoblasts by severing the odontoblastic processes. Deep cavity preparation may destroy most of the dentin and kill primary odontoblasts.[32] Bacteria can sometimes be seen within tubules below a carious lesion or at the base of a prepared cavity, with or without restoration.

Significance of pressure variations: Fluid convection i.e. movement of fluid through dentine tubules towards pulp will occur under positive hydraulic pressure when a crown or inlay is being seated.[33] Regeneration of individual tooth tissue using stem cells is promising but its application may be limited to very ideal cases.[34] If dentinal tubules are open, this produces a sharp, localized pain in the pulp from stimulation of A- fibres.[35] Fluid convection away from the pulp will occur with negative osmotic pressures when concentrated solutions, such as sucrose or saturated calcium chloride, are exposed to open tubules.[32] Clinically, this situation occurs with cervical abrasion or carious lesion. Diffusion occurs through patent dentinal tubules, no matter how small the diameter, establish a diffusion gradient through which ion and molecules can move, even against positive hydraulic pressure. Pulp replaces any odontoblasts lost during cavity preparation or material placement and allows the tooth to form secondary or reparative dentin.[36] The diffusion of bacterial products or material components influence the ability of this repair process to occur, such as calcium hydroxide, seems to promote the reparative dentin formation.[5]

Periodontal interface: The periodontal attachment is an important junction between the outside of the body (oral cavity) and inside of the body.[37] Dentin of the root is covered by a thin layer of cementum that may seal the dentinal tubules. The cementum serves as the attachment point for the collagen fibers of the periodontal ligament.[38] Gingiva normally extends above the level of the cementum and forms a potential space against enamel called as periodontal pocket. This is the site of development of periodontal disease which can destroy junctional epithelium, periodontal ligament and supporting bone.[39] Because many dental restorations are near or in the periodontal attachment area, the biocompatibility of these materials may influence the normal periodontal architecture. Cast posts that do not allow placement of ferrule are prone to violate the periodontal attachment if the interface between the restoration and the tooth is subgingival. Cast posts extract retention and resistance from the root canals and despite imparting strength to the weakened tooth structure they may inadevertently violate periodontium.[24,40] Furthermore, periodontal pocket is a unique microenvironment that may allow concentration of components from materials to reach higher levels than are seen in the rest of the oral cavity.[41] It is often difficult to determine with certainty whether inflammation in this area is caused by periodontal disease, occlusal trauma or other reasons. the dental materials that are antigenic can cause immune hypersensitivity reactions in oral mucosa and gingiva.[35]

Periapical interface: Periapical area is another interface between materials and the inside of the body.[42] Normally, the apex of the tooth is the junction of the pulp of the tooth and alveolar bone below it. Nerves and blood vessels enter through the apical foramen. However, when the pulp of the tooth is destroyed by infection or during restoration of a tooth, endodontic materials are placed in the pulpal space, and these materials interface with the body through the apex of the tooth. Therefore, if procedures not performed correctly, filling material may be extruded from the apex into the periapical area and cause additional damage.[43] Dental materials that are antigenic can cause immune hypersensitivity reactions in oral mucosa and gingiva.[44] At times mucosal discoloration may be normal (melanin pigment) which may appear as allergic response.[45] Local binding of antigens to membrane of WBC (i.e. Lymphocytes, macrophages, basophils, mast cells) or langhrehan cells of the skin and oral mucosal epithelium play a role in activating these various reactions.[46] Few of mucosal reactions are documented as type I reaction (where in vasoactive substances are released from mast cells because of antigen-IgF reactions),[47] most reactions to dental materials are classified as type IV (T- cell mediated) reactions.[48] This type of reaction is sometimes called as contact mucositis.

Correlation Among In Vitro, Animal, And Usage Test: Biocompatibility of a dental material is tested or measured using different approaches as mentioned in **Table 1.** Generally, no single test is used to evaluate the biocompatibility of a new material. Rather, in vitro, animal, and usage tests are used together.[47] All materials are to be tested by primary tests, but many will not have responses favorable enough to be carried to secondary tests. Likewise, only materials that show favorable reactions in the secondary tests will be evaluated by the usage tests. This linear paradigm relies heavily on the accuracy of the primary tests. If these tests are too severe, potentially good materials

will be screened out.[49] If they are too insensitive, materials with little clinical promise will be promoted to the next phase of testing, wasting time and money and placing animals and human at unnecessary risk. Although the linear paradigm persists today within the standard and regulatory agencies, most researches have adopted new paradigms. In these alternative paradigms, the basic linear paradigm is preserved, but the need to consider nonlinear thinking is also infused i.e. A new material may be tested first using classic primary tests followed by secondary and usage tests, but primary tests may be necessary a later stage to answer a question that arose from an early clinical trial. This question may not have arisen until the clinical trial and the in vitro environment may be the only environment with sufficient experimental control to answer the question.

Table 1: Biocompatibility tests used for dental materials

Biocompatibility Measurement		
In Vitro Tests	**In Vivo Tests**	**Usage Tests**
Cytotoxicity Test	Mucous Membrane Irritation Test	Done In Animals Or In Human Volunteers Clinical Trial (In humans) Dental Pulp Irritation Test Dental Implant In Bone Mucosa And Gingival Usage Test
Cellular Metabolism And Function Test	Skin Sensitization Test	
Mutagenic Tests	Implantation Test	

ADVERSE EFFECTS FROM DENTAL MATERIALS

Toxicity: The first screening test used for almost all materials is a toxicity test.[47] Materials may be capable of releasing substances into a patient's body, and the release of certain substances in adequate amounts can cause overt toxicity e.g. Lead leached from the dental material into the patient's body poses a real risk of toxicity. Some materials may be leached out slowly over a period of time like methyl methacrylate monomer in denture base resin. Current CADCAM milled resin have less monomer content because they are manufactured in the industries under controlled conditions.[50] Prefabricated PMMA resin pucks are also manufactured under high pressure and temperature during their polymerization which minimizes leachable monomer thereby improving biocompatibility.[50]

Inflammation: It is the second fundamental type of biological response to a material. Inflammatory response requires activation of the requires host's immune system to ward off some threat.[51] Histologically, the inflammatory response is characterized by edema of the tissues with an infiltration of inflammatory cells such as neutrophils or monocytes and other lymphocytic cells.[52] The contribution of dental materials to inflammatory reactions is especially important because pulpal and periodontal diseases are largely chronic inflammatory responses to long term infections. during dental procedures, it is mandatory to maintain highest level of infection control to prevent inflammatory response from the tissues, besides being mandatory for preventing cross infection especially during the times of pandemics and epidemics.[53]

Allergic Response: Classically an allergic response occurs when the body specifically recognizes a material as foreign and reacts disproportionately.[47] An allergic reaction results histologically in an inflammatory response that can be difficult to differentiate from a nonallergic inflammation or low grade toxicity.[54] The reaction typically involves all dimensions of the immune system including T and B lymphocytes and monocytes or macrophages.[45] A key difference between a nonallergic inflammation response and an allergic is the fact that in an allergic response, the individual's immune system recognizes a substance as foreign. Thus, not all individuals will react to that substance. Also Allergic reactions tend to be dose independent initially and disproportionate to the amount of the substance, whereas the toxic or inflammatory reactions tend to be dose dependent and proportional to the amount of the substance. Nickel content in alloys used for fixed partial denture elicits an allergic response once an individual is exposed to the material.[55] The allergy that occurs intraorally can be uncomfortable to the patient and alloys that have a substitute or are nickel free should be used in such patients.

Mutagenic Reactions: These results when the components of a material alter the base pair sequence of the DNA in the cell, these alterations are termed as mutations. Mutations may be caused by direct interactions between a substance and DNA or indirectly by alterations in cellular processes that maintain DNA integrity.[57, 58]

Effects of materials: Any material used in the body may have local or systemic biological effects.[59] One of the best examples of biocompatibility is perhaps the placement of endosseous titanium implants within the body without invoking any issues in the body.[60] The nature, severity, and location of these effects are determined by the distribution of released substances. For dental materials, local effects might occur in the pulp, in the periodontium, at the root apex, or in nearby oral tissues such as tongue or buccal mucosa. These local effects are a function of the ability of substances to be distributed to these sites, their

concentrations, and exposure times that range from seconds to years.[43] Systemic effects of dental materials are also functions of the distribution of substances released from the materials.[61] These substances might gain access to the body via ingestion and absorption in the gut, inhaled vapor, release at the tooth apex, or absorption through the oral mucosa. Their distribution may occur by simple diffusion or transport via lymph or blood vessels. The systemic biological response depends on: the duration and concentration of the exposure, the excretion rate of the substance, the site of the exposure.[62] There are two key factors that appear to be paramount in determining a material biocompatibility.

Metal Corrosion Or Material Degradation: Corrosion results in the release of substances from material into the host, now this release can take many forms and may caused by many factors e.g. a metallic crown may release metal ions as a result of electrochemical forces,[63] or it may release particles dislodged by mechanical forces such as occlusion or tooth brushing. This corrosion is determined by the material's composition and Biological environment in contact with the material.

Surface characteristics of the material*:* As the surface is the part of the material that the body "sees", the surface composition, roughness, mechanical properties, and chemical properties are critical to the biocompatibility of the material.

CONCLUSION

Use of a dental material must be envisioned to be biologically acceptable at three interfaces of the oral cavity. All materials used on patients should be approved by standard regulations. New materials must be further investigated in clinical trials to measure their long term effects.

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