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# INFLAMMATORY AND ALLERGIC REACTIONS OF DENTAL COMPOSITE RESINS

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## ABSTRACT

Dental composite resin is the preferred material for direct restoration due to its excellent mechanical and optical properties. However, adverse reactions caused by dental composite resins are not uncommon, and the main reason may be related to residual monomers that cannot be completely converted into polymers, and the resin polymers can be degraded and become degradation products in the oral environment. Residual monomers and degradation products can cause inflammation and allergic reactions, and even lead to body damage. This paper reviews the inflammatory and sensitization of dental composite resin.

**Keyword:** dental composite resin; dental material; inflammatory； allergic reaction

## INTRODUCTION

Composite resin is a kind of dental material which is composed of organic resin matrix, inorganic filler and initiator system after surface treatment. It is the most commonly used material in oral prosthodontics and orthodontics. Therefore, it is used for the treatment of dental caries and the bonding of orthodontic brackets. Because of the direct contact with the human body, it needs to consider its biocompatibility, and biocompatibility is mainly determined by its degree of conversion. Low degree of conversion results in decreased physical mechanical properties and increased release of monomers into the oral environment. Some of these released substances have mutagenic and cytotoxic properties and may cause inflammatory responses in the gums, pulp and oral mucosal tissues[1]. A large number of studies have shown that the residual monomers of resin-based materials during polymerization and the release of degradation products produced by polymers in the oral environment can affect the pulp, periodontal and oral epithelial cells, causing inflammation and/or allergic reactions [2, 3]. In addition, resin adhesives directly cap the pulp, resulting in degeneration and necrosis of dental pulp cells, more inflammatory cells, and the formation of dentine Bridges[4].

## 1. Inflammatory

### 1.1 The causes of inflammatory response

#### 1.1.1 Residual Monomers

Resin adhesives, sealers or composite resins can cause transient discomfort after contact with dental tissue, resulting in pulp congestion and even pulpitis. This may be related to the increased release of inflammatory cytokines by monomers. After resin photocuring, the

residual methylpropionate monomer in the polymer that did not participate in the polymerization reaction was released within the first 24 h, which caused the inflammatory reaction of pulp, periodontal and oral mucosa through the following two paths: One is that the hydrophilic monomers can pass through the intact dentin barrier and are able to diffuse into the dentin at concentrations that may cause cytotoxicity and affect the viability of the dentin cells. In addition to affecting odontoblast cells, monomers travel through dentin tubules, reach pulp tissue and penetrate cytosol of different cell phenotypes, resulting in cytotoxicity, genetic damage, and oxidative stress[5]，causing pulpitis reaction [6, 7]. A large number of vitro experiments have shown that Triethylene Glycol Dimethacrylate (TEGDMA），2-Hydroxyethyl methacrylate (HEMA) and Bisphenol A Glycidyl methacrylate (Bis-GMA）that can induce cytotoxicity and apoptosis of human dental pulp cells and cause inflammation of dental pulp tissue [8-11]. Then causing the release of proinflammatory factors[12].In addition to affecting pulp tissue, unpolymerized monomers can be released from dental materials into the oral environment, through saliva, and spread to the gums, mucous membranes, and salivary glands [13]. Causing inflammatory response of periodontal tissue，stimulating oxidative stress in periodontal tissues. Both can lead to periodontal tissue get injuried. Meng analyzed gingival crevicular fluid about before and after resin treatment in a retrospective study, and measured the contents of inflammatory factors, oxidative stress products, apoptotic molecules and protease-related molecules [14]. He found dental resincould cause periodontal tissue damage. Bertoldi C et al. conducted a group of clinical experiments to study the inflammation of gum tissue before and after resin treatment in a group of teeth requiring crown lengthening and crown restoration. The results showed that there was no significant difference in gingival inflammation between the treatment group and the control group, but there was a slight increase in histological inflammation in the treatment group compared with the control group[15].

### 1.1.2 The degradation products of resin polymers

Resin polymers can undergo chemical degradation and mechanical wear in the oral environment. Chemical degradation occurs due to hydrolysis and enzyme-induced catalysis of human salivary esterase and oral liquid in the diet. Mechanical wear is mainly caused by mechanical movements such as brushing and occlusal sliding. In addition, inappropriate polymerization of resin-based composites can enhance these adverse physical and chemical effects[16]. Bisphenol-A（BPA) polymers are the most common degradation products and can be absorbed by oral and gastrointestinal mucosa, causing local and systemic toxicity. In addition, it is an endocrine disrupt or which is associated with diabetes, obesity, polycystic ovary disease, cardiovascular disease, reproductive and neuro developmental disorders[17, 18]
.

## 1.2 The mechanism of inducing inflammatory effect

Inflammatory mediators are a class of molecules that play an important role in many physiological and pathological processes of the body. They can have additive/cooperative and antagonistic effects in this cross-sequence regulatory network. Such as Interleukin-1(IL-1）, Interleukin-6(IL-6）and Tumor necrosis Factor (TNF-α), these inflammatory mediators can initiate inflammatory processes by inducing tissue changes. For example, they can cause vasodilation and recruitment of defense cells. Anti-inflammatory cytokines such as Interleukin-10 (IL-10) can regulate the inflammatory initiation process to promote the balance between tissue damage and response[19]。Inflammatory mediators can be released from different types of cells. For instance, human dental pulp cells produce a variety of pro-inflammatory factors under the action of injury stimulation. LikeInterleukin-2(IL-2）、IL-6[20]、Interleukin-8(IL-8）、Granulocyte macrophage colony stimulating factor (GMCSF)

、Tumor necrosis Factor(TNF）、tumor necrosis factor cell colony[21] all of those can induce immune response.

Alizadehgharib S et al. found that TEGDMA affected the content of pro-inflammatory cytokines , such as Interleukin-1b (IL-1b), IL-6, IL-8, and Interleukin-18 (IL-18) and tumor necrosis Factor-α(TNF-α)[22]. This inflammatory ability gives TEGDMA adjuvant properties, which may interfere with homeostasis between the immune system and its own flora in the mouth. In addition, TEGDMA and HEMA interfere with Reactive Oxygen Species (ROS) by generating REDOX reactions, leading to Deoxyribonucleic acid (DNA) damage[23], and causing cell structure and function damage[24]。

Different resin monomers cause different mechanisms of inflammation. Bis-GMA cause the inflammation reaction by changing some immune cells. Such as$CD_{4+}$ T helper lymphocytes($CD_{4+}$Th),B lymphocytes, Macrophages, Mast cells and Dendritic cells(DCs)，all of those can promote immune response. Bis-GMA induce the inflammation reaction by Mitogen-activated protein kinase(MAPK）,transcription factor，like Nuclear transcription factor activator protein-1（AP-1),Nuclear factor kappa-B（NF- kB) and Families of signal transducer and activator of transcription (STAT). However，It is not known whether Bis-GMA polarize T helper lymphocytes-1(Th1) or T helper lymphocytes-2 （Th2)[25]. HEMA induce the inflammation reaction by increasing cyclo-oxygenase(COX）-2、inducible nitric oxide synthase（iNOS）mRNA 、COX-2 protein and dinoprost[26]. iNOS induced synthesis of nitric oxide (NO) which can increase the level of lactate dehydrogenase in osteoblasts, inhibit the activity of adenosine triphosphate and niacinamide adenine dinucleotide dehydrogenase, reduce mitochondrial membrane protein and cell viability, and lead to mitochondrial dysfunction, DNA breakage and programmed cell death. Moreover, NO further causes oxidative stress and synergies with ROS to accelerate programmed cell death.

## 2. Allergic reaction

### 2.1 Causes of allergic reactions

Incomplete polymerization of monomers and leaching of monomers from polymers are the main causes of allergy. There is evidence to prove that Bis-GMA、HEMA and TEGDMA can cause allergic reaction as allergen[27-29].The pathways of allergens entering the oral cavity can be divided into the following: ①Allergen enters body through oral mucosa which can cause contact stomatitis; ②Allergen enters body through skin which can result in contact dermatitis; ③Allergen enters the pulp cavity through the dentin which will lead to pulpitis. These allergens enter the body through the above pathways, leading to corresponding diseases, causing discomfort. Since these reactions can cause problems not only for patients, but also for doctors, we need to understand the mechanisms and causes, and how to avoid them.

### 2.2 The mechanism of allergic reactions

Allergy is an abnormal immune response to a specific substance. The immune response is usually divided into early stage and late stage. ①Early stage: The body reacts immediately within 15 minutes of contact with the allergen, also known as Type I hypersensitivity; ②Late stage: Delayed reaction occurs 4-12 hours after exposure to the allergen , also known as delayed Type IV hypersensitivity[30].

### 2.2.1 Type I hypersensitivity

Type I hypersensitivity, it also known as Immediate anaphylaxis which is the hypersensitivity mediated by ImmunoglobulinE(IgE). It can be broken down into the following three stages:①Sensitization stage: After the allergen enters the body, the allergen specific B cells can be selectively induced to produce an antibody response, which combines with the surface of mast cells and basophils, so that the body is in a state of sensitization to the allergen. Usually this sensitizing state can be maintained for several months or longer, and can gradually disappear on its own if no exposure to the allergen is prolonged. ②Excitation stage: refers to the stage when the same allergen re-enters the body, through specific binding with the antibodies on the surface of sensitized mast cells and basophil granulocytes, the cells release bioactive mediators. At this stage, the release of bioactive media in addition to histamine, can also be prostaglandin D, leukotriene, platelet activating factor, etc..And their effects are similar, can cause smooth muscle contraction, capillary enlargement and permeability enhancement, gland secretion increase. ③Effect stage: refers to the stage in which the biological active medium acts on the effect tissues and organs, causing local or systemic allergic reactions. According to the speed and duration of the reaction, there are two types of early reaction and late reaction. The early stage reaction is mainly caused by histamine, which usually occurs within seconds of exposure to the allergen and lasts for several hours. The late stage reaction is caused by leukotrienes, platelet activating factors, etc., which occurs 6-12 h after the allergen stimulation and lasts for several days.

Allergic reactions begin with exposure of the skin and mucosal surfaces to the allergen, leading to activation of the characteristic immune pathway, initially by activating mast cells or by the release of intrinsic molecules such as Interleukin-33（IL-33） from damaged epithelial cells.IL-33plays an important role in initiating allergic reactions as an alarm signal. This form of allergy is closely related to Th2-like reactions and involves the production of cytokines such as Interleukin-4（IL-4）, Interleukin-5（IL-5）, and Interleukin-13（IL-13）.IL-4 and IL-13 are key cytokines in Th2-like reactions，because they induce isotropic conversion of antibodies from Immunoglobulin G (IgG) to IgE[31]. Allergic reactions caused by Th2-like is further characterized by the production of IgE. With the increase of eosinophilic granulocyte, the sensitization of leukocyte, in the case of mast cells andbasophilic granulocyte, causes the release of large amounts of mediators upon further exposure to the allergen, leading to allergy.

### 2.2.2 Type IV hypersensitivity

Type IV hypersensitivity is a T-cell-mediated hypersensitivity reaction，also known as delayed anaphylaxis[32]. The allergen that causes T-cell-mediated allergic immune response is usually low-molecule-weight substances. Obvious allergic Contact Stomatitis (ACS) can occur only after repeated exposure to allergen with sub threshold concentration. This is because each exposure is insufficient to produce signs and symptoms of allergy. As a result, it may take weeks or months of repeated allergen exposure before an allergic reaction occurs[33].

### 2.3 Clinical manifestations of allergic reactions

Type I hypersensitivity is present in the mouth and perioral areas, mainly with angioneurotic edema, but sometimes with oral paresthesia and burning, lichenoid inflammatory changes, or oral ulcers[34]. However, there are also some patients with burning symptoms and paresthesia, but no obvious clinical signs. The clinical presentation of a delayed allergic reaction, such as contact stomatitis, depends on the nature, potency, and concentration of the allergen, as well as the duration of exposure. Symptoms disappear only after removal or

withdrawal of allergens, and the main clinical manifestations include mucosal burning, pain, dryness, nonspecific stomatitis, cheilitis, and swelling of the lips[33, 35, 36].

## 3. Summary

At present, it is known that the main reason of dental composite resin causing local inflammatory reaction and allergic reaction is the monomer residue in the polymerization process of composite resin and the leaching of monomer after the polymerization of resin. The residual amount of monomer is closely related to the degree of conversion of resin, and the leaching of monomer after polymerization is closely related to the properties and molecular size of monomer. The monomer residue can be reduced by improving the conversion rate of resin[37], which can reduce the residual exudation of monomer, reduce the inflammation and sensitization of resin. The methods to improve the conversion efficiency of resin are as follows: changing the properties of monomer; selecting a matching photo initiation system which includes appropriate photoinitiator and concentration, and photocuring lamp to match the photoinitiator. In addition, for some allergic patients themselves, anaphylaxis prevention is more important than treatment, enhance their immunity, and avoid contact with allergens as much as possible.

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