Are the Materials We Use Biologically Compatible with Our Patients?

Optimal prosthodontic management requires insightful diagnostics, accurate restorative techniques, technologically advanced dental materials and aggressive maintenance, along with a detailed comprehension of biological processes underlying complex treatment objectives. A thorough understanding of the biologic impact of new dental materials is essential to the health and longevity of oral rehabilitations. A closer look at the biocompatibility of denture base resins, popular dental ceramics, titanium alloys, luting cements and composite restorative resins is needed. The potential for adverse biologic consequences related to all of these materials is worthy of consideration before application. This issue of Prosthodontics Newsletter reviews studies to help practitioners decide which materials should be considered.

Cytotoxicity of Denture Base and Hard Reline Materials

Allergic reactions and chemical irritation caused by denture base materials most frequently manifest themselves as a burning sensation in the mouth, primarily in the palatal mucosa in direct contact with maxillary dentures. The tongue, oral mucosa and oropharynx may also be affected. Typically, the main clinical signs are redness, swelling and pain in the oral mucosa, vesicles and ulcerations, and labial edema. Both acute ulceration and chronic urticaria have also been reported.

Chaves et al from São Paulo State University, Brazil, conducted a systematic review of the published literature concerning the cytotoxicity of denture base and hard reline materials. They searched the MEDLINE, Google Scholar and Scopus databases for English-language articles published in peer-reviewed journals from 1979 through 2009 with assays that monitored the cytotoxic effects of the tested materials. Twenty articles met the inclusion criteria and qualified for analysis.

The materials evaluated in the studies fell into 5 major categories:

- **Heat-polymerized acrylic resins**: When processed in a water bath, these resins caused low cell death, with no signifi- (continued on next page)
Cytotoxicity of Denture Base and Hard Reline Materials
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Significant differences in cytotoxicity among the various brands.

➤ Microwave acrylic resins: These showed effects similar to those of heat-polymerized acrylic resins on cell viability and proliferation, and were rated as slightly or not cytotoxic.

➤ Autopolymerizing acrylic resins: Cytotoxicity in these materials varied, suggesting differences between brands.

➤ Light-polymerized acrylic resins: The few studies that included these resins demonstrated a trend toward similar or lower cytotoxicity than that of heat-polymerized resins.

➤ Hard chairside reliners: Several studies reported higher levels of cytotoxicity for relines materials than denture bases.

Comment
Because of the large number of variables among the included studies, no definitive conclusion could be reached. However, there appears to be some evidence that heat-polymerized resins produce lower cytotoxic effects than do light-polymerized or dual-polymerized reliner resins.


Epithelial Cell Response to Newer Restorative Materials
Several restorative materials introduced in the past 2 decades provided excellent esthetic results, but the biologic response to some of these materials has not been fully tested. For example, while studies have shown that human epithelial cells do not attach as strongly to rough surfaces (e.g., acid-etched or sandblasted) as they do to smooth surfaces, little is known about how well epithelial cells adhere to and grow on these newer restorative materials.

Forster et al from the University of Szeged, Hungary, conducted an in vitro study to measure human epithelial cell attachment and proliferation on 3 restorative materials:

➤ lithium disilicate
➤ yttrium-modified zirconium dioxide (zirconia)
➤ cobalt–chromium alloy

The researchers measured 20 sample discs of each material by scanning electronic microscopy and atomic force microscopy for surface roughness; energy-dispersive x-ray spectroscopy was used to determine chemical composition. Cultured human epithelial cells were grown on the discs and on a plastic control plate for 24 or 72 hours.

The cobalt–chromium discs were significantly smoother than the lithium–disilicate discs, which were, in turn, significantly smoother than the zirconia discs. At 24 hours, the 3 materials showed similar levels of epithelial attachment, although all had significantly lower levels of attachment than that shown on the control plate. The number of epithelial cells increased significantly at 72 hours for all 3 restorative materials; levels of cell proliferation were similar, although the zirconia proved to be the least biocompatible of the materials.

Comment
All 3 tested materials demonstrated acceptable levels of epithelial cell attachment and proliferation; all 3 can be considered possible choices for dental restorations with a subgingival profile.


Allergic Reaction To Titanium Restorations
Because of its superior corrosion resistance, lack of toxicity and acceptance by the body, titanium has been a preferred material for surgical implements and implants such as joint replacements since the 1970s. In dentistry, titanium is used for implants and as a substitute metal for restorations in patients with metal allergies. However, some cases of sensitization to titanium have been reported.

Ko et al from the Osaka University Graduate School of Dentistry, Japan, reported on a 33-year-old woman with a 10-year history of pruritus of the fingers with redness...
and eczema. Lymphocyte stimulation testing (LST) revealed allergies to mercury, nickel and silver but not to gold, palladium, indium and titanium. They removed multiple dental restorations containing mercury or silver.

After 2 months, the pruritus improved. One month later, the restorations were replaced with ones made of 99.6% titanium.

Nine months after the titanium restorations were placed, the patient developed cervical eczema that gradually worsened. LST showed a significant allergic reaction to titanium. The titanium restorations were removed and replaced with resin restorations. The eczema resolved within 3 months and has not recurred for >5 years.

**Comment**

This patient appeared to develop a sensitivity to titanium only after receiving titanium dental restorations. Studies have shown that titanium ions dissolve more than expected under certain conditions, and that topical fluoride solutions can cause stress corrosion cracking in titanium.

While reports of allergic reactions to titanium dental restorations have been rare, the incidence is likely to increase as titanium is more widely used as a substitute for precious metal restorations. Dental practitioners need to be aware that the potential exists for patients to develop titanium allergies.


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**Cytotoxicity of Luting Resin Cements**

Besides cementing ceramic crowns to the prepared tooth surface, luting cement also protects the exposed dentin and pulpal tissues from thermal, mechanical and microbial effects. Resin cements create a high-level tensile bond with lower oral solubility and higher micromechanical bonding. However, luting resin cements have their drawbacks. Studies report allergic reactions among patients, dentists and dental assistants ranging from 0.7% to 2%. While some elements of the resins have demonstrated cytotoxic effects on fibroblastic cells in vitro, cytotoxicity studies of luting resin cements are limited.

Malkoç et al from Inonu University, Turkey, conducted an in vitro study of 3 resin cements: Super-Bond C&B (Sun Medical Co., Shiga, Japan), a self-cured cement made of 4-META/MMA-TBB (4-methacryloyloxyethyl trimellitate/methyl methacrylate-tri-n-butylborane), and 2 dual-cured cements, RelyX ARC (3M ESPE, St. Paul, MN) and Clearfil Esthetic (Kuraray Medical, Inc., Okayama, Japan), made of bisphenol A-glycidyl methacrylate (Bis-GMA), triethylene glycol dimethacrylate (TEGDMA) and/or urethane dimethacrylate (UDMA). Residual monomer or cytotoxic substances were extracted from 12 specimens of each cement and combined with prepared cell cultures. Cell survival in the resin cement groups was compared with survival in an untreated culture medium.

The dual-cured cements showed significantly higher cytotoxicity than the self-cured cement. After 24 hours, cell viability was 55.64% for Clearfil Esthetic, 62.63% for RelyX ARC and 72.75% for Super-Bond C&B, significantly more cytotoxic than the control ($p < .001$; Figure 1).

**Comment**

While Bis-GMA has greater difficulty penetrating and has less mobility, it is the most toxic of the monomers, producing methacrylic acid after undergoing hydrolysis. TEGDMA is water-soluble, which may make it more likely to penetrate thin dentin and diffuse to the pulp up to several days after placement. The type of polymerization used with each cement may also have an impact on its cytotoxicity. Studies focusing on long-term biologic effects of luting resin cements are needed.

Cytotoxicity of Dental Resin Components

Although recent years have seen the development of a large variety of new resin dental restorative materials, little work has been done to improve the resinous matrix of these materials. Most of these matrices consist of:

- A mixture of various methacrylate monomers such as bisphenol A-glycidyl dimethacrylate (BisGMA) and urethane dimethacrylate (UDMA)
- Lower-viscosity comonomers such as triethylene glycol dimethacrylate (TEGDMA), tetraethyleneglycol dimethacrylate (TEEGDMA), neopentyl glycol dimethacrylate (Neopen) and diethyleneglycol dimethacrylate (DEGDMA)
- Initiators such as diphenyliodonium chloride (DPIC), camphorquinone, benzoyl peroxide, diethylaminomethyl methacrylate and dimethyl-para-toluidine
- Contaminants such as triphenylstibane (TPSB) and triphenylphosphane (TPP)

Not only can unpolymerized and leached monomers/copolymers induce mutagenic/carcinogenic effects in cells, but they also have the potential to increase the levels of reactive oxygen species, which can induce adverse toxic effects.

Shehata et al from Ludwig Maximilians University of Munich, Germany, studied the cytotoxicity, induction of DNA double-strand breaks (DNA DSBs) and possible cell death via apoptosis and necrosis in human gingival fibroblasts (HGFs) for the initiator DPIC, the contaminants TTP and TPSB, and the comonomers TEEGDMA and Neopen. To determine the half-maximum effect concentrations (EC_{50}) for cell viability and DNA DSBs, the tetrazolium salt XTT (sodium 30-[1-(phenylaminocarbonyl)-3,4-tetrazolium]-bis(4-methoxy-6-nitro) benzene sulfonic acid hydrate) cell viability assay was used.

All substances induced a dose-dependent loss of HGFs after 24 hours. Based on EC_{50} values, DPIC had the highest toxicity; TEEGDMA had the lowest toxicity (Table 1). DPIC created the highest levels of DNA DSBs, while exposure to TEEGDMA and TPSB evoked the lowest levels; the number of breaks was dose-dependent for all substances. Results for the presence of multifoci cells (cells containing >40 foci each), apoptotic cells and necrotic cells were similar.

**Comment**

All 5 resin-based dental materials tested demonstrated the power to induce DNA DSBs and cell death in primary human oral cells. The extent to which these materials affect the regulation of cell processes in clinical settings needs to be examined.


### Table 1. The EC_{50} values (mM; mean ± SEM; n = 5) of the tested substances and their relative toxicities in HGFs as determined by XTT viability assay

<table>
<thead>
<tr>
<th>Substance</th>
<th>EC_{50} ± SEM (mM)</th>
<th>Relative toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEEGDMA</td>
<td>4.10 ± 0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>TTP^{a}</td>
<td>2.40 ± 0.2</td>
<td>1.7</td>
</tr>
<tr>
<td>TPSB^{a}</td>
<td>1.80 ± 0.2</td>
<td>2.27</td>
</tr>
<tr>
<td>Neopen^{b}</td>
<td>1.10 ± 0.1</td>
<td>3.72</td>
</tr>
<tr>
<td>DPIC^{c}</td>
<td>0.90 ± 0.1</td>
<td>4.55</td>
</tr>
</tbody>
</table>

^{a}Significantly different (p < .05) from TEEGDMA. ^{b}Significantly different (p < .05) from TEEGDMA.

In the Next Issue

Esthetics and modern removable prosthodontic restorations

Our next report features a discussion of these issues and the studies that analyze them, as well as other articles exploring topics of vital interest to you as a practitioner.

Do you or your staff have any questions or comments about Prosthodontics Newsletter? Please write or call our office. We would be happy to hear from you.

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