Metal Allergies, Genetic Susceptibility to Mercury, and Toxic Dental Materials Other than Mercury

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2014

What every dentist needs to know about metal allergies

There is no question that patients can be allergic to dental materials used in their mouth, and even the American Dental Association recognizes this health complication.[1] While allergic reactions have been reported to a wide-range of products including acrylic resin, resin composite, impression materials, and eugenol-containing products,[2] the issue of allergies to dental metals is an area of growing concern. A 2011 article by Hosoki and Nishigawa explains why dentists should be educated about this possible side effect: "Current data indicate that practicing dentists need to obtain further specialized knowledge about dental metal allergy in order to ensure the correct treatment of patients in their clinics."[3]

There are a variety of estimates as to how many patients suffer from allergies to dental metals. A 1993 study by Inoue reported that 3.9% of healthy subjects tested positive for metal reactions.[4] If this figure is applied to the current US population,[5] this would mean that dental metal allergies potentially impact as many as 12.4 million Americans. Yet, the figure could be even higher because more recent studies and reports tend to agree that dental metal allergies are on the rise.[6] [7] A 2007 article in *Nature* specifically warns of reactions in dental patients wearing braces and goes on to describe a study from Singapore that found nickel allergies increased from 14% in 1984 to 20% in 2003.[8]

Nickel allergies have received a great deal of attention due to their prevalence. Research has demonstrated that approximately 10% of women and 1-2% of men are allergic to this metal.[9] [10] Because of the high number of female patients potentially impacted, nickel has been considered by some to be the dental material most likely to cause allergic reactions in American women.[11]

A number of other dental metals are also known to cause problems for sensitive and allergic patients. The first case of report of dental metal allergies offered clinically was in 1928 due to the mercury in amalgam fillings.[12] Since that time, in addition to mercury and nickel, allergies have been documented for dental metals such as titanium, gold, chromium, platinum, cobalt, tin, beryllium, and cadmium. Typically, reactions occur in the mouth, but they can also occur on the hands, feet, and other parts of the body.[13]

Researchers are currently delving deeper into understanding the complex factors that lead to the development of metal allergies. Genetics are one variable being studied,[14] [15] [16] [17] and some researchers predict that specific genotypes will be correlated with adverse immune responses to metals.[18] Additionally, there is an overall consensus that T-cells in the immune system trigger the negative reactions.

Furthermore, ionization of metals appears to play a major role in allergies. While a "stable" metal is generally regarded as non-reactive, if ionization of the metal occurs, this can cause an allergic response. In the oral cavity, ionization can result from pH changes initiated by saliva and diet.[19] The electrolytic conditions can also cause corrosion of the dental metals and generate electrical currents in a phenomenon known as oral galvanism.[20] Not surprisingly, oral galvanism has likewise been established as a factor in sensitivities to dental metals.[21 22 23 24]

Researchers at Tohoku University in Japan are also exploring the role of molecules known as lipopolysaccharides in metal allergies. Dr. Endo and his team theorize that lipopolysaccharides in bacteria can cause an allergic reaction to metals, as Endo described in a 2008 article in *Nature*: "'If people come in contact with a metal during infection, I speculate that this could lead them to develop metal allergies later in life.'"[25]

Nature reporter Matt Kaplan went on to explain this concept, "This implies that a complex made of lipopolysaccharides and nickel may be the thing that triggers the immune system, which then becomes sensitive to any kind of lipopolysaccharide-metal complex. If so, then wearing a nickel bracelet during an infection may predispose you to a silver allergy later in life."[26]

Indeed, jewelry has been mentioned as part of the reason dental metal allergies are increasing. In their 2011 article, Hosoki and Nishigawa explain that the growing popularity of ear piercing since the 1990's could be part of the cause for the rise in dental metal allergies.[27] This is because being exposed to a metal increases the chance for the allergy to develop, so the current body piercing trend could mean that even more allergies are occurring. In fact, Hosoki and Nishigawa cite a study by Jensen purporting that after Denmark imposed nickel regulations, there was a decline in nickel sensitivities among Danish girls who had pierced ears.[28]

However, one issue with calculating the number of patients with a negative reaction to a metallic material is that the onset of symptoms can be delayed and therefore might not be associated with the exposure. Hosoki and Nishigawa have noted that a minimum of one week is necessary to assess metal allergy test results, and research by Djerassi and Berova about amalgam allergies warns, "Sensitization appears most frequently after the amalgam has been present in the mouth for more than 5 years."[29]

Another issue is the wide-range of symptoms patients allergic to dental metals can exhibit. The most commonly reported side effects from a dental metal allergy include pustulosis palmaris and dyshidrotic eczema (usually in the form of erythema, blisters, and scaly and crusty skin), lichen planus (usually in the form of spots on the skin), glossodynia (usually in the form of pain or burning of the tongue), generalized eczema and pseudoatopic dermatitis (usually in the form of an itching rash), and atopic dermatitis (chronic eczema with itching).[30]

Yet, a gamut of other health conditions has also been linked to dental metal allergies. These include oral lichenoid lesions,[31 32 33 34] autoimmunity,[35 36] chronic fatigue syndrome,[37 38 39] multiple chemical sensitivities,[40 41] metallic pigmentation,[42] myalgic encephalitis,[43] orofacial granulomatosis,[44] fibromyalgia,[45] multiple sclerosis,[46] and even infertility in both women and men.[47]

Moreover, a 2006 study of patients diagnosed with intraoral squamous cell carcinoma found that dental metal allergies are a potential factor for this type of cancer.[48] A summary of the researchers' results explains this serious health risk: "Ten patients (91%) had positive patch tests to metals. In eight (73%), the oral cancer was adjacent to a dental restoration containing a metal to which the patient was allergic. Prevalence of gold, mercury, silver, and copper allergy among these patients was substantially higher than that reported in the available worldwide patch-test clinic population."[49]

In addition to patients exhibiting allergic responses to dental metals placed in their mouths, research has also shown that dental personnel working with these metals are at risk for developing metal allergies. This includes dentists,[50] dental technicians,[51] and dental students.[52] [53] While the researchers of one of these studies did not consider their results to be significant, their data correlated dental students' allergies to mercury with the number of their own amalgam fillings.[54]

In the past, testing for allergies was most often conducted by skin patch testing. The method is still commonly used today, but because it requires applying the potential allergen to the skin, and some people might be highly reactive to such an application, there is controversy about this technique.[55] Another problem with skin patch testing is evaluating what constitutes an allergic reaction since there are such a wide variety of symptoms[56] and since the onset of these symptoms can be delayed. Patch testing detects type 1, immediate hypersensitivity, and many symptoms of immune reaction to metals are a result of type IV, delayed hypersensitivity.

One relatively new alternative to skin patch testing is known as the Lymphocyte Transformation Test (LTT), which was first used in the 1960s to evaluate certain types of antigens. In 1994, Stejskal introduced the MELISA test, a modified version of the LLT designed to test for type IV delayed hypersensitivity to metals, including sensitivity to mercury.[57] This blood test is gaining popularity because it does not expose patients to the same materials that could be making them ill.

Another option for testing has been created specifically for dental materials. If this biological testing is used, a patient's blood sample is sent to a laboratory where the serum is evaluated for the presence of IgG and IgM antibodies to the chemical ingredients used in dental products.[58] The patient is then provided with a detailed list of which name-brand dental materials are safe for their use and which ones could result in a reaction. Two labs that currently offer this service are Clifford Consulting and Research[59] and Biocomp Laboratories.[60]

As far as recovery from symptoms related to dental metal allergies, there is promising research that suggests in some cases, patients improve or are cured of their reactions after removal of the material suspected to be causing the allergy. Conditions reportedly improved and cured as a result of removing dental metal allergens include eczema,[61] dermatitis,[62] [63] chronic fatigue syndrome,[64] multiple sclerosis,[65] orofacial granulomatosis,[66] oral lichen planus,[67] [68] [69] and oral lichenoid lesion.[70] [71] [72] In their 2011 report, Hosoki and Nishigawa suggest, "In principle, all restorations with allergy-positive metal elements need to be removed."[73]

It is important to note here that removal of any metallic dental material requires a number of precautions. For example, Hosoki and Nishigawa provide recommendations for prioritizing which dental materials should be removed first, as well as advice for being very careful of metal dust exposures and the use of a patient dam during the removal process. The IAOMT has also created a safe protocol for removal of amalgam fillings, including the use of masks, cold water irrigation, high volume suction, and other protective techniques. (The IAOMT's safe protocol is the subject of Unit 2 in this Accreditation Program.)

It's in the genes: reactions to dental amalgam mercury

Evaluating a person's genetic traits as a risk of disease is a relatively new discovery. Probably the most well-known example of this is testing for the BRCA gene mutation to identify those at high risk for breast cancer. This type of genetic testing has received publicity in recent years, especially last year when actress Angelina Jolie opted for a mastectomy rather than taking a chance on her genetic potential for developing breast cancer.[74]

While much of the medical community and general public have not yet embraced the concept of genetic susceptibility, science is showing that, like breast cancer, issues with mercury can be traced to certain genetic traits.[75] Although this innovation has been slow to be heeded and accepted on a wide-scale basis, it offers an exciting possibility for finding new methods to prevent a number of incurable diseases.

Perhaps the easiest way of understanding this concept as it relates to dental mercury is simply by considering a commonly-used argument to defend the use of amalgam fillings: Only some people claim to have a horrible reaction to dental mercury, but others appear to be healthy. If you think about such a statement, it actually sheds light on the factor of genetic susceptibility: Certain people have negative responses to dental amalgam because they are genetically predisposed.

In work headed by Dr. Diana Echeverria and colleagues at the Battelle Centers for Public Health and Education in Seattle, an association was demonstrated between a specific genetic marker, dental mercury, and neurobehavioral parameters.[76] The marker, a polymorphism in a gene called CPOX4 (for coproporphyrinogen oxidase, exon 4), was linked to decreased visuomotor speed in response to mercury exposure and indicators of depression in dental professionals. Echeverria's work has also pointed toward a link between the BDNF gene (brain-derived neurotropic factor) and mercury susceptibility.[77]

Furthermore, the CPOX4 genetic marker was identified as a factor for neurobehavioral issues in a study of children with dental amalgam tooth restorations by Dr. James Woods, Dr. Diana Echeverria, and others. The researchers noted, "…among boys, numerous significant interaction effects between CPOX4 and Hg [mercury] were observed spanning all 5 domains of neurobehavioral performance…These findings are the first to demonstrate genetic susceptibility to the adverse neurobehavioral effects of Hg [mercury] exposure in children."[78]

Another area of genetic susceptibility that has merited scientific attention in relation to dental mercury is the APO-E4 (Apo-lipoprotein E4) genotype. A 2006 study found a correlation

between individuals with APO-E4 and chronic mercury toxicity.[79] The same study found that removal of dental amalgam fillings resulted in "significant symptom reduction," and one of the symptoms listed was memory loss.

The APO-E4 genotype has also been associated with a higher risk for Alzheimer's disease.[80] [81] [82] One study notes, "The increased AD [Alzheimer's disease] risk through APO E4 might be caused by its reduced ability to bind heavy metals. Latest therapeutic approaches to the treatment of Alzheimer disease embrace pharmaceuticals which remove or bind metals from the brain."[83]

Notably, one study, which found a connection between number of mercury fillings and neurotoxic effects for those with APOE genotype, explains, "Apo-E genotyping warrants investigation as a clinically useful biomarker for those at increased risk of neuropathology, including AD [Alzheimer's disease], when subjected to long-term mercury exposures…An opportunity could now exist for primary health practitioners to help identify those at greater risk and possibly forestall subsequent neurological deterioration."[84]

Research has also shown that dental mercury fillings can potentially play a role in immune system problems for genetically predisposed patients. Whereas animal studies have established a connection between dental mercury and autoimmunity,[85] [86] human studies have confirmed that genetic susceptibility to reactions from dental mercury is potentially related to chronic fatigue syndrome,[87] and multiple sclerosis, rheumatoid arthritis, and amyotrophic lateral sclerosis.[88]

Furthermore, scientific data has linked mercury and genetic traits to chemical sensitivities,[89] autism,[90] [91] and Kawasaki's disease,[92] and research has also suggested that genetic transporters could be involved in the toxicokinetics of mercury.[93]

Yet, even with the recognition that genetic susceptibility plays a role in reactions to dental amalgam, research warns that there are most likely a variety of other factors tied into health risks of mercury as well. In addition to genetic predisposition, the number of amalgam fillings in the mouth,[94] [95] [96] [97] [98] [99] [100] [101] [102] [103] [104] [105] [106] gender,[107] [108] [109] [110] [111] [112] dental plaque,[113] selenium levels,[114] exposure to lead,[115] [116] [117] [118] consumption of milk[119] [120] or alcohol,[121] and other circumstances[122] can play a role in each person's unique response to mercury.

One of the most promising aspects of this new multi-factorial research in relation to health risks from dental amalgam is that this perspective offers science an opportunity to re-evaluate many diseases that are currently not well understood. It also demonstrates that research which fails to take into account variables such as genetic susceptibility is missing a major piece of the puzzle required to accurately assess health risks, prevention, treatment, and potential cures.

Old habits die hard: the continued use of arsenic and lead in dentistry

Less than thirty years ago, most food packaging did not include a list of ingredients and nutritional facts. However, consumers and other groups demanded this information be disclosed, and in 1990, food labeling became a requirement by the United States Food and Drug Administration (FDA).[123] Yet, even before this legislation was passed, Ulf Bengtsson, a research engineer at Linköping University in Sweden, had been working to accomplish this type

of open disclosure for dental products, and his years of analyzing the issue have produced many reasons why detailed ingredient lists of dental materials for medical professionals and consumers are essential.

In 1990, Bengtsson wrote an article about the toxic composition of some endodontic materials,[124] and his report attracted publicity from the Swedish press. Most people were not aware that for many decades, arsenic and other poisons were commonly used for dental treatments, and they were likewise shocked that Bengtsson suggested the materials were sometimes still being used. After his paper received attention and discussion, Bengtsson says that health authorities assured him the harmful ingredients had been removed from practice.

Yet, in January 2014, Bengtsson once again discovered that outdated, poisonous dental materials were easily available. For example, the catalogue of a Swiss company named Produits Dentaires,[125] which has distributors in the United States,[126] included a number of such items. At least one item, Devitec AS, was removed from their online catalogue in early 2014, although it could still be on the shelf of dealers and dentists. At any extent, a further search of the internet in 2014 produced additional manufacturers selling toxic dental products of the past.[127] [128] [129] [130]

Arsenic and other poisonous endodontic treatments

When Shearjashup Spooner endorsed the use of arsenic for killing pulp as part of endodontic treatments in 1836,[131] the practice became accepted in dentistry. Arsenic is now known to be carcinogenic[132] and is one of WHO's "10 chemicals of major public health concern" due to its toxicity.[133] A 1974 article published in *Oral Surgery*, *Oral Medicine*, *Oral Pathology, and Oral Radiology* described the historical use of arsenic and other noxious chemicals in root canal treatment:

> Highly irritating caustic chemicals such as sulfuric acid, phenosulfonic acid and hydrochloric acid were used as adjuncts in enlarging root canals. Additionally, chemicals such as formocresol, phenol, camphorated chlorphenol, eugenol and ammoniated silver nitrate solution were used as intracanal medicaments. Pulp mummification was performed by first placing arsenic and then using paraformaldehyde over the dead pulp tissue. Root canals were filled with cotton moistened with creosote, tricresol-formalin, or an essential oil such as Blacks 1,2,3 or oil of cinnamon or cassia. In other cases, canals were filled with gutta-percha and a paste to which thymoliodide was added.[134]

The use of arsenic in dentistry drastically declined as the twentieth century progressed, especially after complications and cases of bone necrosis were reported. That being said, for obvious reasons, Bengtsson was frustrated in 2014 to find again that these antiquated products were still being sold, usually without warning to the dentist or disclosure to the patient.

Unfortunately, research has confirmed Bengtsson's concern, and a 2013 study from Italy featured a case study of a patient who had been treated with arsenic in 2012.[135] Demonstrating the dangerous fact that this product is still being allowed and applied, the researchers conclude,

"Arsenic compounds cause severe consequence and should not be used in endodontic practice."[136]

Additionally, an April 2014 press release from the European Medicines Agency (EMA) suggested revoking the marketing authorizations for two dental arsenic-containing products. Specifically, the EMA release states:

> In a review of the benefits and risks of these dental products, analyses of data from laboratory and population studies indicate that the arsenic contained in them may pose a risk of genotoxic effects that could increase the risk of cancer. In addition, there have been a small number of cases where arsenic is thought to have leaked into the areas around the teeth, causing parts of the tissue to die, including bone (osteonecrosis).[137]

Lead in crowns, bridges, and dentures

One way lead was used in past dental practices was for endodontic treatments developed by Pierre Fauchard in 1728[138] and Leonard Koecker in 1820.[139] Since then, lead has been removed from paints and other products because of its known hazards to the nervous system, kidneys, and reproductive system.[140] However, a 2008 news story by Lee Howard of *The Day* identified the issue of modern dental materials being contaminated with lead.[141]

Howard's article mentioned an Ohio woman who had help from her local TV station in discovering that her negative response to a dental bridge, manufactured in China, could have been caused by the fact it had lead in it, as did a number of other dental crowns that were eventually tested.[142]

Similar to Bengtsson's concerns about the simplicity of ordering toxic products from companies around the globe, Howard's report offered an estimate given from one of the directors of the National Association of Dental Laboratories about dental materials shipped to the US: "'…about 15 to 20% of all crowns, bridges, and dentures in the United States are now manufactured offshore – and the percentage is rising every year.'"[143]

These statistics and examples offer evidence as to why dentists and consumers need to be aware of the ingredients used to create crowns, bridges, and dentures, especially if they are being constructed in countries that might not have the same safety standards as the United States.

Other poisonous dental products

In addition to arsenic, lead, and endodontic materials such as creosote, cresol, paraformaldehyde, and phenol, Bengtsson is also concerned about the continued use of other poisonous dental products including old copper amalgams, radioactive compounds in dental materials, and formocresol in children.

Furthermore, he is concerned about how the common use of toxic dental products in the past can still be impacting people's health today. For example, asbestos was used in periodontal dressings beginning in 1923.[144] According to the United States Occupational Safety and Health

Administration (OSHA), asbestos is a group of minerals used in products to "resist heat and corrosion."[145] OSHA also states, "The inhalation of asbestos fibers by workers can cause serious diseases of the lungs and other organs that may not appear until years after the exposure has occurred."[146]

A 2009 investigation published in the *British Dental Journal* reported that asbestos-containing periodontal dressing was still regularly being used in the 1970's:

> In 1976, the American Dental Association Council on Dental Therapeutics took the decision to no longer accept these products, although producing a statement that 'there is no apparent health danger from inhalation to patients for whom asbestos containing periodontal dressings are used since the fibres cannot be appreciably released from the dressings whilst they are mixed and applied.' At that time, the article goes on to conclude, there were only 'several commercially available preparations on the market' which did not contain asbestos.[147]

The same 2009 investigation revealed that even in 1991, it was not unusual for students at dental schools to cast dentures, some of which were done using asbestos fiber. The researchers warn, "It follows that if it takes 35 to 40 years for symptoms to materialise, then many dentists, dental assistants and technicians may well become symptomatic with respiratory problems now that maybe attributable to using these powders and rolls in the past."[148]

Indeed, there have been reports of dentists suffering from asbestos illness such as mesothelioma, and researchers have suggested that this could be related to the presence of asbestos in periodontal dressings. [149]

Next steps

Bengtsson continues to evaluate and collect information about harmful practices of the past, as well as toxic ingredients used today such as the mercury in dental amalgam. A portion of his research has been conducted by using patents and scientific articles written about different dental products and procedures since he reports that finding information about the ingredients from other sources has been imprecise and of poor quality.[150]

In some ways, Bengtsson's work was validated by a November 2013 policy paper from the Council of European Dentists. The paper acknowledges that the signing of the United Nations Environmental Programme's "Minamata Convention on Mercury" has encouraged the phase-down of dental mercury, and it also includes a statement about the need for evaluating alternative materials. Two areas included in this statement can be applied to listing the ingredients of dental products:

- The first one states, "The profession urges manufacturers to fully declare the chemical composition of the alternative materials."[151]
- The second one establishes, "In the best interest of the patient, dental professionals should consider not choosing to use a material where the manufacturer has not made a full qualitative declaration of its chemical composition."[152]

Bengtsson suggests this same policy be applied to *all* dental materials, even ones that are supposedly not being used anymore. He explains, "When the National Board of Health and Welfare [Sweden] said the products I mentioned were removed from use some years ago, I argued that is not relevant. What is, however, is if there are patients out there who still have these materials in their bodies or were exposed to them. This means it could be argued that materials used at least 80 years ago are still relevant."

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