IAOMT ACCREDITATION--
Checklist for Completing Unit 4: Clinical Nutrition and Heavy Metal Detoxification for Biological Dentistry

INTRODUCTION TO UNIT 4

☐ Take the Unit 4 Pre-test. Click here to go to page 3.

☐ Read the “Clinical Nutrition for Biological Dentistry” article by Rehme.
  Click here to go to pages 4-19.

REQUIRED (MANDATORY) CONTENT OF UNIT 4

☐ Read the “Relationship between Vitamin D and Periodontal Pathology” article by Jagelaviciene et al.
  Click here to go to pages 20-27.

☐ View the IAOMT online learning video activity “Nutrition in Dentistry” at https://iaomt.org/nutrition-dentistry-video-activity.
  Click here to go to page 28.

☐ Read the “A Hypothetical Role for Vitamin K2 in the Endocrine and Exocrine Aspects of Dental Caries” article by Southward.
  Click here to go to pages 29-33.

☐ Read the “Heavy Metal Detoxification for Biological Dentistry” article by Kall and Just. Click here to go to pages 34-43.

☐ View the IAOMT online learning video activity “Mercury Detoxification” at https://iaomt.org/mercury-detoxification-video-activity.
  Click here to go to page 44.

Continued on next page...
Read “Chelation Therapy to Prevent Diabetes-associated Cardiovascular Events” by Diaz et al. article.
Click here to go to pages 45-61.

Read the “Integrative Medicine Approach To Peripheral Neuropathy-Avoiding Pitfalls Of Ineffective Current Standards In Assessing Chronic Low-Grade Mercury Toxicity And Functional Musculoskeletal Lesions” article by Carter et al.
Click here to go to pages 62-68.

TEST FOR UNIT 4

Take the Post-Test for Unit 4 at https://www.cvent.com/d/pvq54h.
Click here to go to page 69.

If you are interested in learning more about any of the topics in this unit, explore the readings in the OPTIONAL Unit 4 PDF file. *Note that these are not required materials.*

Continue on to Unit 5!
Click here to go to https://iaomt.org/accreditation-materials/.

Record of Unit 4 Updates---
1/2020: “Dental Diseases and Oral Health” article by the World Health Organization (removed from Introduction); “Clinical Nutrition for Biological Dentistry” article by Rehme (moved to Introduction); “[On the proposition that] a Clean Tooth Does Not Decay and that Mouth Cleanliness Affords the Best Known Protection Against Dental Caries” article by Price (moved to Optional to make room for new research); “Relationship of Fluid Transport through the Dentin to the Incidence of Dental Caries” study by Steinman and Leonora (moved to Optional to make room for new research); Online Learning Videos for “Nutrition in Dentistry” and “Mercury Detoxification” (revised for new formatting); “Relationship between Vitamin D and Periodontal Pathology” article by Jagelaviciene et al. (added new research); “A Hypothetical Role for Vitamin K2 in the Endocrine and Exocrine Aspects of Dental Caries” article by Southward (added new research); “Heavy Metal Detoxification for Biological Dentistry” article by Kall and Just (updated with 2019 version); “Chelation: Harnessing and Enhancing Heavy Metal Detoxification” review by Sears (moved to Optional to make room for new research); “Chelation Therapy to Prevent Diabetes-associated Cardiovascular Events” by Diaz et al. article (added new research); “Integrative Medicine Approach To Peripheral Neuropathy-Avoiding Pitfalls Of Ineffective Current Standards In Assessing Chronic Low-Grade Mercury Toxicity And Functional Musculoskeletal Lesions” article by Carter et al. (added new research); Unit 4 Test (revised all test questions to incorporate new materials)
PRE-TEST FOR UNIT 4 TO BE TAKEN BEFORE STUDYING CLINICAL NUTRITION AND HEAVY METAL DETOXIFICATION FOR THE BIOLOGICAL DENTIST

*This is a pre-test, and the results are for your records only. You are not expected to know the answers since you have not studied this material yet. The pre-test is simply designed to assist you in recognizing some of the important information that will be presented in this unit. There is no time limit for this test. Choose the option that BEST answers each question.

1. Understanding how diet relates to teeth is a concept only explored in the past few decades.
   A. True
   B. False

2. Melvin Page, DDS, studied which concepts?
   A. body chemistry analysis and its relation to nutritional practice in dentistry
   B. the calcium/phosphorus ratio
   C. excess free calcium
   D. harmful effects of white sugar, flour, refined foods and chemical additives on body chemistry
   E. all of the above

3. Vitamin _____ has been linked to preserving the endocrine controlled centrifugal dentinal fluid flow.
   A. C
   B. K2
   C. B6
   D. B12

4. Testing for mercury exposure can be done using hair, urine, blood, and/or feces.
   A. True
   B. False

5. Science has established that most of the mercury burden is contained in the __________, while the remaining portion is distributed throughout the rest of the body.
   A. brain
   B. glands
   C. urine
   D. kidney

**Answers:** 1. B; 2. E; 3. B; 4. A; 5. D
Introduction: Healthy Diet, Healthy Teeth

While most dentists are not trained in nutrition, having a basic understanding of dietary health can assist dentists in teaching patients that poor nutrition invites a decay process to develop within the oral cavity.

Not eating properly and following the Standard American Diet (SAD) promote a condition within the body that usually produces a more acidic environment. To illustrate this point, studies show that on an annual basis, the average person in the United States consumes approximately 2100 lbs. of acid-forming foods compared to 380 lbs. of alkaline-forming foods. This unfortunate imbalance in diet can certainly have a devastating effect on health. In fact, it contributes to a plethora of chronic illnesses and degenerative diseases.

What happens to teeth during this process? Research by Ralph Steinman, DDS, of Loma Linda University, has shown that the metabolism of teeth and the oral cavity in general are extensions of the overall metabolism of the body. Thus, the occurrence of tooth decay, abscessed teeth, and even dental sensitivities are not primarily due to external contamination of the teeth through acid-producing foods and bacteria. Rather, these deteriorating conditions occur as a result of the internal effects of the body’s acidic environment because the acidic environment produces a change in the internal action of the fluids flowing within the teeth.

This is essentially because teeth are not solid; they consist of a series of dentin tubules and parallel enamel rods. In a healthy situation, fluids from within the tooth travel from the inside-out, working their way through the dentin, through the enamel, and into the mouth. This is thought to be a self-cleansing mechanism, and the constant flushing of the tooth structure prevents the movement of microbes into the tooth and the destructive effects of acids formed by foods.

However, major problems occur when hormonal imbalances, circulatory problems, and/or poor diet lead to a reverse fluid flow within the dentin tubules. A reverse flow “sucks” bacteria, acids, and other materials from the mouth or surrounding periodontium back into the tooth. Reverse fluid flow triggers a compromised condition otherwise known as decay, infection, or simply tooth pain.
Acid and Alkaline Foods: Balancing the Diet

For over a decade, a number of health care professionals have been encouraging a more balanced acid-alkaline diet as a means of preventing illness. For example, in 1999, Michael J. Porter of the Sedona Health Foundation explained the connection of an acid-alkaline diet to health:

Our very life and health depends on the ability of the body's physiological power to maintain the stability of blood pH at approximately 7.4. This process is called homeostasis. The acid-base balance of the body is critical to good health. One cannot seriously think about individualizing a diet without considering how the diet affects one's acid-base balance. We are constantly generating acid waste products of metabolism that must be neutralized in some way if life is to be possible. We, therefore, need a continual supply of alkaline food to neutralize this on going acid generation.1

Research has confirmed these statements. A 2011 PubMed literature review conducted by Gerry K. Schwalfenberg of the University of Alberta found, “From the evidence outlined above, it would be prudent to consider an alkaline diet to reduce morbidity and mortality of chronic disease that are plaguing our aging population.”2

Schwalfenberg also described how such a diet relates to survival by citing research from 2007 by Waugh and Grant: “Life on earth depends on appropriate pH levels in and around living organisms and cells. Human life requires a tightly controlled pH level in the serum of about 7.4 (a slightly alkaline range of 7.35 to 7.45) to survive.”3

My first-hand clinical experiences as a dentist support this concept. In our dental office, we measure saliva pH as an indicator of dental health as well as the body’s overall wellness. We check the saliva pH every six months when our patients visit us for their scheduled cleaning appointment. A pH reading of 7.0 (neutral) is good. However, 7.5 (slightly alkaline) is the best. I don’t believe I’ve ever seen any decay when I see a measurement of 7.5. When I see consistent readings of 6.5 and lower, the body’s “internal environment” is compromised and the conditions are usually ripe for decay and inflammation within the oral cavity.

The Acid – Alkaline Foods Chart provides a detailed ranking of foods by acid versus alkaline effects, which can help people make healthier food choices.

Alkaline-Producing Foods
For general health, alkaline-producing foods should comprise 60%-70% of overall food consumption, but for therapeutic care, they should be 90%-100%. Unfortunately, the average American consumes approximately only 10%-15% alkaline foods, which means that most people need to eat much more of these foods. The list below identifies some alkaline-producing foods:

<table>
<thead>
<tr>
<th>Alkaline-Producing Foods</th>
<th>Alkaline-Producing Foods</th>
<th>Alkaline-Producing Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>agar agar</td>
<td>fruit juices– no added sugar</td>
<td>pears, sweet</td>
</tr>
<tr>
<td>alfalfa sprouts</td>
<td>garlic</td>
<td>peas, sweet</td>
</tr>
<tr>
<td>almonds</td>
<td>ginger, fresh</td>
<td>peas, fresh, sweet</td>
</tr>
<tr>
<td>amaranth</td>
<td>gooseberry</td>
<td>peas less sweet</td>
</tr>
<tr>
<td>apples</td>
<td>grapefruit</td>
<td>persimmon</td>
</tr>
<tr>
<td>apples, sour</td>
<td>grapes, less sweet</td>
<td>pickles, homemade</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pineapple</td>
</tr>
</tbody>
</table>
Acid-Producing Foods

For general health, acid-producing foods should comprise 30%-40% of overall food consumption, but for therapeutic care, they should be 0%-10%. Unfortunately, the average American consumes approximately 80%-90% acid foods. The list below identifies some acid-producing foods:
artificial sweeteners  
bananas, green  
barley  
barley malt syrup  
beef (all)  
beer  
blueberries  
bran: oat, wheat  
breads: refined – corn, oats, rice, rye buckwheat  
butter, salted  
carbonated drinks  
cashews  
cereals, unrefined & refined  
cheeses: mild, crumbly, sharp  
chicken  
chocolate  
cigarette tobacco  
cigarettes  
coconut, dried  
coffee  
corn, corn syrup  
cornmeal  
crackers: rice, wheat, unrefined rye  
cranberries  
cream of wheat, unrefined  
currants  
custard with white sugar  
deer  
dried beans  
drugs  
eggs: whites, whole, hard cooked  
fish  
flour: white, wheat, whole wheat  
fructose  
fruit juices with sugar  
goat  
honey, pasteurized  
jams  
jellies  
ketchup  
lamb  
lentils  
liquor  
maple syrup, processed & unprocessed  
mayonnaise, store purchased  
milk, homogenized & most processed dairy products  
milk, homogenized goat  
molasses, unsulphured, organic  
mustard  
nutmeg  
nuts: brazil, pecans, macadamias, pistachios, walnuts  
peanuts  
oats, oatmeal  
olive oil  
olives, pickled  
pasta, white & whole grain  
pastries, all  
peanut butter  
peanuts  
peas, dried  
pickles, commercial  
plums  
popcorn, with butter & plain  
pork, bacon  
potatoes with no skin  
prunes  
rabbit  
rice: basmati, brown & white  
rye grain  
rye bread, organic & sprouted  
salt: refined & iodized  
seeds: pumpkin, sunflower  
semolina flour  
shellfish  
sodas  
soy sauce, commercial  
spelt  
squash, winter  
sugar, brown & white  
sunflower seeds  
tapioca  
te, black  
turkey  
veal  
vinegar, white & processed  
walnuts  
wheat bread, sprouted organic  
wheat germ  
wine  
yogurt, sweetened
Sugar: A Sticky Situation and a Danger to Your Health

A discussion about maintaining oral health with positive dietary choices would be incomplete without examining the impact of sugar on teeth, especially because it relates to the acidic conditions previously discussed.

New studies continue to confirm the long-suspected association between sugar and cavities, and researchers of a 2014 systematic review published in the Journal of Dental Research found, “Of the studies, 42 out of 50 of those [studies] in children and 5 out of 5 [studies] in adults reported at least one positive association between sugars and caries.”

Nutrition Australia has provided a simple description of how sugars result in acid in the mouth and tooth decay:

The bacteria in plaque use sugars in food and drinks to produce acid. This acid dissolves the tooth’s strengthening minerals (calcium and phosphate) from the tooth surface. Saliva is the body’s natural defence against dental caries. It helps wash sugars from the mouth and reduces the effect of the acid produced by the plaque bacteria. The calcium and phosphate present in saliva also help to replace the minerals on the surface of your teeth. But if ‘acid attacks’ occur too often, your saliva won’t have enough time to repair the damage done, and a hole will eventually develop in the tooth.

Due to the fact that acid is present in the mouth after sugar consumption for 20 minutes or more, people are advised to consider the frequency of sugar intake as opposed to just monitoring the amount of sugar eaten. Notably, the Canadian Dental Association suggests eating sugar-free snacks, avoiding sugar in coffee, soda pop, and fruit drinks, being especially cautious of “sticky” sugar snacks, brushing teeth, and eating fibrous fruit and vegetables.

The British Dental Health Foundation encourages balancing alkaline foods in the diet, while also clarifying how to recognize different types of sugar:

All sugars can cause decay. Sugar can come in many forms, for example: sucrose, fructose, maltose and glucose. These sugars can all damage your teeth.

Many processed foods have sugar in them, and the higher up it appears in the list of ingredients, the more sugar there is in the product. Always read the list of ingredients on the labels when you are food shopping.

When you are reading the labels remember that ‘no added sugar’ does not necessarily mean that the product is sugar free. It simply means that no extra sugar has been added.

Research is also establishing that in the United States, socioeconomic status and cultural perspectives can impact diet and tooth decay. A 2009 article published in the journal Academic Pediatrics described the situation, “Lack of availability of quality food stores in rural and poor neighborhoods, food insecurity, and changing dietary beliefs resulting from acculturation including changes in traditional ethnic eating behaviors, can further deter healthful eating and increase risk for Early Childhood Caries and obesity.”

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In other countries, sugar accessibility also plays a role in the issue of dental caries. A World Health Organization Collaborating Centre report by Moynihan and Petersen notes that countries without access to sugar tend to have low rates of dental caries. Specifically, the report mentions an increase in cavities in parts of Africa that have had increased accessibility to sugar. The report also cites data from World War II suggesting that less dental caries occurred in areas that had reduced accessibility to sugar.

Only a few studies about sugar and its ill-effects on teeth have been mentioned here, but research is abundant that restricting sugar intake in one’s diet results in better oral health.

**Soda Pop: The Tooth and Body Connection**

It’s probably not surprising that soda pop is the most popular beverage consumed in the U.S. As a matter of fact, American consumption of soft drinks, including carbonated beverages, fruit juice, and sports drinks have increased by 500 percent in the past 50 years.

What’s the soft drink attraction? Studies have shown, for both regular and diet soft drinks, the sugar and artificial sweeteners both create a yearning for that sweet taste of sugar. Thus, sugar can become an addiction that our bodies crave on a daily basis.

Is it possible that this “addiction” to sodas may be creating more problems to our overall health and wellness than we ever bargained for? We know that these beverages provide lots of calories, sugars, and caffeine but no significant nutritional value. But how much negative impact do they really have?

As a dentist, I’m certain based on my professional experiences that the constant, topical exposure of sugar, whether from regular soda or other sugar-laced products, creates serious and detrimental effects to the teeth and the periodontium (the specialized tissues that surround and support the teeth). Tooth decay, recurrent decay, gingival inflammation, and periodontal infections are all common side effects of sugar loading.

Some alarming statistics indicate that soda may create ill effects ranging from obesity, osteoporosis, heart disease, tooth decay, and even caffeine addictions. Although the scientific community and special interest groups continue to debate these issues, one particular area of this controversy to consider is that the body’s acid/alkaline balance is indicated by pH levels of body fluids, and our extracellular fluids, approximately 86% of total body fluids, should range between 7.0 to 7.5 in healthy conditions. The average pH level of soda is approximately 3.00! If normal body fluids range from 7.0 – 7.5, then drinking a can of soda is approximately 10,000 times more acid. OUCH! Phosphoric acid is usually the culprit found in sodas. However, there are no labeling requirements at this time to indicate the amount used in these beverages.

At any extent, I discovered it takes approximately 32-8oz. cans of water to neutralize one 8oz. can of soda. Thus, common sense tells us that a person is creating a huge imbalance in the body when consuming these soft drinks. Furthermore, metabolic acidosis can result in acidemia, or acid in the blood or body tissue, which creates all sorts of problems with health. For one, it
creates anaerobic metabolism. This, in turn, produces a reduction of energy levels and chronic fatigue, with chronic inflammation, connective tissue breakdown, and oxidative stress (free radical exposure). The immune system continues to break down and deteriorate.

A 2004 review entitled “Diet, nutrition and the prevention of dental diseases” published in *Public Health Nutrition* warns, “Dental erosion is increasing and is associated with dietary acids, a major source of which is soft drinks.” The review goes on to evaluate evidence linking the amount and frequency of sugar consumption to tooth decay and cavities.

**Three Foods for Healthy Gums and Hearts**

Just as certain beverages and foods can negatively impact health, other beverages and foods can positively impact the body. For the record, pure water, a natural and basic staple for life, has a pH of approximately 7.0 and is just what the doctor ordered when it comes to a healthy beverage, healthy body, and healthy teeth.

Interestingly, some foods are now known to improve oral health and the cardiovascular system. Take into account that dental research indicates people with gum disease are two to three times as likely to suffer from heart disease. As a result, doctors who treat gum disease and doctors who treat heart disease are teaming up with a message: Dealing with one problem can help a patient avoid the other. In the summer of 2009, a major heart journal and a major periodontal journal simultaneously published a consensus paper outlining the link between the two diseases (inflammation) and urging both types of doctors to look at the body as a whole rather than a set of unrelated parts.

That being said, it has also been recognized that besides exercising and, of course, getting regular dental checkups, choosing certain beverages and foods can help protect both the gums and the heart:

- **Raisins** are an excellent antioxidant and can fight the growth of certain bacteria that cause inflammation and gum disease.

- **Green tea** can significantly lower the risk of developing gum disease. In 2009, scientists found an antioxidant called catechins in green tea that impede the body’s inflammatory response to the bacteria that causes gum disease.

- **Eating four or more servings of whole grains a day** reduces the risk of periodontal disease by 23% in men, according to a study in the *American Journal of Clinical Nutrition*. The researchers discovered that whole grains (oatmeal, brown rice) when compared to refined carbohydrates (white bread, white rice) digest more slowly, causing a steadier and more controlled rise in blood glucose. Avoiding spikes in blood sugar reduces the body’s production of inflammatory proteins and lowers the risk of both gum and heart disease.

The concept of using a healthy diet to protect the body is simple, and putting it into practice can have a significant impact on peoples’ lives. It’s undeniably clear that what people eat and drink today can make a major difference in their overall health and wellness tomorrow.
Supplements: Extra Benefits Waiting to be Discovered

Science has shown that the Standard American Diet fails to provide the adequate nutritional values needed to support good health, and in 2005, researchers who examined this issue concluded, “Although both scientists and lay people alike may frequently identify a single dietary element as the cause of chronic disease (e.g., saturated fat causes heart disease and salt causes high blood pressure), evidence gleaned over the past 3 decades now indicates that virtually all so-called diseases of civilization have multifactorial dietary elements that underlie their etiology, along with other environmental agents and genetic susceptibility.”

Since it is known that people with chronic illness tend to have stores of nutrients in their bodies depleted faster than normal, some people use supplements such as vitamins, minerals, and other natural products in an effort to increase the intake of essential nutrients and to obtain a level of health critical for well-being.

Yet, it should be noted here that any supplement should be evaluated for safety. Due to situations that have actually occurred involving illegal and/or misleading sales of supplements, it is necessary for patients and medical professionals to research the distributor and the ingredients in supplements. This is to make sure that the product was manufactured safely and does not contain toxic substances or other dangerous ingredients. Patients should be made aware of this concern, especially since some consumers have reportedly bought supplements online without checking the authenticity of claims made about the product, how it was manufactured, and/or its safety.

With that important consideration in mind, the following supplements are what I consider to be the six basic building blocks for creating a competent, healthy foundation in the body. Although other nutrients could easily be added, we'll keep it as simple as possible for now by discussing these six types of supplements:

- Vitamins
- Minerals
- Essential Fatty Acids
- Probiotics
- Digestive Enzymes
- Amino Acids

1. VITAMINS

Background: There are 13 different known vitamins, each with its own special role. Without them, key body processes would halt. Vitamins and enzymes work together, acting as catalysts that speed up the making or breaking of chemical bonds which join molecules together. They are necessary for human bodily functions, including energy production.

Main Sources:
- Whole natural foods - fruits, vegetables, and grains
- High-quality commercial preparation
**Additional information:**
Research continues to link Vitamin D deficits to illnesses, and supplementation with Vitamin D has been encouraged to promote well-being.\(^{18}\)\(^{19}\) The chart below identifies levels of Vitamin D and doses related to health:\(^{20}\)

![Vitamin D Levels Chart]

**2. MINERALS**

**Background:** At least 18 minerals are important in human nutrition. Along with vitamins, they function as components of body enzymes. Our bodies need minerals for proper composition of bones and blood and for maintenance of normal cellular function. Minerals are classified into two categories—major and minor. On a daily basis, our bodies require more than 100 milligrams of major minerals and less than 100 milligrams of minor minerals.

Dr. Richard Anderson, ND, has said that “electrolyte deficiency is the first step in heart disease, cancer, AIDS, and most of the other chronic and degenerative diseases. It is also the first and most important thing to correct. Though the body can compensate for electrolyte deficiencies, it pays a high price. Don't be without a full reserve of electrolytes - ever!”\(^{21}\)

**Main Sources:**
- Whole natural foods - fruits, vegetables and grains
- High-quality commercial preparation

**Additional Information:** As part of the tooth decaying process, Ralph Steinman DDS, of Loma Linda University, identified the early loss of magnesium, copper, iron, and manganese.\(^{22}\) These minerals are all active in cellular oxidation. They’re necessary for the energy production that allows the cleansing flow through the dentin tubules. He also noted that the addition of copper, iron, and manganese to a decay-producing diet almost abolishes the decay rate.

Research has also suggested that iodine\(^{23}\) and selenium\(^{24}\) can promote oral health.

**3. ESSENTIAL FATTY ACIDS**

**Background:** Essential fatty acids are also known as healthy essential oils or EFA’s. They are essential because our bodies cannot produce these on their own; therefore, they must come from the foods that we eat. Essential fatty acids are important to our health because they produce compound structures called prostaglandins which help to regulate the following:
- inflammation, pain, and swelling
- blood pressure heart function
gastrointestinal function and secretion
• kidney function and fluid balance
• blood clotting and platelet aggregation
• allergic response
• nerve transmission
• steroid production and hormone synthesis

Unfortunately, mass commercial refinement of fats, oil products, and the foods containing them has effectively eliminated fatty acids from our food chain. Omega-3 (alpha linolenic acid) and omega-6 (linoleic acid) are two essential fatty acids. The balance of omega-3 to omega-6 oils is critical to proper prostaglandin metabolism. The optimal ratio of omega-3 to omega-6 fatty acids is 1:2 to 1:4, or four times the amount of omega-6 fatty acids as omega-3 fatty acids.24F

High levels of omega 6’s are easily found in the extraction of cooking oils and most processed foods; however, the omega 3’s are much harder to acquire. Research has shown that most Americans are deficient in omega-3 fatty acids and that this deficiency in mothers could impact the neurological development of children.25

Main Sources: The following omega-3 supplements will help re-establish the proper ratios for the body again:
• Flaxseed oil (this is the best source available)
  o for general health= 1 tbs/day
  o for therapeutic dose= 2tbs/day
• Flaxseed capsules
• Fish oil or marine lipid capsules (gaining more popularity for omega 3’s)
• 2-3 servings of fish/week

Additional information: A blood serum test for Fatty Acid Analysis can be ordered to determine an accurate assessment of a person’s omega-3 to omega-6 ratio.

4. PROBIOTICS

Background: Probiotics literally means "for life" and is a term used to signify the health-promoting effects of friendly bacteria. There are at least 400 different species of microflora in the human gastrointestinal tract. The most important friendly bacteria are Lactobacillus acidophilus and Bifidobacterium bifidum; therefore, it makes sense to maintain a high level of these bacteria in our intestines. Probiotic supplements help to support:
• proper intestinal environment
• post-antibiotic therapy
• protection from vaginal infections
• protection from urinary infections
• cancer prevention

Main Sources:
• Yogurt
  o Obtain through foods, such as yogurt at 14 oz./day
  o Check to see if there's friendly bacteria in your yogurt product by leaving it out of the refrigerator overnight. If live bacteria is present, you should see bubbles on top of the yogurt. If there are no bubbles, then there is no friendly bacteria.
5. DIGESTIVE ENZYMES

Background: The process of digestion is dependent on several dozen digestive enzymes that are produced by the body at different sites along the digestive tract in the mouth, stomach, and small intestine. These enzymes break down the foods consumed into particles small enough to pass through the intestinal wall and be absorbed by the cells. It is within the cells that the molecules of food are converted into usable energy.

If digestive-enzyme production is diminished, none of the food that we eat can be properly absorbed and assimilated by the body. This concept is often a surprise to many Americans, who assume that if they eat a lot of food, they'll be well nourished and healthy. However, a full plate doesn't always translate into a healthy body and vital life, particularly if the body is unable to properly use the food due to a lack of adequate digestive enzymes.

Of all the digestive enzymes, pancreatic enzymes are among the most critical for the absorption of food and maintenance of good health. These enzymes are capable of breaking down all types of food--carbohydrates, protein, and fat.

Main Sources:
- Support healthy digestion with an enzyme-rich diet of fresh fruits, especially melons and papayas (these are low in acid content), and vegetables, along with sprouted seeds (alfalfa sprouts) and legumes (beans)
- High-quality commercial preparation

6. AMINO ACIDS

Background: Amino acids are the chemical units or "building blocks" that make up proteins. They are found in every tissue of the body and play a major role in nearly every chemical process that affects physical and mental function. As a result, amino acids have more diverse functions than other nutrient groups. They contribute to the formation of proteins, muscles, neurotransmitters, enzymes, antibodies, and receptors and are involved in basic cellular energy production.

Main Source:
- High-quality commercial preparation is probably the most effective way to acquire the proper amount of amino acids on a daily basis
The Mediterranean-Type Diet

Overview

Over the last 10-15 years, the Mediterranean-Type Diet has received notable attention as being one of the mosthealthiest and nutritional type diets in the world. It is considered a "low-carb" diet that not only promotes weight loss, but also helps to balance blood sugar and hormone levels, help with adrenal fatigue (the stressed-out person's lifestyle syndrome), prevent the ups and downs that we commonly experience due to our body's unstable energy supply, and reduce the frequent mood swings that can impact our mental disposition. It is also considered an extremely heart-healthy diet plan.

The following information provides some important guidelines and suggestions to assist in adapting a new dietary plan.

How to Eat

- Eat every 2-3 hours. Although many people only eat 2 or 3 times a day, the body's metabolism will become much more efficient if healthier, smaller portions are eaten throughout the entire day. This helps to relieve the stress handling glands from the job of maintaining normal blood sugar levels between meals.

What to Eat

- Eat real, natural, organic, whole, fresh foods.

- Drink plenty of water. Remember, 70-75% of the body contains water. The body must be hydrated or else the system will continually be stressed. (Filtered water, not tap water, is recommended).

- Salting your food. Stress-handling glands need plenty of salt for normal function. Research has challenged the notion that salt consumption causes high blood pressure or heart disease, and using salt in a moderate fashion is considered acceptable by many. However, sea salt is recommended over "regular" salt because it contains the trace minerals that have been refined out of "regular" salt.

- In the beginning, minimize fruits. If adrenal fatigue is suspected, have a test for adrenals. Keep in mind that 98% of population has adrenal fatigue!

What NOT to Eat

- Avoid dead, devitalized, processed, junk foods. These "foods" CANNOT re-build a healthy body. They are also anti-nutrients which means they rob any remaining nutrient storages from the body.

- Avoid caffeine, sugar, alcohols. These will provoke the stress-handling glands into...
releasing epinephrine and cortisol to raise blood sugar and release energy. Chronic
and habitual use of caffeine, sugars, and alcohols can lead to adrenal fatigue
syndrome.

- **Avoid trans-fatty acids (hydrogenated or partially hydrogenated oils) and rancid
  fats.** These are prevalent in margarine, vegetable shortening, and almost all
  commercially packaged foods.

- **Do not eat carbohydrates alone.** You want to avoid unnecessary spikes in blood
  sugar levels; therefore, always add protein to your meals and snacks. It is
  especially important NOT to eat a carbohydrate-only breakfast.

**Celiac Disease and the Oral Cavity**

I recently discovered an interesting connection between patients suffering from celiac disease
and its effects on the oral cavity. Celiac disease is an autoimmune digestive disease that damages
the micro-villi of the small intestine and interferes with absorption of nutrients from food. This
means that celiac disease is triggered by consumption of the protein called gluten, which is found
in wheat, barley, rye, and oats. When people with celiac disease eat foods containing gluten,
their immune system responds by damaging the fingerlike villi of the small intestine. When the
villi become damaged, the body is unable to absorb nutrients into the bloodstream, which can
lead to malnourishment.

According to the National Foundation for Celiac Awareness, roughly one out of every 133
Americans has celiac disease, but 97% remain undiagnosed. Thus, almost three million
Americans have the illness, but only about 100,000 know they have it. The National Foundation
for Celiac Awareness warns that if celiac disease is not treated, individuals can end up suffering
from other conditions such as autoimmune diseases, osteoporosis, thyroid disease, and cancer.

Symptoms of celiac disease may or may not occur in the digestive system. For example, one
person might have diarrhea and abdominal pain, while another person might have irritability or
depression. In fact, irritability is one of the most common symptoms in children. Some of the
most common symptoms of celiac disease include bloating or gas, diarrhea, constipation, fatigue,
joint pains, tingling/numbness, headaches, irritability, and infertility.

Dental symptoms include discolored teeth, loss of enamel, and/or canker sores. I must admit,
over the years, I’ve seen plenty of these symptoms in my patients’ mouths but never once made
this connection. It’s also interesting to note that there are no known etiologies for the causes of
canker sores. Remember, the oral cavity is like a window to the rest of the body, and Biological
Dentistry offers this unique interpretation to our patients, as we continue to think outside the box
and search for these “tooth and body” connections. In our office, a clinical examination of the
oral cavity offers more than just a casual evaluation of the teeth and gums. Looking for clues
that may suggest systemic imbalances or a compromised condition in general health is our main
focus for our patients.
Accurately diagnosing celiac disease can be quite difficult largely because the symptoms often mimic those of other diseases including irritable bowel syndrome, Crohn’s disease, ulcerative colitis, diverticulosis, intestinal infections, chronic fatigue syndrome, and depression. Blood tests will usually be ordered to gain a proper diagnosis of celiac disease.

It is important to continue eating a normal, gluten-containing diet before being tested for celiac. If the blood tests and symptoms indicate celiac disease, a physician may suggest a biopsy of the lining of the small intestine to confirm the diagnosis.

As of now, the only treatment for celiac disease is a gluten-free diet eliminating all foods with wheat (including spelt, triticale, and kamut), rye, oats, and barley. Despite these restrictions, people with celiac disease can eat a well-balanced diet with a variety of foods, including bread and pasta. For example, instead of wheat flour, people can use potato, rice, soy, or bean flour. Or, they can buy gluten-free bread, pasta, and other products from specialty food companies. Just keep in mind that some people may also have sensitivities to other foods such as soy.

The gluten-free diet is a lifelong commitment for people with celiac disease. Eating any gluten, no matter how small an amount, can damage the intestine. This is true for anyone with the disease, including people who do not have noticeable symptoms. As with other chronic illness, the immune system is continuously attacked over time, and other more serious illnesses may develop.

Finally, many patients and dentists are not aware that some dental polishes contain gluten. As with other patient allergies, dentists should be familiar with the ingredients in the products they use so they can protect patients from being exposed to allergens.

29 National Foundation for Celiac Awareness and the American Society of Health-System Pharmacists. What is Celiac Disease? National Foundation for Celiac Awareness website

30 National Foundation for Celiac Awareness and the American Society of Health-System Pharmacists. What is Celiac Disease? National Foundation for Celiac Awareness website

31 National Foundation for Celiac Awareness and the American Society of Health-System Pharmacists. What is Celiac Disease? National Foundation for Celiac Awareness website

32 Fis BS. Avoiding common dental allergens. Living Without’s Gluten Free and More website.
The Relationship between Vitamin D and Periodontal Pathology

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Abstract: Osteoporosis and periodontal diseases are common problems among the elderly population. Vitamin D is a secosteroid hormone that is either synthesized by human skin cells under the effect of UV radiation or consumed through diet. Deficiency in vitamin D leads to reduced bone mineral density, osteoporosis, the progression of periodontal diseases and causes resorption to occur in the jawbone. Sufficient intake of vitamin D can decrease the risk of gingivitis and chronic periodontitis, as it has been shown to have immunomodulatory, anti-inflammatory, antiproliferative effects and initiates cell apoptosis. In addition, vitamin D is also important for bone metabolism, alveolar bone resorption and preventing tooth loss. It increases antibacterial defense of gingival epithelial cells and decrease gingival inflammation, improves postoperative wound healing after periodontal surgery and is an important supplement used as prophylaxis in periodontology. This publication aims to update the recent advances, stress the clinical importance, and evaluate vitamin D in the prevention of periodontal diseases to reach a successful outcome of conservative and surgical treatment. An analysis of the literature shows that vitamin D plays a significant role in maintaining healthy periodontal and jaw bone tissues, alleviating inflammation processes, stimulating post-operative healing of periodontal tissues and the recovery of clinical parameters. However, further research is needed to clarify the required vitamin D concentration in plasma before starting periodontal treatment to achieve the best outcome.

Keywords: osteoporosis; jaw; vitamin D deficiency; bone mineral density (BMD); 25-hydroxyvitamin D; serum levels

1. Introduction

Vitamin D is a secosteroid, which is synthesized from 7-dehydrocholesterol during a photochemical reaction under the effect of ultraviolet radiation on the skin or is consumed through digestion [1]. Vitamin D3 is further hydroxylated in the liver into 25-hydroxyvitamin D3 (25(OH)D3) [2]. This is the main and most stable form of vitamin D in blood plasma. It is a biologically active metabolite, one of the functions of which is maintaining the balance of calcium and phosphorus concentration in blood by regulating their absorption in the intestines and reabsorption in kidney. It also assists in promoting the remodeling of the bones [2,3]. Constant low uptake of vitamin D and calcium leads to a negative calcium balance, disrupted bone mineralization, and loss of bone structure [1]. Vitamin D deficiency leads to rickets in children, and osteoporosis (OP) in adults as well as an increased probability of bone fracture [1,4]. 1,25(OH)2D3 is vital to the immune system as it stimulates the
non-specific immune response to fight against infectious diseases [2,5]. Vitamin D receptors (VDR) in monocytes, macrophages, neutrophils and dendritic cells bind to 1,25(OH)2D3 molecules and stimulates the release of antimicrobial peptides [5]. Such regulation of the immune system is an important defense mechanism for digestive, respiratory and genitourinary system cells, skin, eyes, and mouth [6]. Vitamin D affects the pathogenesis of periodontal diseases (PD) via immunomodulation, increases bone mineral density (BMD), reduces bone resorption, and is important in fighting against agents that cause periodontal diseases. There has been an increase in interest in and publication of articles investigating the importance of vitamin D in prophylaxis and treatment of dental caries and periodontal diseases [6]. The purpose of the following literature analysis is to analyze the role of vitamin D in the pathogenesis of PD, its influence on the quality of the alveolar bone, the correlation between 25-hydroxyvitamin D concentration in plasma and PD as well as the importance of vitamin D in chronic periodontitis prophylaxis and treatment.

2. Significance of Vitamin D in Immune Response of Periodontium

Liu et al. discovered that, during an inflammatory process, dental pulp fibroblasts and periodontal cells produce 25-hydroxylase, which stimulates the production of 25(OH)D3 [7]. As pathological microorganisms affect the cell membrane receptors, 1α-hydroxylase synthesis is activated, during which 1,25(OH)2D3 is formed from 25(OH)D3 [6]. The resulting molecule binds with the VDR in the immune and epithelial cells and participates in the epithelium defense mechanism against the pathogen [5,6]. 1,25(OH)2D3 activates the synthesis of proteins which are required in the tight, gap and desmosome junctions of epithelial cells [6]. The junctional epithelium connects to the tooth through loose junctions, thus, creating favorable conditions for a bacterial invasion from dental plaque, which initially causes inflammation of the periodontal tissue (PT), and, as the process advances, resorption and tooth loss occurs [8].

1,25(OH)2D3 regulates the non-specific immune response, activates hydrogen peroxide secretion in monocytes, stimulates the synthesis of antimicrobial peptides, e.g., β-defensin and cathelicidin LL-37. Cathelicidin LL-37 plays a role in chemotaxis, production of cytokines and chemokines, cellular reproduction, vascular permeability, wound healing, and neutralization of bacterial endotoxins [6]. McMahon et al. studied human gingival cell cultures and the effect of vitamin D on the expression of non-specific immune system of these cells. After affecting gingival cell cultures with 1,25(OH)2D3, cathelicidin, LL-37 secretion increased, and its antimicrobial effect against Actinobacillus actinomycetemcomitans lasted for 24 h [9].

1,25(OH)2D3 takes place in specific immune system by affecting B-lymphocytes and T-lymphocytes [6]. These cells emit cytokines and immunoglobulins, and they specifically destroy bacterial pathogens which are transferred by macrophages and dendritic cells. Such immune processes harm the PT and aggravate the course of PD. Vitamin D suppresses the proliferation of T-lymphocytes, secretion of immunoglobulins, transformation of B-lymphocytes into plasma cells, it inhibits the unwanted process, and protects the organism from excessive specific immune response by decreasing the secretion of IL-1, IL-6, IL-8, IL-12, TNFα cytokines [1,7]. These cytokines are released in PD pathogenesis during a bacterial invasion. They cause lymphocyte infiltration, bone resorption, deterioration of extracellular matrix. Tang et al. studied the human periodontal tissue cell cultures trying to discern the anti-inflammatory effect of vitamin D on the cells. Less IL-8 was discovered in the cell cultures affected by Porphyromonas gingivalis and 1,25(OH)2D3 than in cell cultures affected only by Porphyromonas gingivalis. Thus, the hypothesis that vitamin D is effective in PD prophylaxis and treatment was confirmed [10]. Teles et al. confirmed anti-inflammatory properties of vitamin D by determining that higher concentrations of vitamin D in blood serum contain less IL-6 and leptin and more adiponectin, which regulates the immune response. An increase in leptin signifies the presence of an infectious process and inflammation (proliferation and activation of T-lymphocytes, production of cytokines), adiponectin suppresses the production and activity of cytokines [11].
3. Concentration of 25-Hydroxyvitamin D in Plasma and Periodontal Disease

The quantity of vitamin D in a human organism is determined by the concentration of its metabolite 25(OH)D$_3$ in plasma; it normally fluctuates from 25 to 138 nmol/L. A concentration lower than 37.5 nmol/L shows vitamin D deficiency. A concentration higher than 200 nmol/L signifies hypervitaminosis [12]. To have an effect on periodontium, the plasma concentration should reach 90–100 nmol/L [3]. The correlation between varying 25(OH)D$_3$ plasma concentrations and PD is shown in Table 1.
### Table 1. The relationship between 25-hydroxyvitamin D₃ (25(OH)D₃) concentrations in the plasma and periodontal diseases.

<table>
<thead>
<tr>
<th>Authors, Year of Publication</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Outcome Measure</th>
<th>Outcome Measurement</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietrich et al., 2004 [13]</td>
<td>cross-sectional</td>
<td>11 202</td>
<td>Periodontitis</td>
<td>attachment level</td>
<td>decreased concentration is associated with changed (poor) periodontal condition</td>
</tr>
<tr>
<td>Dietrich et al., 2005 [14]</td>
<td>cross-sectional</td>
<td>6 700</td>
<td>Gingivitis</td>
<td>level of gingival inflammation (bleeding index)</td>
<td>decreased concentration is associated with gingival inflammation and higher bleeding index</td>
</tr>
<tr>
<td>Berggess et al., 2011 [15]</td>
<td>case-control</td>
<td>123 cases, 123 controls</td>
<td>PD in pregnant women</td>
<td>probing depth, bleeding index</td>
<td>women with vitamin D deficiency in the plasma (&lt;75 nmol/L) are more prone to chronic periodontitis during pregnancy</td>
</tr>
<tr>
<td>Zhou et al., 2012 [16]</td>
<td>case-control</td>
<td>193 cases, 181 controls</td>
<td>PD and chronic obstructive pneumonia</td>
<td>pockets depth, periodontal attachment level, gingival bleeding index, teeth number</td>
<td>decreased concentration is associated with poor periodontal condition</td>
</tr>
<tr>
<td>Teles et al., 2012 [11]</td>
<td>exploratory</td>
<td>56</td>
<td>Chronic periodontitis</td>
<td>bleeding index, probing depth, periodontal attachment level, teeth number</td>
<td>decreased concentration is associated with poor periodontal condition</td>
</tr>
<tr>
<td>Antonoglou et al., 2013 [17]</td>
<td>comprehensive</td>
<td>80</td>
<td>Chronic periodontitis with type 1 diabetes</td>
<td>amount of plaque, probing depth, attachment level</td>
<td>authors did not find correlation between 25(OH)D₃ concentration in the plasma and chronic periodontitis</td>
</tr>
<tr>
<td>Millen et al., 2013 [18]</td>
<td>multi-center</td>
<td>920</td>
<td>Chronic periodontitis in postmenopausal age</td>
<td>X-ray, attachment level, probing depth, bleeding index</td>
<td>decreased concentration is associated with chronic periodontitis</td>
</tr>
<tr>
<td>Liu et al., 2009 [19]</td>
<td>preliminary</td>
<td>178</td>
<td>Aggressive periodontitis</td>
<td>probing depth, attachment level, bleeding index</td>
<td>increased concentration is associated with aggressive periodontitis</td>
</tr>
<tr>
<td>Zhang et al., 2013 [20]</td>
<td>case-control</td>
<td>44 cases, 32 controls</td>
<td>Generalized aggressive periodontitis</td>
<td>probing depth, attachment level, bleeding index</td>
<td>increased concentration is associated with generalized aggressive periodontitis</td>
</tr>
</tbody>
</table>
During acute periodontal inflammation, 25(OH)D\textsubscript{3} concentration increases due to increased 25-hydroxylation activity of periodontal cells. During a chronic inflammation, it decreases [19]. Due to the production of this enzyme in aggressive periodontitis, 25(OH)D\textsubscript{3} concentration in periodontal pockets is 300 times greater than in blood plasma [7]. Zhang et al. argue that, in the case of aggressive periodontitis, an increase in IL-6 and 25(OH)D\textsubscript{3} concentration, leukocytes and neutrophils is observed [20]. Low concentration of 25(OH)D\textsubscript{3} in blood plasma indicates vitamin D deficiency, unbalanced immune reactions in the organism, and the progression of periodontal disease [18].

4. Significance of Vitamin D in Mandibular Bone

The effect of vitamin D and calcium supplements in treating systemic BMD decrease is based on its activity—regulation of calcium and phosphorus concentration in blood [2,3]. Constant low ingestion of vitamin D and calcium leads to a negative calcium balance, disrupted bone mineralization, and loss of bone structure [1]. Vitamin D deficiency causes rickets in children and OP in adults [1] as well as an increased risk of bone fracture [1,5]. The optimal 25(OH)D\textsubscript{3} recommended concentration in blood plasma for skeletal bone tissue is no lower than 80 nmol/L, for periodontal tissue—approximately 90–100 nmol/L. Lower concentrations are associated with periodontal disease progression and tooth loss [3].

Mandibular bone is one of the four tissues forming the periodontium. For this reason, OP and periodontal disease are closely related. In case of OP, the BMD decreases in all bones, including the jawbone, where the resorption of the alveolar ridge and tooth loss increases [2,21]. After studying 400 older women in 2010, Al Habashneh et al. determined that women with lower skeletal BMD display a more progressed form of chronic periodontitis. They were also diagnosed with increased alveolar process resorption than with normal BMD. A survey of these participants revealed that women who took vitamin D suffered from chronic periodontitis less often than those who did not [22].

The systemic increase of cytokines, which influence bone resorption in the entire skeleton and jawbone, can be noted in people with low systemic BMD. As mentioned previously, periodontal infection causes a local increase in cytokines which stimulates the activity of osteoclasts and bone resorption [23]. In 2011, Jabbar et al., studied the correlation between cytokine and 25-hydroxyvitamin D concentration in blood plasma in OP. The study subjects were 185 women of postmenopausal age suffering from OP and 185 healthy women of the same age. The study showed that 25-hydroxyvitamin D concentration in blood plasma of the subjects was significantly lower than that of the control group (66.62 nmol/L and 97.21 nmol/L, respectively), while the quantity of cytokines, receptor activator of nuclear factor κB ligand (RANKL) and osteoprotegerin (OPG) were significantly higher. The RANKL and OPG balance is regulated by glucocorticoids, vitamin D, and oestrogens [24]. Wactawski-Wende et al. argued that due to vitamin D’s ability to increase BMD and reduce resorption, vitamin D\textsubscript{3} supplements may be used in prophylaxis and treatment of periodontal disease in postmenopausal age women [23].

5. Vitamin D in Prophylaxis and Treatment of Periodontal Diseases

In case of vitamin D hypovitaminosis, getting less than 400 IU of vitamin D daily may cause a decrease of calcium concentration in blood plasma, an increase of parathyroid hormone secretion, disruption of bone tissue remodeling, and may develop a secondary hyperparathyroidism [25]. The recommended daily dosage of vitamin D for people under 70 years old is 600 IU; for people older than 70 years—800 IU [26]. During vitamin D deficiency treatment, daily dosage may be increased to 2000 IU, without tracking 25(OH)D\textsubscript{3} concentration in blood plasma. If the daily dosage of vitamin D reaches 40,000 IU, vitamin D hypervitaminosis may occur in healthy individuals. This quantity of vitamin D taken daily for extended periods of time disrupts calcium metabolism, causes parathyroid gland hyperfunction [3], and forms conditions for the development of nephrolithiasis [27]. Approximately only 90 IU of vitamin D may be absorbed from food every day without consumption of supplements. Human body synthesizes approximately 10,000 IU of vitamin D from tanning under
natural sunlight until light redness of the skin. The recommended dosage of vitamin D may be absorbed by exposing the face, hands, and palms to natural sunlight 2–3 times a week without reaching light redness of the skin [3]. Hildebolt investigated the correlation between the daily intake of vitamin D supplements and the increase in 25(OH)D$_3$ concentration in blood plasma. According to Hildebolt, consuming 200 IU of vitamin D supplements per day increases the concentration of 25(OH)D$_3$ in blood plasma by 10 nmol/L, whereas consuming 1000–2000 IU increases it by 47 nmol/L [3].

Bashutski et al. published the results of a long-term clinical study where the correlation between the quantity of vitamin D in blood plasma and periodontal surgeries was studied. Researchers determined that research subjects with a vitamin D deficiency in blood plasma showed less effective results (lower tissue attachment level and probing depth change) after periodontal surgery. The authors argue that to improve post-surgery results, it is advised to examine vitamin D level in the patients’ blood prior to the treatment and avoid vitamin D deficiency by taking supplements [27].

Alshouibi et al. studied the correlation between the quantity of vitamin D and state of periodontium in 562 older men. Study results showed that subjects who received more than 800 IU of vitamin D daily had a lower risk of having a more severe form of chronic periodontitis (results were based on probing depth, attachment level, loss of alveolar bone), whereas those receiving less than 400 IU of vitamin D suffered from a more advanced level of alveolar bone resorption [28].

Hiremath et al. conducted a random sampling of clinical research to prove the anti-inflammatory effect of vitamin D on gingiva. Results showed that a 500–2000 IU dosage of vitamin D is safe and effective in gingival inflammation treatment. Notable results were shown after three months. Results were observed after one month where subjects took a dose of 2000 IU of vitamin D or higher. Consumption of higher doses led to a change in 25(OH)D$_3$ concentration in blood plasma. While not consuming vitamin D, the concentration increased by 0.87 nmol/L. During consumption of 500 IU, the concentration increased by 32.03 nmol/L. During consumption of 1000 IU, the concentration increased by 42.12 nmol/L. During consumption of 2000 IU, the concentration increased by 74.22 nmol/L [29]. This randomized clinical trial demonstrates the effect of vitamin D on gingival inflammation and the required vitamin D dosage to reach this effect.

6. Conclusions

In conclusion, vitamin D is significant in periodontology as it takes part in the synthesis of proteins that are needed in formation of mucous membrane. This creates a physical barrier and, thus, hinders the transfer of pathogens further into deeper tissues. The antimicrobial protein synthesis by immune and epithelial cells as well as nonspecific immune responses are activated. Vitamin D also takes part in specific immune response by suppressing the destructive effect of chronic periodontitis. Moreover, it maintains systemic and jawbone density homeostasis. In order to prescribe vitamin D for treatment of periodontal diseases, further research is needed.

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**References**


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A hypothetical role for vitamin K2 in the endocrine and exocrine aspects of dental caries

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ABSTRACT

The growing interest in oral/systemic links demand new paradigms to understand disease processes. New opportunities for dental research, particularly in the fields of neuroscience and endocrinology will emerge. The role of the hypothalamus portion of the brain cannot be underestimated. Under the influence of nutrition, it plays a significant role in the systemic model of dental caries. Currently, the traditional theory of dental caries considers only the oral environment and does not recognize any significant role for the brain. The healthy tooth, however, has a centrifugal fluid flow to nourish and cleanse it. This is moderated by the hypothalamus/parotid axis which signals the endocrine portion of the parotid glands. High sugar intake creates an increase in reactive oxygen species and oxidative stress in the hypothalamus. When this signaling mechanism halts or reverses the dentinal fluid flow, it renders the tooth vulnerable to oral bacteria, which can now attach to the tooth's surface. Acid produced by oral bacteria such as Streptococcus Mutans and lactobacillus can now de-mineralize the enamel and irritate the dentin. The acid attack stimulates an inflammatory response which results in dentin breakdown from the body's own matrix metalloproteinases. Vitamin K2 (K2) has been shown to have an antioxidant potential in the brain and may prove to be a potent way to preserve the endocrine controlled centrifugal dentinal fluid flow. Stress, including oxidative stress, magnifies the body's inflammatory response. Sugar can not only increase oral bacterial acid production but it can concurrently reduce the tooth's defenses through endocrine signaling. Saliva production is the exocrine function of the salivary glands. The buffering capacity of saliva is critical to neutralizing the oral environment. This minimizes the de-mineralization of enamel and enhances its re-mineralization. K2, such as that found in fermented cheese, improves saliva buffering through its influence on calcium and inorganic phosphates secreted. Data collected from several selected primitive cultures on the cusp of civilization demonstrated the difference in dental health due to diet. The primitive diet group had few carious lesions compared to the group which consumed a civilized diet high in sugar and refined carbohydrates. The primitives were able to include the fat soluble vitamins, specifically K2, in their diet. More endocrine and neuroscience research is necessary to better understand how nutrition influences the tooth's defenses through the hypothalamus/parotid axis. It will also link dental caries to other inflammation related degenerative diseases such as diabetes.

Introduction

A healthy tooth is well designed to withstand a harsh oral environment because it cleanses itself from the inside out. Dental caries is evidence that the tooth's fluid flow has been halted or reversed and the tooth's defenses have been compromised. The local process of enamel de-mineralization by bacterial acid is significantly influenced by nutrition, specifically refined carbohydrates such as sugar. The caries process to render the tooth vulnerable, however, starts in the hypothalamus part of the brain and changes are initiated in the dentinal fluid flow [1]. Nutrition plays a significant role in both the systemic and local aspects of this process.

Following enamel de-mineralization of a compromised tooth due to acid, dentin breakdown is accomplished by the body's own matrix metalloproteinases (MMP's) [2,3] as a result of an uncontrolled inflammatory response to the acid irritant. This phase of the caries process commences as reversible inflammation or ‘dentinitis' and proceeds to irreversible dentin caries. This is similar to reversible or irreversible pulpitis and the terms gingivitis and periodontitis when referring to the periodontium [4].

The systemic concept of dental caries recognizes that the process is multi-factorial. While decreasing the insult side of the
process by reducing sugar intake and oral bacteria counts is important, increasing the body’s defense side with an antioxidant rich diet of fruits, vegetables and K2 may be relatively more important in reducing vulnerability.

It has been documented that K2 can assist in significantly reducing dental caries [5,6]. Much research, however, is needed to determine why this vitamin can enhance defenses locally through changing saliva composition and systemically through its influence on the hypothalamus and the endocrine aspect of the parotid gland.

This systemic concept is a significant paradigm shift from the traditional ‘acid theory’ of dental caries. It has many implications for future efforts in dental prevention.

The hypothesis

Oral and other systemic stress responses are similar

The understanding of stress originated in the 1950’s [7]. The word ‘stressor’ was coined to describe the irritant and the body’s reaction to the irritation became known as a stress response. If a stressor was local, such as enamel demineralization due to acid, or plaque irritating the periodontal tissues, the body responded with a ‘Local Adaptation’. The local adaptations are controlled, inflammatory responses and are similar throughout the body so they are termed a ‘Local Adaptation Syndrome’ (LAS). In the dentin portion of the tooth, ‘dentinitis’ represents the local inflammatory response.

A local response can be exaggerated when the whole body becomes involved through the endocrine system. This system wide response is termed a ‘General Adaptation Syndrome’ (GAS) because the effects on the body are similar despite the location or type of stressor [7]. The hypothalamus/pituitary/adrenal axis controls the body’s general response.

Refined carbohydrates like sugar locally stimulate the oral bacteria to produce acid. This causes de-mineralization of enamel and ‘dentinitis’ in the dentin. This is a local inflammatory adaptation and is part of the LAS. Traditional caries theory is usually limited to this phase.

Beyond this local effect, however, sugar has a significant impact on the body when it is absorbed. Blood sugar spikes need to be managed and centrifugal dentinal fluid flows through the tooth are disrupted by signals coordinated through the hypothalamus of the brain. This general adaptation or GAS is mainly an endocrine driven response, which affects the whole body. The hypothalamus/parotid axis is the endocrine axis most relevant to dental health [8]. The effects of local irritation are magnified in the presence of a GAS response [7,9].

This systemic understanding explains why not all oral acids are equal in their effect. Sucking on lemons, for example, induce enamel demineralization but are not as significantly related to dental caries. The inflammatory stimulus of acid demineralization is handled with local resources through the LAS. Sugar, however, with its significant effect on the whole body, magnifies the local acid attack by triggering the GAS. It does this by causing the hypothalamus/parotid axis to decrease the dentinal fluid flow. This makes the tooth more vulnerable to the acid exposure [1].

The tooth must first become vulnerable to caries

A healthy tooth is nourished by a centrifugal fluid flow through the dentin. This flow can stop or reverse when influenced by a systemic stressor such as a high sugar intake [10]. This step now allows oral bacteria to attach to the surface of the tooth and produce acid which de-mineralizes the enamel surface and irritates the dentin causing inflammation.

The fluid flow through the tooth is stimulated by an endocrine hormone secreted by the parotid gland, hence the term parotid hormone [8]. It is a 30 amino acid protein [11]. The parotid gland is not commonly recognized as a dual function exocrine/endocrine gland. This characteristic makes it similar to the pancreas. Both parotid hormone and insulin [12] are regulated by the hypothalamus part of the brain. This influence is part of the GAS affecting the adrenal glands through the hypothalamus. The stimulus or stressor for parotid signaling can be initiated by sugar intake and it can be manipulated in lab studies with carbamyl phosphate [13], which served as an antioxidant [1].

Once the tooth has become vulnerable, the fibroblasts in the tooth can become irritated or stressed by the low pH or acid attack, which has already demineralized the enamel. This response is a normal inflammatory reaction (LAS). The corresponding increased metabolism increases reactive oxygen species (ROS) production and activates MMPs such as collagenase. Tissue inhibitors of metalloproteinases (TIMPs) neutralize activated MMPs when they are no longer necessary and serve as the body’s way of controlling inflammation. Antioxidants help to control inflammation by neutralizing ROS, thus decreasing the need to stimulate the MMP activation. Optimum nutrition can play a role here. Temporary irritations are thus managed by controlled inflammation causing a reversible state but healing occurs. This is ‘dentinitis’ [14,15]. Excessive irritation causes uncontrolled inflammation which is largely irreversible in the tooth and recognized in dentin as caries.

The systemic approach reveals the overlooked importance of antioxidants

The systemic view of dental caries links dental caries to diabetes. When high blood glucose in the hypothalamus increases metabolic activity, more positively charged free radicals, specifically reactive oxygen species (ROS), are produced. They are the warning signs for the hypothalamus to down regulate parotid hormone while up regulating the pancreas to produce insulin. Antioxidants help manage the free radical storm in the hypothalamus [16] caused by the blood glucose spike.

Methamphetamine produces a hurricane of free radicals [17] which could shut down all parotid hormone and dentinal fluid flow. The dental caries devastation known as “meth mouth” demonstrates the exaggerated response [18].

Antioxidants are a powerful defense to free radical damage, as evidenced by the “Asian Paradox”, which refers to high rates of cigarette smoking but less heart disease and cancer amongst green tea drinkers [19]. Green tea is well known for its antioxidant properties, especially epigallocatechin gallate (EGCG). The same paradox applies to periodontal disease [20]. Green tea and its antioxidants have also proven effective in reducing caries rates [21]. This study also demonstrated that the tea was just as effective when all fluoride was removed, thus eliminating fluoride as a confounding factor. While the systemic antioxidant effects of green tea on dental caries and tooth vulnerability are significant, vitamin K2 may prove a more potent antioxidant [22–24].

The critical importance of antioxidants, such as resveratrol and curcumin, is now emerging relative to oxidative stress caused by fluoride. The fluoridation of drinking water has long been touted by the dental profession as beneficial for dental health. Now it appears that fluoride causes significant oxidative stress and antioxidants are the antidote. [25,26]

A brief description of K2

K2 is in the quinone group and is known as menaquinone. K1 is phylloquinone and Co-enzyme Q10 is ubiquinone. Quinones have oxygen containing ring structures, which can make them very
active in electron transport reactions [27]. K2 was placed in the K vitamin category because it is produced in the body from K1 [28].

K1 is essential to blood clotting. Accordingly, the body has found ways to re-cycle K1 for repeated use and, thus, depend less on dietary intake of K1. The anti-coagulant, warfarin, interferes with the re-cycling process to decrease K1 and reduce the body's ability to clot. High dietary intakes of K1 defeat warfarin's effect because the K1 is available without re-cycling.

K2 has several forms, which are numbered according to side chains. (eg. MK4 and MK7) While MK4 is the form the body produces from K1, supplemental MK4 is synthetic. MK7 is a biologically active form that has a longer half-life in the body so it is often preferred in supplementation [29].

K2 acts in the body as a co-factor of 'vitamin K dependant carboxylase'. This enzyme, when enabled by its cofactor K2, can alter the structure of proteins by the process of gamma-carboxylation. Two examples of proteins are osteocalcin, found in bones and teeth, and matrix GLA protein found in cardiovascular tissues. Both of these proteins require the fat soluble vitamins A and D in their production [30]. Carboxylation of osteocalcin by K2 permits it to attract and retain calcium, which is good in bones [31,32]. The reverse of this process happens in cardiovascular tissues because matrix GLA proteins allow calcium to settle in arteries when they are uncarb oxylated but shed calcium when they are carboxylated with sufficient K2 [33–35]. Calcification or 'hardening of the arteries' is not good. Essentially, K2 helps direct calcium to where it is supposed to be and away from where it is not supposed to be. With an understanding of the importance of calcium signaling relative to mitochondrial associated membranes (MAMs) [36], it may be that K2 will be found to be involved but this has not been reported as yet. There is growing recognition of its importance in the nervous system, specifically in the Gaba6 protein and shingolipids, plus the actions of K2 with respect to oxidative injury and inflammation [37].

Dietary K2, after absorption, is processed in the liver and released into the circulation via high and low density lipoproteins. This makes them available for extrahepatic tissue uptake [38]. Fermented foods such as cheese have significantly higher levels of K2 than milk. The higher levels are provided by the bacteria. Natto (fermented soy), while not common in the American diet, is by far the post potent source of K2 [30]. Most K2 supplements are cultured from natto.

Menquinones are stored in several tissues of the body. Some of the highest concentrations are in the pancreas and the salivary glands [39]. There is a close relationship between both of these exocrine/endocrine glands through the hypothalamus. High concentrations of K2 are also found in the brain, heart and bone. Recent research begins to shed light on some of the antioxidant potential of K2 in the brain [40,41]. The significance of this potential cannot be underestimated with relation to all degenerative diseases, including dental caries, that have been related to oxidative stress. K2 is also starting to receive much more of the public's attention that it deserves in the literature [6,24].

Teeth are also nourished from the outside

Saliva is the medium for nourishment from the outside of the tooth [42]. Human saliva is made up of water, minerals, enzymes and buffering agents. Cytosolic free calcium plays the most critical role in signaling the salivary gland secretions [43–45]. Given calcium's dependency on K2 assisted carboxylation with respect to osteocalcin and matrix GLA proteins, further study may show that K2 is similarly involved in activation of salivary signaling and composition. It has already been demonstrated with insulin [46] and the exocrine secretions of the pancreas [47]. Saliva is a significant factor in the mineralization and demineralization of the erupted tooth's enamel as pH changes. It buffers against acid demineralization and provides minerals for re-mineralization when necessary. The critical pH of the tooth, or the pH at which it will de-mineralize, is variable rather than fixed at 5.5 [48]. This variability is based on saliva composition and flow. In common circumstances, this is why it is best to store an evulsed tooth in milk, which has calcium and phosphorus in it, rather than water. It is not presently known how saliva is connected to K2, but it has been associated with increased inorganic phosphate, the buffering agent, which leads to decreasing counts of lactobacillus acidophilus [5]. This would be indicative of an increasing pH or less acid saliva since lactobacillus thrive at lower pH levels.

Cheese has been classified as having anti-cariogenic properties while milk has been classified as non-cariogenic [49]. Milk may have a local effect on the caries process due to its mineral composition. Cheeses, on the other hand, are fermented in bacteria, which contributes to a significantly higher amount of K2 [30,50]. The beneficial effect of cheese then could be systemic as a source of K2 rather than local as a non-acid producing food or mineral provider. Alternately or additionally, there is a possibility that K2 may be absorbed across the oral mucous membranes. Recent studies have effectively applied ubiquinone as a topical to suppress periodontal inflammatory reactions due to oxidative stress [51].

Briefly, K2's effect on the outside of the tooth is accomplished through its influence on saliva composition. Primary prevention or maintaining mineralization is best focused on dietary nutrients. Secondary prevention or re-mineralization success will be largely determined by whether the composition of saliva can be altered to create a pro re-mineralization environment.

Designing a randomized controlled trial

To research the potential of K2 to prevent dental caries requires a properly designed randomized controlled trial (RCT). The ideal first step would be to identify an appropriate 'control group' who have never exhibited any dental caries. Secondly, a 'comparative group' would have to be identified with minimal confounding factors. Latitude, altitude, age, water fluoridation, income and education levels, professional care availability, smoking, diabetes, pharmaceuticals, food quality, supplementation and even behavioral differences due to monitoring could all be considered confounding factors. In an ideal RCT, the only difference would, in general, be diet and specifically the key nutrients involved.

Dentistry is very fortunate. The data has already been collected and documented. It needs to be re-analyzed with fresh eyes and a broader understanding of the dental caries process.

Collecting the data

Scientific research has always been a priority of the American Dental Association (ADA). Its’ research department was chaired by Dr. Weston A. Price from 1914 to 1928 [52].

Price was an experienced researcher who knew how to collect and record data. In the 1930’s, he focused on nutrition, particularly its effect on dental caries. Price collected data, photographs and reported on 14 groups of primitive cultures from different parts of the world. This was not a random selection of cultures. Each group was specifically selected because they were on the cusp of civilization. Some members of the group were still primitive in nutrition and customs while others had shifted to a modern, civilized diet and routine. Only this primitive/civilized blend could provide both the control and the study group. Importantly, studying a variety of racial groups from around the world would eliminate virtually all of the confounding factors listed previously. It would be safe to say that this quantity and quality of data could never be collected again due to the spread of modern culture and diet. The significant differences in the caries rates are summarized in Table 1.
Price subsequently had food samples from these groups sent to his lab for analysis. Repeatedly, he found the primitive diets to be high in nutrients including the fat soluble vitamins A and D and, in particular, a critical factor which he called Activator X. Price knew Activator X could be found in butter from grass fed animals, especially in the early growing season when the grass was growing quickly [5]. He understood it was a fat soluble nutrient. It was not till the year 2007, almost 60 years after his death, that Activator X was linked to menaquinone or K2 [6]. Since that time, it has received growing attention in the fields of cardiovascular disease, osteoporosis and diabetes.

Dentistry is in the fortunate position of having the evidence of what works based on Price’s research and documentation. Activator X can positively affect the outside of the tooth through saliva and the inside by helping regulate dentinal fluid flow. While this can be determined in lab research, we cannot duplicate the primitive control group in society. New research will have to focus on the ability of a K2 rich diet to arrest an existing caries process. This would provide the greatest benefits to children.

**Evaluation of the hypothesis**

The traditional theory of dental health, known as the ‘acid theory’, has been limited to the oral environment as though it is a unique process. Oral bacteria collect on the tooth’s surface as plaque. Refined carbohydrates like sugar feed these bacteria which produce acid. This de-mineralizes the enamel of the tooth. The incorrect assumption is that bacterial MMP’s then break down the dentin collagen in the caries process. There is no evidence to support this theory when it comes to dentin caries. Preventive efforts have focused on tooth brushing and flossing to reduce the bacteria, limiting sugar or substituting xylitol to reduce acid production and applying fluoride to re-mineralize enamel. After decades of the same approach, dental caries remains a significant problem despite valiant efforts to prevent it. Clearly a new approach is warranted.

The systemic theory of dental caries recognizes the impact of refined carbohydrates on the body through the influence of the hypothalamus and endocrine system. This is beyond traditional dentistry. Meticulous research done in the 1980’s and 90’s has been pushed aside because it did not suit the ‘acid theory’ model. This lab research can be duplicated and enhanced with better measuring tools. Free radicals, specifically reactive oxygen species, (ROS) have typically been considered the exhaust of energy production in mitochondria and a critical weapon for our immune system. Now we are seeing them as critical signals to trigger the production in mitochondria and a critical weapon for our immune system. Free radicals, specifically reactive oxygen species, have typically been considered the exhaust of energy production in mitochondria and a critical weapon for our immune system. 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<tr>
<th>Table 1</th>
<th>Percentage of teeth attacked by caries in primitive and modernized groups. Source: Nutrition and Physical Degeneration, 8th edition, page 402.</th>
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<td></td>
<td><strong>Primitive</strong></td>
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<tr>
<td>Gaels</td>
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**Consequences of the hypothesis**

Nature has provided the evidence to prevent dental caries. Nutrition is the dominant factor in this process. It affects the endocrine aspects of enhancing the tooth’s defenses by maintaining a nourishing dentinal fluid flow. The exocrine aspects of salivary glands or saliva secretion and composition are also nutritionally related. In terms of prevention of dental caries, optimum nutrition with fat soluble vitamins like K2 plays a far more significant role than the traditional dental recommendation to simply eat less sugar to minimize oral bacterial acids. Dental disease will be recognized as another inflammation related degenerative lifestyle disease like cardiovascular disease, osteoporosis and diabetes.

Who will lead this new nutrition paradigm? Will a field of ‘neurodentistry’ emerge as dentists expand their research to include the brain? The dental profession has an advantage in application because optimal nutrition can be added to the beneficial ‘cradle to grave’ services presently being provided. The impact, however, may be felt well beyond dental disease. It could affect all degenerative diseases that are inflammation based. Expanding beyond the silo of the oral cavity may meet some resistance. Alternately, other disciplines such as nutritionists may offer dental nutrition programs that may prove more effective than present dental prevention programs. In the end, public health teams may play the key role.

**Author’s information**

Dr. K. Southward received his dental degree from the University of Toronto in 1971. He maintained a private dental practice for
43 years with a focus on preventive dentistry and nutrition. He has published articles in dental journals relative to dental caries theory and periodontal health. He has recently retired.

**Conflict of interest**

The author declares that he has no conflicts of interest.

**Acknowledgement**

Dr. Weston A. Price's research data, which is presented in Table 1, is used with the kind permission of the Price-Pottenger Nutrition Foundation.

**References**

While dentists do not prescribe pharmaceutical drugs or supplements for detoxification, it is important for dental professionals to understand the basics of “chelation.” This is especially because a growing number of patients are seeking out biological dentists to remove their mercury fillings as part of a detoxification program. More specifically, in some cases, a health care practitioner recommends mercury-free dentistry and detoxification (chelation) to assist the patient in recovering from a medical condition or in achieving a more optimal level of well-being.

Derived from the Greek word for claw, the verb chelate (pronounced “key-late”) is defined as “1. To combine a metal ion with a chemical compound to form a ring. 2. To remove a heavy metal, such as lead or mercury, from the bloodstream by means of a chelate.” Thus, chelation is used to detoxify the body by assisting it in excreting heavy metals.

Chelation was first developed for industrial purposes in the early twentieth century, and research during World War II for its effectiveness as an antidote to poison gas advanced the use of chelation for other forms of poisoning. Due to a burgeoning awareness of the impacts of heavy metals on health, chelation is currently being practiced for medical purposes more often.

Importantly, heavy metals testing and chelation address mercury as well as other metals such as cadmium and lead, all of which are stored within the body through a lifetime of exposures. This means that the combination of testing and detoxification has the potential to improve a wide-range of health conditions associated with these heavy metals.

This concept is essential considering that scientific research has linked metals to the risk of cardiovascular disease, diabetes, and obesity, and even more specifically, in a series of studies from 2011-2015, mercury was associated with increased body mass index, cardiometabolic risk factors, insulin resistance, and metabolic syndrome. Relating this body burden of heavy metals to medical interventions, researchers of a study published in 2014 warned that metals and environmental chemicals should be considered as factors “when studying the complex etiology of cardiometabolic diseases which could result in targeted interventions to decrease health disparities and the associated risks of ongoing exposures.”

Scientific literature also supports the potential of heavy metal detoxification in improving health outcomes. Perhaps the most well-known study documenting the efficacy of chelation is from the National Heart, Lung, and Blood Institute, which sponsored the first large-scale clinical trial on detoxification in patients with coronary heart disease. The results, published in 2014, showed that chelation therapy with disodium EDTA benefitted patients with diabetes, producing the following statistics: “Patients with diabetes, who made up approximately one third of the 1,708 TACT participants, had a 41 percent overall reduction in the risk of any cardiovascular event; a 40 percent reduction in the risk of death from heart disease, nonfatal stroke, or nonfatal heart attack; a 52 percent reduction in recurrent heart attacks; and a 43 percent reduction in death from any cause.”
Not surprisingly, a variety of products and practices related to detoxification have emerged due to the interest in detoxification and the scientific evidence of its benefits. Most therapeutic protocols involve plant-based or nutritional compounds that stimulate the body’s innate free-radical and toxin control systems, with focus on glutathione and total thiol status.12 13 14 15 16 17 18 19 20 21

However, there is no overall consensus among medical practitioners as to what the best, safest, or most effective way to chelate is. In fact, the gamut of chelation products and protocols available for use today have found themselves at the root of a debate because both health care practitioners and patients have distinct preferences.

Needless to say, as a biological dentist, it is highly likely that you will encounter patients following a number of different detoxification methods in your practice. So, being familiar with the wide-range of chelation options, which are still rapidly evolving, is beneficial for your interactions with patients and health care professionals alike.

However, before continuing with an overview of the practices and products related to chelation, it is essential to note that ANY and ALL chelating agents and detoxification programs can cause adverse reactions, especially if a patient is allergic to any of the ingredients. Chelation can also remove essential nutrients, so patients need to be closely monitored. Thus, chelating agents are very powerful tools, and they should be used only under the supervision of a qualified medical professional.

Since baseline testing for heavy metals is often used prior to and after chelation, the first portion of this article, adapted from Sam and Michael Ziff’s book Dentistry without Mercury, reviews the types of testing available. The second portion of this article summarizes some of the products and protocols commonly used for chelation and is mainly compiled from scientific reviews by Margaret E. Sears22 and Joseph Mercola with Dietrich Klinghardt.23

Commonly Used Testing for Mercury Exposure24

This testing portion of the article has been adapted from Sam and Michael Ziff’s book Dentistry without Mercury. Note that this material is copyrighted by the IAOMT. Michael Ziff, DDS, MIAOMT, was a founding member of IAOMT.

For years, the American Dental Association (ADA) maintained that urine and blood tests for mercury content were a valid means of determining safe exposure levels and dangerous exposure levels. However, after the 1984 Workshop on the Biocompatibility of Metals in Dentistry, the ADA finally agreed with the overwhelming scientific evidence (existent since the early 1960's) indicating that blood and urine tests are invalid for determining toxicity or cellular damage that may be occurring in the body.

Since that time, some urine and blood tests have been updated based on new information, and a variety of other tests for mercury exposure have also been developed. Many of these tests are employed to help document levels of mercury in the body potentially caused by dental amalgam fillings or other sources. It should be noted again that some individuals can have reactions to these tests, and any test for heavy metals should only be pursued with the care of a knowledgeable medical professional.
Of course, the first criterion for testing in relation to potential toxic side effects from mercury fillings is that evaluation be done prior to amalgam replacement and prior to the implementation of any detoxification protocols. This is necessary to establish a “base line” of values. Once a base line has been established for all the values to be monitored, then these values can be monitored by subsequent testing to determine whether changes that occur in the individual's health and base line values have any relationship to the elimination of mercury-containing dental fillings.

1. Hair Analysis

This is a simple test that has been around for many years, and published research studies clearly document the validity of hair analysis for heavy metal screening. For example, a 1980 U.S. Environmental Protection Agency (EPA) report indicated that human hair is excellent for biological monitoring of mercury.25

Although human hair primarily reflects organic mercury exposure, studies have indicated that 10-20% is from inorganic mercury.26 Regardless of the composition, high mercury hair values, without any external source of exposure should be a matter of concern.

2. Urine mercury, lead, copper, tin, and albumin testing

Testing the urine for the presence of mercury, lead, copper, tin and albumin is another route for establishing base line values.

The reason for testing lead levels is two-fold. First, it can rule out lead toxicity, or it can show that the toxic effects of mercury are increased when lead is present. Second, lead inhibits the enzyme delta-aminolevulinic acid dehydratase (ALA-D) and causes an increased excretion of delta-aminolevulinic acid (ALA). Mercury inhibits delta-aminolevulinic acid dehydrogenase (different from what is listed above, but also known as ALA-D) and causes an increased excretion.27 Therefore, if lead is not a factor but urine ALA-D is increased, then blood levels of ALA-D should be checked to evaluate which enzyme (dehydratase or dehydrogenase) has been inhibited. If dehydrogenase has been inhibited, that would further tend to support the toxicity of the mercury body burden.

Copper, silver, and tin are also given off by amalgam fillings. The presence of high copper, silver, or tin in the urine could further indict amalgam fillings.

Urine albumin may be indicative of mercury burden, too. This is because the excretion of albumin is decreased during acute or chronic exposure to mercury. Research has shown an increase or normalization of urine albumin after replacement of amalgam fillings.28 29

3. Urine mercury porphyrin profile

The testing of porphyrins can produce a profile specific to mercury.30 John Wilson, MD, explains, “Urinary porphyrin tests...start off showing impaired enzyme function, and subsequently, following detoxification of mercury, show restored enzyme function, suggest that mercury levels have dropped to a point at which the enzymes are functioning again for that patient.”31
4. Fecal metal screen

This is a single-sample, one-pass analysis of a stool specimen that provides information on 25 different elements. The feces are a major route of excretion for mercury and silver; yet, while this is a valid test, it is seldom, if ever, performed to check for heavy metal body burden.

Production and collection of this type of data would permit establishing correlations between the health condition of an individual, the numbers and surfaces of amalgam dental fillings, and the fecal content of mercury, as well as other amalgam metals such as silver, copper, tin and zinc.32

5. Intra-oral mercury vapor levels

By testing intra-oral mercury vapor levels, it is possible to establish how much mercury is being released from an individual’s amalgam fillings. A measurement is taken before stimulation by chewing gum for 10 minutes and after chewing gum for 10 minutes. If this is conducted, the approved IAOMT intra-oral protocol should be utilized. This test is not diagnostic of mercury intoxication, but it does provide data about releases from a person’s mouth.

The significance of this information is that science has clearly demonstrated that over 80% of inhaled mercury vapor is absorbed through the lungs, where it is then distributed throughout the body.33 From a documentation standpoint, intra-oral mercury vapor readings pre-amalgam removal and post-amalgam removal will clearly demonstrate exposure to mercury vapor caused by stimulation from dental amalgam fillings.

6. Blood mercury levels

Whenever possible, any other blood base lines desired should be done at the same time blood samples are taken to determine blood mercury levels. Although blood mercury levels are not diagnostic of chronic mercury toxicity, there is published research showing a decline in blood mercury levels after elimination of mercury-containing dental fillings.34 35

7. Mercury levels in saliva

Testing salivary mercury content is relevant because dental amalgam fillings are in the mouth, and they can logically impact the amount of mercury in saliva. One textbook explains, "No mercury has been detected in saliva samples unless there was a mercury vapor exposure. Salivary glands are primary organs of excretion of mercury, and excessive exposure to inorganic mercury can result in salivary gland enlargement as well as excessive salivation....Salivary mercury levels can be much higher than blood mercury levels...."36

8. Cysteine and glutathione status

Scientific research is demonstrating that cysteine and glutathione status have a very definite influence on efficiency of immune function.37 38 This could be of extreme significance to show a variation in blood and/or urine sulfur amino levels pre- and post- amalgam replacement.
9. Quicksilver Scientific’s Tri-test

Christopher W. Shade, PhD, of Quicksilver Scientific, has patented a new testing technology that specifies which forms of mercury, inorganic or methylmercury, are in the patient’s body. It also measures the mercury in blood, urine, and hair, identifying mercury exposures and excretion abilities.

10. Mercury challenge or mobilization testing

After establishing a mercury baseline, it is extremely important to then evaluate the potential mercury body burden of the individual. Science has established that in most cases, much of the mercury body burden is contained in the kidneys, while the remaining portion is distributed to the brain, other organs, and glands.

The express purpose of a challenge test is to administer a chelating agent that has been scientifically documented to bind to mercury and cause its excretion from the body. The challenged excretion levels are then compared pre- and post-replacement of amalgam and often several times during a detoxification protocol after replacement.

Several challenge tests are available. At the present time, there are several FDA approved drugs that can be used for this purpose:

1) British Anti-Lewisite (BAL), or Dimercaprol, is effective and has been used for more than 80 years, but it is known to have many disagreeable and serious side-effects.

2) Penicillamine has also been used by the medical profession for a great number of years, but it has many side-effects as well.

3) 2,3 Dimercaprol succinic acid (DMSA) is a water soluble derivative of BAL that was approved by the FDA in March of 1991 as a product to remove lead from children. It is also very effective for mercury and has fewer side effects than Dimercaprol, although individuals have been known to have adverse reactions to DMSA as well.

Similarly, in Europe, 2,3-Dimercapto-1-Propanesulfonic Acid (DMPS), manufactured by Heyl of Germany, is extensively used in the treatment of mercury intoxication. It is marketed under the trade name Dimaval in 300 mg capsules for oral use and as a 250 mg injectable preparation.

Dimaval is a water-soluble derivative of Dimercaprol, with fewer side effects. DMPS binds to mercury very aggressively and can be utilized for the mercury mobilization testing.

Some individuals have reported an adverse allergic reaction after receiving DMSA and DMPS. If an individual is allergic or chemically sensitive, the administering physician should test for a possible reaction prior to administering DMSA and DMPS. Notably, some patients with sulfa drug allergies have reported side effects from taking DMSA.

Another problem with DMSA and DMPS is that they will also combine with thiols forming conjugated mixed disulfides. Once conjugated with cysteine or glutathione, its ability to combine with or detoxify mercury and other heavy metals has been compromised. Nevertheless, DMSA and DMPS remain a popular option for chelation.
Summary of Commonly Used Detoxification Products and Protocols
This summary was compiled largely due to the assistance of a 2013 scientific review by Margaret E. Sears and a 2011 review by Joseph Mercola and Dietrich Klinghardt.

1. Pharmaceutical products

- **EDTA (ethylene diamine tetraacetic acid):** FDA approved for chelation of lead, EDTA is often given intravenously to excrete toxins via urine. It was used in a clinical trial.

- **Penicillamine:** This drug, often used for treating rheumatoid arthritis, binds with copper, cadmium, lead, arsenic, and mercury to excrete them in the urine, although DMPS and DMSA are usually preferred as chelators.

- **DMSA (meso-2, 3-dimercaptosuccinic acid):** Demonstrated to cross the blood-brain barrier in reaching methylmercury, DMSA is orally administered as a means of causing arsenic, lead, and mercury to be excreted in the urine. Some doctors recommend that DMSA only be used after amalgam fillings are removed.

- **DMPS (Sodium 2,3-dimercaptopropane-1-sulfonate):** DMPS should not be used in patients who still have amalgam fillings, but for those without dental mercury, it is administered to excrete heavy metals in the urine.

2. Natural supplements, products, and practices

- **Chlorella**, a type of algae, has been reported to assist in removing mercury from body tissues and to cause the excretion of mercury through the feces; however, as much as one-third of the population suffer gastrointestinal problems from chlorella.

- A **fibrous diet** has been suggested to lower the levels of mercury in the brain and blood.

- **Sulphur-containing foods** including garlic, cilantro, and broccoli have been said to assist in reducing mercury levels in the body, and cilantro is sometimes used with other chelators.

- **Supplements** including taurine, alpha lipoic acid (ALA), N-acetyl cysteine (NAC), glutathione, and selenium have been used with varying success rates and experiences for inducing mercury excretion. Vitamin E, Vitamin C, hyaluronic acid, and methylsulfonylmethane (MSM) have also been applied as chelators.

- **Oxidative Stress Relief (OSR)** is a natural supplement made by IAOMT’s Dr. Boyd Haley. It was developed to increase glutathione levels for heavy metal detoxification. In spite of the fact that OSR is natural, the U.S. Food and Drug Administration demanded the product undergo a formal approval process, and this resulted in OSR being taken off the market in 2010. OSR has since been renamed Irminix® and is in the process of going through clinical trials in Europe and the USA.

- **Sweating** was used historically by Spanish miners to release toxins, and some medical professionals continue to encourage its use to reduce mercury levels.

- **Lymphatic massage, exercise, clay baths, saunas, and foot baths** have likewise been recommended as natural ways to detoxify.

- **Spagyric remedies**, which are plant-based medicines, are sometimes used for detoxification.
3. Detox Protocols

- Hal Huggins, DDS, MS, is considered one of the pioneers in mercury-free dentistry, and he is the author of *It’s All in Your Head: The Link Between Mercury Amalgams and Illness*. His protocol involves a dental revision (including removing dental mercury and toxins from root canals) and a number of other changes. According to the protocol, for nutritional changes, “blood chemistry will divulge how much carbohydrate, protein and fat your specific body requires, as well as telling how well you digest these foods. In addition, blood tells us which supplementation (if any) that you need.”

- Andrew Cutler, PhD, PE, brought wide-scale attention to the issue of mercury toxicity in his 1999 book *Amalgam Illness* and developed what is commonly referred to as “the Cutler Protocol.” He has described his popular protocol by noting that it “uses alpha lipoic acid (ALA), an over the counter nutritional supplement, and may optionally also use DMSA or DMPS. All are administered orally with adequate frequency to maintain reasonably steady blood levels.”

- Dietrich Klinghardt, MD, PhD, has addressed barriers to detoxification including nutritional deficiencies, infections such as Lyme disease, and yeast issues. His protocol uses high protein, mineral, fatty acid, and fluid intake, cilantro, chlorella, garlic, and fish oil to release toxins.

- Christopher W. Shade, PhD, is the President and Founder of Quicksilver Scientific, LLC, which offers the Tri-test described above to help establish a baseline. In regards to heavy metal detoxification, Quicksilver offers a variety of supports such as its IMD Intestinal Cleanse, Clear Way Cofactors Phytonutrients, and Nanosphere Glutathione Support.

- Amy Yasko, PhD, NHD, AMD, HHP, FAAIM, is the author of *Autism: Pathways to Recovery*, and her work is designed to assist those with “autism and other forms of chronic neurological inflammation.” Based on a personalized test, her protocol “targets genes that need nutritional support for optimal function. Specific foods and supplements are used address areas of genetic weakness, in order to promote the body’s ability to detoxify and heal.”

- A number of other protocols are now also suggesting genetic testing to assist patients in understanding limitations they might have in excreting toxins. One area that is currently receiving attention involves the MTHFR gene (methylenetetrahydrofolate reductase (NAD(P)H)) and its role in detoxification.

Concluding Remarks

Patients and their health care providers obviously have many options when devising a detoxification plan. Understanding the array of tests, products, and protocols associated with chelation and detoxification allows the dentist to recognize and understand decisions being made and processes taking place as part of each patient’s individualized health plan.

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Chelation therapy to prevent diabetes-associated cardiovascular events

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Abstract

\textbf{Purpose of review—}For over 60 years, chelation therapy with disodium ethylene diamine tetraacetic acid (EDTA, edetate) had been used for the treatment of cardiovascular disease (CVD) despite lack of scientific evidence for efficacy and safety. The Trial to Assess Chelation Therapy (TACT) was developed and received funding from the National Institutes of Health (NIH) to ascertain the safety and efficacy of chelation therapy in patients with CVD.

\textbf{Recent findings—}This pivotal trial demonstrated an improvement in outcomes in postmyocardial infarction (MI) patients. Interestingly, it also showed a particularly large reduction in CVD events and all-cause mortality in the prespecified subgroup of patients with diabetes. The TACT results may support the concept of metal chelation to reduce metal-catalyzed oxidation reactions that promote the formation of advanced glycation end products, a precursor of diabetic atherosclerosis.

\textbf{Summary—}In this review, we summarize the epidemiological and basic evidence linking toxic metal accumulation and diabetes-related CVD, supported by the salutary effects of chelation in TACT. If the ongoing NIH-funded TACT2, in diabetic post-MI patients, proves positive, this unique therapy will enter the armamentarium of endocrinologists and cardiologists seeking to reduce the atherosclerotic risk of their diabetic patients.

\textbf{Keywords} cardiovascular disease; chelation; diabetes; metals; Trial to Assess Chelation Therapy

INTRODUCTION

In November 2012, we presented the results of the NIH-funded Trial to Assess Chelation Therapy (TACT) at the American Heart Association Scientific Sessions in Anaheim,
Metal chelation for atherosclerosis had long been thought to be quackery by traditional cardiologists, yet persisted in clinical use. In spite of the absence of actionable data, a safety and efficacy trial of edetate disodium (disodium ethylene diamine tetra acetic acid, Na$_2$EDTA) chelation in patients following myocardial infarction was funded in 2002 by the NIH, and completed over a decade [1,2].

The results of the primary analysis of TACT were surprising. Instead of debunking a quack therapy, the results of this double-blind, placebo-controlled clinical trial demonstrated benefit of 40 intravenous edetate disodium-based chelation infusions in reducing cardiovascular disease events in a secondary prevention population [1,2] (Fig. 1a). The effect of metal chelation on diabetic patients with cardiovascular disease (CVD, defined as prior myocardial infarction) is the focus of this review.

Of the 1708 post-MI patients studied in TACT, 633 had diabetes [3**]. Diabetic patients assigned to chelation therapy demonstrated a 41% relative risk reduction in combined cardiovascular events compared with placebo infusions ($P=0.0002$, 5-year number needed to treat to prevent one event = 6.5) (Fig. 1b). There was a 52% relative reduction in the risk of recurrent myocardial infarction ($P=0.015$; Fig. 1c); and a 43% relative risk reduction in mortality ($P=0.011$, 5-year number needed to treat to prevent one death = 12; Fig. 1d) [3**]. This review will touch upon the key role that essential and toxic metals, may play upon the development of vascular complications, particularly in patients with diabetes, the results of a clinical trial of metal chelation, particularly in diabetic patients, and ongoing research.

**BRIEF HISTORY OF CHELATION BEFORE THE TRIAL TO ASSESS CHELATION THERAPY**

Chelation, etymologically from *chelos*, the Greek word meaning claw, refers to the pincer like manner in which cations are incorporated into an organic molecule referred to as a chelating agent, forming a complex ring structure. The chelate–chelator complex is usually more stable, soluble and resistant to dissociation, allowing for effective removal from tissue and excretion in the urine or in bile [4].

A nearly ideal chelator, edetate is a synthetic amino acid with high affinity for metallic and non-metallic cations. EDTA is water soluble and excreted in the urine, forming strong coordinate bonds with certain ions such as calcium, zinc, cadmium and lead [5]. It was first developed in Germany in the late 1930s for chelation of calcium stains from textiles, and later applied to the treatment of heavy metal poisoning and hypercalcemia. The strong bond of EDTA with calcium led early proponents to hypothesize that it might reduce the calcium burden of atheromatous plaque [6,7].

In 1956, Clarke et al. [8] described the first use of chelation therapy and showed that 19 out of 20 patients with severe angina had improvement of symptoms and/or electrocardiographic findings after edetate disodium chelation infusions. The beneficial effects reported in this small study were followed by other small case reports and case series that failed to corroborate the efficacy of chelation in treating atherosclerosis. By the 1970s, chelation
therapy had firmly moved into the realm of complementary and alternative medicine (CAM). Clinical trials were eventually performed, but were too small individually or in aggregate to exclude a small-to-moderate beneficial effect [9–13]. Yet over the decades, patients continued to seek and receive chelation from practitioners. Owing to the unsupported use of chelation, the NIH released a Request for Applications (RFAs) in 2001 for a safety and efficacy clinical trial of edetate disodium chelation in cardiovascular disease. The Trial to Assess Chelation Therapy (TACT) was the result. The positive results in patients with diabetes suggest that toxic metals may have a role in the excess atherosclerotic risk of such patients. In order to better understand the TACT results, it is worthwhile; therefore, to consider the epidemiological and mechanistic links between toxic metals and atherosclerosis.

**TOXIC METALS AND VASCULAR DISEASE MECHANISMS AND EVIDENCE**

Essential metals are crucial in maintaining cellular homeostasis, but excessive exposure may lead to metal-induced toxicity by increasing production of reactive oxygen species (ROS). ROS can overwhelm and deplete the cell’s intrinsic antioxidant defenses leading to oxidative stress. Iron and copper are the two best-known metals that have the potential of generating ROS. They are both effectively chelated by the edetates. Other metals, referred to as xenobiotic or toxic metals, have no role in human physiology and, like lead, may be toxic even in dilute concentrations. Some of the most commonly found toxic metals in humans include lead, cadmium, arsenic, and mercury, all of which cause – or at the very least are associated with – CVD.

Diabetes-related macrovascular complications, particularly CVD, have been found to be mediated by advanced glycation end products (AGEs), advanced lipoxygenation end products (ALEs), and protein oxidation products (PrOPs) [14]. AGEs are heterogeneous cross-linked complexes formed by the nonenzymatic glycation and oxidation of aldose sugars with proteins, lipids and nucleic acids [15]. There is also convincing evidence that formation of chemically active, cross-linked aldose sugars requires metal catalyzed oxygen chemistry to produce oxygen and hydroxyl radicals. AGEs have a deleterious effect on the integrity of the vessel walls through several mechanisms, including activation of the receptor for AGE (RAGE) [16]. RAGE activation triggers rapid generation of ROS and a pro-inflammatory signaling cascade with expression of pro-atherogenic adhesion molecules [17]. This interaction between AGE and its receptor perpetuates chronic vascular injury, which may play a role in the progression of diabetic atherosclerosis. These reactions may require metals that donate or accept electrons, in order to create oxygen and hydroxyl-free radicals. There is abundant evidence linking toxic metal accumulation and CVD [18–24]. We restrict our discussion below to lead and cadmium because of their effective chelation by the edetates.

Lead is a toxic metal found in contaminated water, air, food and soil because of its nonbiodegradable nature and continuous use. Human exposure to lead occurs mainly through leaded gasoline still used in piston engine aircraft, lead-containing pipes, smelting of lead and its combustion, lead-based paints and battery recycling (Fig. 2) [25]. Over the past three decades, there has been a dramatic drop in mean lead blood levels in the United States. Arsenic is another toxic metal that is found in water, food, and soil, and is released into the environment from industrial processes. Arsenic exposure is associated with an increased risk of CVD and cardiovascular mortality [26]. Cadmium, a toxic metal found in cigarette smoke, food, and soil, is also associated with an increased risk of CVD [27]. Mercury, another toxic metal found in food, water, and soil, is associated with an increased risk of CVD [28].
States because of banning lead-based paints and leaded gasoline used by ground vehicles. However, environmental exposure continues, as evident in the recent public health crisis in Flint, Michigan because of lead seepage into drinking water. Lead contamination of drinking water is typically caused by metal corrosion of water pipes, particularly lead service lines. The incidence of elevated blood lead levels after the city of Flint changed its water source to the Flint River increased from 2.4 to 4.9% \((P < 0.05)\) [26]. Lead can be inhaled or ingested, and then absorbed into the bloodstream [27]. Once absorbed, lead moves into the red cell compartment, where it is bound by metallothionein-like protein, a thiol-containing protein. Lead has a half-life of about 28–36 days in blood, 1–1.5 months in soft tissue, and about 25–30 years in bone [28–29]. When lead completes its lifespan in blood, it is released and displaces calcium in bone. Bone then acts as an endogenous source of lead, releasing lead back into the bloodstream years after exposure [29]. A single disodium edetate infusion of 3 g will increase lead excretion by nearly 4000% in a few hours [30,31*].

Epidemiological data from various National Health and Nutrition Examination Surveys (NHANES) support an association between toxic metal exposure and CVD events. The prospective analysis of NHANES III participants showed an increase in all-cause and cardiovascular mortality, with cause specific deaths highest for myocardial infarction and stroke at lead blood levels greater than 0.10 μmol/l [32,33]. Several possible mechanisms have been postulated for the association of lead accumulation and its direct and indirect effect on CVD. In-vivo and in-vitro studies have shown that one mechanism by which chronic lead exposure causes CVD is by increasing production of ROS leading to oxidative stress, limiting nitric oxide availability and disrupting the nitric oxide signaling cascade [34–37]. Nitric oxide has important cardioprotective roles including regulation of blood pressure and vascular homeostasis such as regulation of vascular dilation, local cell growth and protection of the vessel from injury because of platelet aggregation. Therefore, the impaired synthesis or excessive oxidative degradation of nitric oxide leads to endothelial dysfunction, a starting point for atherosclerosis.

Lead increases protein kinase C (PKC) activity and promotes atherogenicity [38,39]. PKC regulates many functions including cell growth, vascular smooth muscle contraction, blood flow and permeability [39]. Lead additionally promotes inflammation, fibrosis and apoptosis via activation of nuclear factor-κB. Lead also increases the production of endothelin, vasoconstrictor peptides primarily synthesized and secreted by endothelial cells that can raise arterial pressure. Khalil-Manesh et al. [40] found that rats exposed to low levels of lead for 1–12 months had a significant rise in arterial pressure and marked increase in plasma endothelin 3 concentrations. These and other proposed mechanisms may explain how lead causes vascular injury in humans. If more than one of these mechanisms is relevant to human diabetes, then lead may act as a risk factor multiplier, perhaps at least partially explaining the effect of lead chelation.

Cadmium is another toxic metal that accumulates in the environment and is associated with atherosclerotic disease. Environmental sources of cadmium include rechargeable batteries, electronics, building construction, jewelry, toys, plastic production, paint pigments and metal coating [41–43]. Tobacco leaves, spinach and root vegetables naturally accumulate and concentrate high levels of cadmium from the soil, dependent on the cadmium content of
fertilizers. Tobacco use, therefore, is one of the single most important sources of cadmium exposure [44]. Cadmium accumulates in both the liver and kidneys, protein bound to metallothionein [45,46]. Because of its slow urinary excretion, cadmium has a half-life up to 38 years [41]. A single disodium edetate infusion of 3 g will increase cadmium excretion by about 700% in a few hours [30,31].

Similar to lead, there are several mechanisms that have been suggested to explain the role of cadmium in atherosclerosis. In a systematic review, Tellez-Plaza et al. [47] found evidence supporting cadmium as a cardiovascular risk factor. Cadmium can indirectly interfere with antioxidant response by binding to metalloproteins, thereby increasing ROS causing lipid peroxidation and cellular injury and DNA damage [48]. The Atherosclerosis Risk Factors in Female Youngsters study examined carotid intima–media thickness in 195 young healthy women and measured serum metal concentrations, including cadmium. They reported an independent association between high cadmium levels and intima–media thickness, exceeding the 90th percentile in distribution, representing early atherosclerotic vessel wall thickening [49]. Cadmium has also been found to raise blood pressure, an established risk factor for cardiovascular disease [50,51]. In a large population study of NHANES III participants between 1988 and 1994, creatinine-corrected urinary cadmium levels in men were associated with an increase in risk of all-cause and cardiovascular mortality, including coronary artery disease-associated mortality [52]. Finally, Tellez-Plaza et al. [53] examined 3348 American Indian adults ages 45–74 years who participated in the Strong Heart Study from 1989 to 1991 and measured urine cadmium levels. Urine cadmium levels were associated with an increased incidence of cardiovascular disease and mortality. The diabetic subgroup in this study showed a stronger, statistically significant association between cadmium and cardiovascular disease endpoints when compared with those without diabetes.

THE TRIAL TO ASSESS CHELATION THERAPY

Coincident with the interest of the diabetes scientific community in metal-catalyzed oxygen chemistry as an important part of the formation of AGEs and complications of diabetes, the cardiology community was in the final phases of planning a metal chelation trial. As noted above, edetate disodium chelation had been used to treat atherosclerotic complications for many years. A literature review in 2000 concluded that there was insufficient evidence for or against the practice [12]. This was followed by a more formal 2002 Cochrane Review again concluding that there was insufficient evidence to decide on the effectiveness of edetate sodium to treat atherosclerotic disease [13]. This conclusion sparked the interest of the NIH to release a RAF for a randomized double-blind, placebo-controlled trial to test the efficacy and safety of chelation therapy in patients with coronary artery disease. The study that resulted, TACT, was widely expected to be negative. During the planning phase, high-dose oral multivitamins and minerals (OMVM) were added in a factorial design, as most chelation practitioners also recommended that patients take large doses of OMVM during intravenous chelation [1]. The four randomized groups in the 2 × 2 factorial trial included:

1. active chelation and active OMVM
2. active chelation and placebo OMVM

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Eligible patients had to be at least 50 years of age, have had prior myocardial infarction at least 6 weeks prior to enrollment, and have a serum creatinine level 2.0 mg/dl or less. Enrollment took place between 2003 and 2010. There were 1708 patients enrolled in the clinical trial across 134 sites in the United States and Canada. The blind was broken and analyses were completed, in 2012.

**STUDY TREATMENTS**

Intravenous chelation regimens developed organically through the years, and although the consistent chelating drug was edetate disodium, other components were often added (Table 1). The TACT infusion regimen included 30 weekly infusions followed by 10 maintenance infusions, the latter 2 weeks to 2 months apart. By 18 months after randomization, over 90% of the infusions had been administered. The randomized OMVM or oral placebo was taken throughout the duration of the trial and consisted of three caplets twice daily, containing 28 individual components (Table 2).

**ENDPOINTS AND STATISTICAL POWER**

The primary end point was a composite of all-cause mortality, myocardial infarction, stroke, coronary revascularization and hospitalization for angina. The principal secondary end point was cardiovascular mortality, recurrent myocardial infarction and stroke.

**OVERALL RESULTS**

The intention-to-treat analyses revealed a statistically significant reduction in the primary endpoint (hazard ratio 0.82; 95% CI 0.69–0.99; \( P = 0.035 \)). Although the individual components of the primary endpoint did not reach statistical significance, all but total mortality had point estimates favoring active chelation treatments.

**TRIAL TO ASSESS CHELATION THERAPY DIABETES SUBGROUP**

Patients with diabetes were defined as those who self-reported diabetes, were receiving pharmacotherapy for diabetes, or had a fasting glucose of at least 126 mg/dl at baseline. Of the 1708 participants enrolled in the study, 633 (37.1%) patients had diabetes mellitus.

**BASELINE CHARACTERISTICS**

Among the patients with diabetes, 322 were randomized to receive edetate disodium-based infusions and 311 received placebo infusions. There were no significant between-group differences in important baseline characteristics. The median age was 65 years, with 19% women and 11% minorities. The trial encouraged patients to maintain standard, evidence-based treatments for patients with prior MI and diabetes.
Mean fasting blood sugar was 132 mg/dl, and low-density lipoprotein (LDL) cholesterol was 81 mg/dl. Within the diabetic population, 81% had undergone prior coronary revascularization (either percutaneous or surgical). There were 92% of patients on aspirin, clopidogrel or warfarin, and 76% on statins. Treatment of diabetes required insulin in 26%, and oral hypoglycemics in 61%.

RESULTS OF TRIAL TO ASSESS CHELATION THERAPY IN PATIENTS WITH DIABETES

In spite of the arduous nature of the study therapy, 73% of patients completed 30 infusions, and 61% completed all 40. There was a statistically significant interaction ($P$ of interaction of the primary endpoint = 0.004) between edetate disodium therapy effect and the presence of diabetes mellitus at baseline. There was a striking benefit of the edetate disodium infusions in the diabetic patients randomly assigned to receive active infusions compared with placebo with 25% vs. 38% incidence of the primary outcome (hazard ratio 0.59; 95% CI 0.44–0.79; $P$ = 0.0002). There was a 15% absolute decrease in the 5-year Kaplan–Meier primary event rate. The number of patients that needed to be treated to prevent a single event over 5 years was 6.5 (Fig. 1b). The prespecified major secondary end point, cardiovascular death, recurrent myocardial infarction or stroke, was also reduced in those randomized to the active chelation treatment, with a 40% relative risk reduction (hazard ratio 0.60; 95% CI 0.39–0.91; $P$ = 0.017). Patients with diabetes randomized to EDTA chelation treatment had a reduction in recurrent MI (hazard ratio 0.60; 0.48; 95% CI 0.26–0.88; $P$ = 0.015) (Fig. 1c), all-cause mortality (hazard ratio 0.57; 95% CI 0.36–0.88; $P$ = 0.011; Fig. 1d), and coronary revascularization (hazard ratio 0.68; 95% CI 0.47–0.99; $P$ = 0.042; Table 3). When compared with diabetic patients, the patients without diabetes did not have this treatment effect in primary or secondary event outcomes. In patients with diabetes, the Kaplan–Meier curves continued to separate after infusions were completed, a legacy effect unlike most in cardiology, and perhaps supporting the beneficial effect of toxic metal removal by EDTA.

DISCUSSION

In the United States, 23.3 million people have diabetes mellitus [54]. Another 7.2 million are estimated to have undiagnosed diabetes. Diabetes is a key risk factor for cardiovascular disease with a two-fold to three-fold increased likelihood of vascular death. The cause of this excess cardiovascular morbidity and mortality is not completely clear, but the results of TACT inevitably point to mechanistic speculation. The chelation infusion did not treat hyperglycemia. In TACT, there were no differences in mean fasting blood glucose levels from baseline to the 30th infusion in neither the placebo nor the active chelation groups. There were no differences in pharmacotherapy for diabetes between the treatment groups throughout the study. This evidence suggests that although hyperglycemia, the hallmark of diabetes, is a risk factor for cardiovascular disease, it is clearly not the only modifiable risk factor in diabetic patients.
CONCLUSION

Edetate disodium chelation, far from standard therapy, is currently a Class 2B indication in the Stable Ischemic Heart Disease Guidelines [55]. As such, the results of TACT require replication and mechanistic investigation. With this in mind, NIH (NCCIH, NHLBI, NIDDK, NIEHS) has funded the second Trial to Assess Chelation Therapy, TACT2. TACT2 will have identical inclusion criteria as TACT, with the exception of including only diabetic patients post-MI.

TACT2 is currently enrolling with a target sample size of 1200 post-MI diabetic patients. We welcome potentially interested sites, investigators and patients to contact us for more details, or log on to www.tact2.org.

Acknowledgments

We gratefully acknowledge the advice and critical review of our manuscript by Dr Ana Navas-Acien, MD, PhD and Dr David M. Nathan, MD.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest
▪▪ of outstanding interest


KEY POINTS

- TACT showed a marked reduction in CVD events and all-cause mortality in the subgroup of patients with diabetes.
- The results may support the concept that metal chelation reduces metal-catalyzed oxidation reactions that promote the formation of advanced glycation end products.
- TACT2, in diabetic post-MI patients, is currently enrolling patients in an effort to replicate these findings, and define a mechanism of benefit.
FIGURE 1.
The Trial to Assess Chelation Therapy Kaplan–Meier estimates of the primary composite endpoint: edetate disodium (EDTA) chelation therapy versus placebo (a), primary composite end point: edetate disodium chelation therapy versus placebo, subset of patients with diabetes mellitus (b), myocardial infarction in patients with diabetes mellitus by infusion group (c), mortality in patient with diabetes mellitus by infusion group (d). CI, confidence interval; TACT, Trial to Assess Chelation Therapy.
FIGURE 2.
Central illustration. Heavy metals as a risk factor for atherosclerotic cardiovascular disease and the benefits of chelation therapy. Major sources and routes of exposure, mechanisms at the molecular and cellular level, responses at the tissue and organ level, and subclinical and clinical cardiovascular effects on the basis of experimental and epidemiological evidence are shown for lead and cadmium. Arrows denote direction of flow. Na₂EDTA, disodium ethylene diamine tetra acid; NO, nitric oxide; TACT, Trial to Assess Chelation Therapy.
Table 1
The Trial to Assess Chelation Therapy chelation components

<table>
<thead>
<tr>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 3 g of disodium EDTA&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 g of magnesium chloride</td>
</tr>
<tr>
<td>100 mg of procaine HCl</td>
</tr>
<tr>
<td>2500 U of heparin</td>
</tr>
<tr>
<td>7 g of ascorbate</td>
</tr>
<tr>
<td>2 mEq KCl</td>
</tr>
<tr>
<td>840 mg sodium bicarbonate</td>
</tr>
<tr>
<td>250 mg pantothenic acid</td>
</tr>
<tr>
<td>100 mg of thiamine</td>
</tr>
<tr>
<td>100 mg of pyridoxine</td>
</tr>
</tbody>
</table>

Add with sterile water to 500 ml

<sup>a</sup>The maximum dose of EDTA was 3 g for patients who have at least 60 kg of lean body weight and normal kidney function. Reduction in kidney function and/or lower lean body weight led to a reduction in the total EDTA dose infused.
### Table 2

<table>
<thead>
<tr>
<th>High-dose regimen (taken twice daily)</th>
<th>Total amount for 6 pills</th>
<th>% RDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>25 000 IU</td>
<td>500%</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>1200 mg</td>
<td>2000%</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>100 IU</td>
<td>25%</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU</td>
<td>1333%</td>
</tr>
<tr>
<td>Vitamin K1</td>
<td>60 μg</td>
<td>75%</td>
</tr>
<tr>
<td>Thiamin</td>
<td>100 mg</td>
<td>6667%</td>
</tr>
<tr>
<td>Niacin</td>
<td>200 mg</td>
<td>1000%</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>50 mg</td>
<td>2500%</td>
</tr>
<tr>
<td>Folate</td>
<td>800 μg</td>
<td>200%</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>100 μg</td>
<td>1667%</td>
</tr>
<tr>
<td>Biotin</td>
<td>300 μg</td>
<td>100%</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>400 mg</td>
<td>4000%</td>
</tr>
<tr>
<td>Calcium</td>
<td>500 mg</td>
<td>50%</td>
</tr>
<tr>
<td>Iodine</td>
<td>150 μg</td>
<td>100%</td>
</tr>
<tr>
<td>Magnesium</td>
<td>500 mg</td>
<td>125%</td>
</tr>
<tr>
<td>Zinc</td>
<td>20 mg</td>
<td>133%</td>
</tr>
<tr>
<td>Selenium</td>
<td>200 μg</td>
<td>286%</td>
</tr>
<tr>
<td>Copper</td>
<td>2 mg</td>
<td>100%</td>
</tr>
<tr>
<td>Manganese</td>
<td>20 mg</td>
<td>400%</td>
</tr>
<tr>
<td>Chromium</td>
<td>200 μg</td>
<td>167%</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>150 μg</td>
<td>200%</td>
</tr>
<tr>
<td>Potassium</td>
<td>99 mg</td>
<td>3%</td>
</tr>
<tr>
<td>Choline</td>
<td>150 mg</td>
<td>a</td>
</tr>
<tr>
<td>Inositol</td>
<td>50 mg</td>
<td>a</td>
</tr>
<tr>
<td>PABA (para-aminobenzoic acid)</td>
<td>50 mg</td>
<td>a</td>
</tr>
<tr>
<td>Boron</td>
<td>2 mg</td>
<td>a</td>
</tr>
<tr>
<td>Vanadium</td>
<td>39 μg</td>
<td>a</td>
</tr>
<tr>
<td>Citrus bioflavanoids</td>
<td>100 mg</td>
<td>a</td>
</tr>
</tbody>
</table>

RDA, recommended daily allowance.

*Recommended daily allowance not established. Other ingredients: croscarmellose sodium, microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose, and silicon dioxide.
Table 3
Clinical end points by infusion arms for patients with diabetes mellitus in TACT

<table>
<thead>
<tr>
<th>End point</th>
<th>EDTA chelation (n = 322)</th>
<th>Placebo (n = 311)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>80 (25%)</td>
<td>117 (38%)</td>
<td>0.59 (0.44–0.79)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Death</td>
<td>32 (10%)</td>
<td>50 (16%)</td>
<td>0.57 (0.36–0.88)</td>
<td>0.011</td>
</tr>
<tr>
<td>MI</td>
<td>16 (5%)</td>
<td>30 (10%)</td>
<td>0.48 (0.26–0.88)</td>
<td>0.015</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (1%)</td>
<td>3 (1%)</td>
<td>1.19 (0.27–5.30)</td>
<td>0.829</td>
</tr>
<tr>
<td>Coronary</td>
<td>48 (15%)</td>
<td>62 (20%)</td>
<td>0.68 (0.48–0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
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<tr>
<td>Hospitalization for angina</td>
<td>5 (2%)</td>
<td>6 (2%)</td>
<td>0.72 (0.22–2.36)</td>
<td>0.588</td>
</tr>
<tr>
<td>Secondary end point</td>
<td>35 (11%)</td>
<td>52 (17%)</td>
<td>0.60 (0.39–0.91)</td>
<td>0.017</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>19 (6%)</td>
<td>27 (9%)</td>
<td>0.63 (0.35–1.13)</td>
<td>0.118</td>
</tr>
</tbody>
</table>

CI, confidence interval; MI, myocardial infarction.
Integrative Medicine Approach To Peripheral Neuropathy—Avoiding Pitfalls Of Ineffective Current Standards In Assessing Chronic Low-Grade Mercury Toxicity And Functional Musculoskeletal Lesions

Jené Andrea Carter, MD; Sachi M. Desai, MS, DO(c); Jessica Probst, PT, DPT, MTC; Mikhail Kogan, MD

Abstract

Introduction: Mercury is a toxic metal that exists in elemental, inorganic, and organic states. Humans are exposed to mercury through industrial sources, consumption of seafood, or healthcare. Over time, this compound can accumulate in the body and cause symptoms. The authors of this study report a case of mercury toxicity and the detoxification treatment regimen provided to the patient from a functional medicine standpoint.

Case presentation: The patient is a 62-year-old woman of Mexican descent with a past medical history of hypertension, insulin resistance, hyperlipidemia, and anxiety disorder who presented, after visits with multiple allopathic physicians, with worsening neuropathic pain, fatigue, short term memory loss, and RUQ abdominal pain. She was found to have 10 aged mercury amalgams and elevated blood levels of inorganic mercury. Amalgam removal was recommended, in addition to dietary changes, a natural supplement regimen, and manual/physical therapy. After following the treatment for one year, the patient experienced a 70% decrease in total blood mercury levels and a dramatic improvement of all her symptoms.

Discussion: This patient’s chronic mercury toxicity from dental amalgams was effectively treated using a functional medicine approach to care. More studies are needed to compare pharmacologic versus supplemental chelation.
study report a case of both inorganic and organic mercury toxicity in a patient treated at an integrative medicine clinic affiliated with a large academic health center and the detoxification treatment regimen. The diet, supplement regimen, and other aspects of her treatment were derived from a functional medicine standpoint, the branch of integrative medicine which allows for a systems-based approach to healing and considers all factors of the patient's health and lifestyle.

Case Presentation/Presenting Concerns

The patient is a 62-year-old woman of Mexican descent with a past medical history of hypertension, insulin resistance, hyperlipidemia, vision changes, and "life-long" anxiety disorder. She presented to the clinic with decades-long, worsening neuropathic pain in her left lower extremity, chronic fatigue, worsening short term memory, and chronic right upper quadrant abdominal pain. The patient had several prior visits to allopathic providers to investigate her symptoms, but, despite various attempts at treatment, her symptoms remained. This led to her pursuit of an integrative medicine approach for diagnosis and treatment of her symptoms.

Upon initial evaluation, the patient was found to have at least ten large oxidized or dated mercury amalgams in her mouth, and a HgbA1c of 5.8%, placing her in the pre-diabetic range. These findings, in conjunction with her hypertension, long standing psychiatric symptoms, and neuropathy, were cause for high clinical suspicion of mercury toxicity.5

To confirm this diagnosis, the QuickSilver Scientific Mercury Tri-Test was conducted to evaluate the patient's mercury levels. The results of this test (see Table 1 and Table 2) led to the diagnosis of toxic effects of chronic mercury exposure.

Therapeutic Intervention and Treatment

Informed consent was obtained from the patient. Per her lab results, which were discussed with the patient at her 3-month follow-up visit, the patient had elevated levels of inorganic mercury, of which her ten large mercury-containing amalgams were likely the source. As such, she was recommended to have her amalgams removed as soon as possible and was given a referral to an experienced holistic dentist for safe removal. The patient's amalgams were removed shortly thereafter.

With such a high suspicion for mercury toxicity at her initial visit, the patient was recommended to make some immediate modifications to her diet and started on a supplement regimen. Her diet was modified by increasing the amount of cilantro consumed each week, as this has been found to enhance mercury excretion, particularly after dental amalgam removal, although there is limited evidence reported.6,7 She was instructed to add about 50 grams of cilantro (half a typical bundle) to her diet at least two to three times per week. In addition, she was recommended to limit her fish/seafood consumption to only those which are low in mercury, such as salmon, sardines, haddock, tilapia, shrimp, clams, oysters and mussels, and no more than two servings per week.

As for her supplement regimen, she was recommended to take Metabolic Synergy (Designs for Health), a multivitamin containing high dose alpha lipoic acid known to assist in recycling of glutathione.8 She was recommended to take Hepatatone Plus (Designs for Health), a product containing N-acetyl cysteine (NAC),
Timeline.

<table>
<thead>
<tr>
<th>Dates</th>
<th>Clinical Appointments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td><strong>Follow-Up 1:</strong> Patient reports no major changes. PE: Grossly unchanged from previous visit. <strong>Lab results:</strong> Quicksilver Mercury TriTest reports inorganic mercury toxicity. <strong>Diagnosis:</strong> Toxic effect of inorganic mercury. <strong>Recommendations:</strong> - Continue diet and supplement regimen - Add additional supplements:  ○ Hepatotone Plus (Designs for Health)  ○ Metal X Synergy (Designs for Health) - Use a sauna twice/week - Use an organic coffee enema - Dry skin brushing before showering - Use a water filter - Referral to holistic dentist for amalgam removal - Lab tests: Repeat Quicksilver Mercury TriTest 3 months after last amalgam removal</td>
</tr>
<tr>
<td>02/2017</td>
<td><strong>Follow-Up 2:</strong> Patient reports significant improvements in neuropathic pain in LLJ and RUQ abdominal pain. Patient also reports an increase in her energy level and improvement in short term memory and vision changes. She experienced some persistent pain in her hip, right flank, sacrum and bladder. PE: Right shoulder was lower than left, unequal hips. <strong>Recommendations:</strong> - Continue previous regimen - Referral to physical/manual therapy for persistent pain</td>
</tr>
<tr>
<td>05/2017</td>
<td><strong>Revisit Amalgam Removals:</strong> Patient received mercury amalgam removals.</td>
</tr>
<tr>
<td>06/2017</td>
<td><strong>Follow-Up 3:</strong> PE: Blood pressure decreased to roughly 138/80. <strong>Lab results:</strong> Cholesterol and HbA1c still high, but lower than previous year. <strong>Recommendations:</strong> - Continue previous regimen - Add more unsaturated fats to diet, (i.e. olive or avocado oil) - Add red yeast rice to diet as a natural form of a statin - Lab tests: Urine metal tests to be performed in 6 months</td>
</tr>
<tr>
<td>09/2017</td>
<td>Repeat Quicksilver Mercury TriTest (3 months post amalgam removal) showed significant decreases in inorganic, organic and total mercury levels.</td>
</tr>
<tr>
<td>11/2017</td>
<td><strong>Initial Consult:</strong> Physical Therapy. PE: Patient presents with abnormal gait, pain at right flank, bladder, left hip and LLJ. <strong>Recommendation:</strong> Follow plan designed by PT to decrease stress throughout system, increase flexibility and decrease pain.</td>
</tr>
<tr>
<td>12/2017</td>
<td><strong>Initial Consult:</strong> Mind Body Stress Reduction therapies helped with chronic stress, but not hypertension or pain.</td>
</tr>
<tr>
<td>02/2018</td>
<td><strong>Outcome:</strong> 62-yr female with a history of HTN, insulin resistance, hyperlipidemia, hip and bladder pain, short term memory loss, vision changes, and anxiety p/w worsening neuropathic pain in LLJ, RUQ abdominal pain, and fatigue, found with ten large mercury-filled amalgams leading to mercury toxicity, showed improvement in all symptoms and decreased mercury blood levels after one year of treatment: functional medicine, restorative dental treatment, and PT.</td>
</tr>
</tbody>
</table>
# Table 3

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Ingredients</th>
<th>Dose</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic Synergy</strong></td>
<td>[Designs for Health]</td>
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<tr>
<td></td>
<td>Serving Size: Three Capsules</td>
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<td></td>
<td>Amount Per Serving:</td>
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<tr>
<td></td>
<td>1500IU Vitamin A (from Palmitate and Mixed Carotenoids from Palm Tree Fruit), 250mg Vitamin C (as Ascorbic Acid), 200IU Vitamin D (as Cholecalciferol), 14 IU Vitamin E (as d-alpha Tocopherol), 38mg Thiamin (Vitamin B-1) (as Thiamin HCl and Benfotiamine), 13mg Riboflavin (Vitamin B-2), 25mg Niacin (Vitamin B-3 (as Nicotinamide), 25mg Vitamin B-6 (as Pyridoxine HCl and Pyridoxal-5-Phosphate), 200mcg Folate (NatureFolate® blend), 500mcg Vitamin B-12 (as Methylcobalamin), 2000mcg Biotin (as d-Biotin), 25mg Pantothenic Acid (as d-Calcium Pantothenate), 37mcg Iodine (as Potassium Iodide), 50mg Magnesium (as Di-Magnesium Malate), 15mg Zinc (as Zinc Bisglycinate Chelate), 100mcg Selenium (as Selenium Glycinate Complex), 2mg Manganese (TRAACS® Manganese Bisglycinate Chelate), 250mcg Chromium (TRAACS® Chromium Nicotinate Glycinate Chelate), 50mcg Molybdenum (TRAACS® Molybdenum Glycinate Chelate), 100mg Potassium (as Potassium Glycinate Complex), 300mg Alpha Lipoic Acid, 300mg Taurine, 250mg Inositol, 100mg Green Tea Extract (Camellia sinensis) (leaves) [standardized to contain 98% polyphenols, 45% EGCg], 100mg Carnosine, 82mg High Gamma Mixed Tocopherols (as d-gamma, d-delta, d-alpha, d-beta), 100mcg Vanadium (TRAACS® Vanadium Nicotinate Glycinate Chelate)</td>
<td>3 capsules once per day, 5 days per week</td>
<td>Feb 2017</td>
</tr>
<tr>
<td></td>
<td>Other Ingredients: Cellulose (capsule), silicon dioxide, vegetable stearate.</td>
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<tr>
<td><strong>Hepatatone Plus</strong></td>
<td>[Designs for Health]</td>
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<tr>
<td></td>
<td>Serving Size: Four capsules</td>
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<td></td>
<td>Amount Per Serving:</td>
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<td></td>
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<tr>
<td></td>
<td>600mg N-Acetyl-Cysteine, 500mg Milk Thistle seed (Silybum marianum) [standardized to contain 80% silymarin], 500mg Reishi Full Spectrum (Ganoderma lucidum, Ganoderma applanatum) (mycelium, fruiting body, primordia, spores and extracellular compounds), 500mg Cordyceps (Cordyceps sinensis) (mycelium) [standardized to contain 8% cordycepic acid and 0.28% adenosine] (from soy), 300mg Chinese Skullcap Extract (Scutellaria baicalensis) (root) [standardized to contain 30% flavones], 250mg Schisandra Extract (Schisandra chinensis) (fruit), 250mg Burdock Extract (Arctium lappa) (root)</td>
<td>2 capsules twice per day, 5 days per week</td>
<td>May 2017</td>
</tr>
<tr>
<td></td>
<td>Other Ingredients: Microcrystalline cellulose, vegetable stearate.</td>
<td></td>
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<tr>
<td><strong>Metal X Synergy</strong></td>
<td>[Designs for Health]</td>
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<td></td>
<td>Serving size: Six capsules</td>
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<td></td>
<td>Amount per serving:</td>
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<td></td>
<td>1g Dietary Fiber, 120mg Sodium, 130mg Potassium, 1.5g Modified Citrus Pectin (as PectaSol-C®), 1g Organic Cholla-broken cell wall (Cholla regularis)(whole plant), 900mg N-Acetyl-L-Cysteine, 750mg Modified Alginate Complex (as Algimate®), 400mg Garlic (Allium sativum)(bulb), 200mg L-Glutathione (reduced), 200mg Alpha Lipoic Acid</td>
<td>3 capsules twice per day, 2 days per week, between meals</td>
<td>May 2017</td>
</tr>
<tr>
<td></td>
<td>Other ingredients: Cellulose (capsule), microcrystalline cellulose, vegetable stearate, silicon dioxide</td>
<td></td>
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<tr>
<td><strong>Carditone</strong></td>
<td>[Ayush Herbs]</td>
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<td></td>
<td>Serving Size: One capsule</td>
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<td></td>
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<tr>
<td></td>
<td>Amount Per Serving:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>200mg Magnesium (as aspartate), 350mg Proprietary Blend (Rose Powder, Boerhaavia diffusa, 100mg Paval (Indian Coral) (Convolvulus Pluricaulis), 100mg Terminalia Arjuna, 100mg Tribulus Terrestris, 50mg Rauwolfia serpentine, 25mg Rosa Vinca</td>
<td>1 capsule twice per day</td>
<td>Feb 2017</td>
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<tr>
<td></td>
<td>Other ingredients: Dicalcium phosphate, Stearic acid, Magnesium stearate, and silicon dioxide</td>
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<tr>
<td><strong>Wright Salt</strong></td>
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<tr>
<td></td>
<td>Serving Size: as desired</td>
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<tr>
<td></td>
<td>324mg Sodium, 54 mcg Iodine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other Ingredients: Sodium chloride, Pottasium chloride, Magnesium sulphate, Lysine hydrochloride, Silicon dioxide, Zinc chloride, Copper glucinate, Selenium and Potassium iodide.</td>
<td>Replace household salt with this product</td>
<td>Feb 2017</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Serving Size: One capsule</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Amount Per Serving:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000IU Vitamin D3 (as cholecalciferol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other Ingredients: Rice Powder, Vegetable Cellulose Capsule, and Leucine.</td>
<td>Take home vitamin D tables more consistently (daily). Can replace with this if needed.</td>
<td>Feb 2017</td>
</tr>
</tbody>
</table>
which is a known glutathione (GSH) precursor and mercury mobilizer, milk thistle, and other liver supportive nutrients. She was also recommended to take Metal-X-Synergy (Designs for Health), a product which provides several non-pharmacological gut heavy metal binders such as modified citrus pectin, chlorella, and additional amounts of NAC and glutathione. Glutathione is known to be a key nutrient to prepare mercury for excretion. In fact, glutathione is essential in detoxification of all heavy metals.7 Table 3 provides a complete list of all vitamins and supplements which the patient was recommended to take. To optimize the removal of toxins from her body, the patient was also recommended to use a sauna twice per week for 10-15 minutes, and to take a shower immediately afterwards, in order to wash off any toxins.9 In addition, she was told to switch to filtered water only, to ensure that there was no mercury or lead in her drinking water. The patient was also given the recommendations to utilize an organic coffee enema and to do dry skin brushing before showering for additional toxin removal.

Follow-up and Outcomes

Six months after the initiation of the patient’s integrative treatment regimen, and three months after her mercury-containing amalgams were removed, the QuickSilver Scientific Mercury Tri-Test was repeated. The results showed significantly decreased blood mercury levels, along with substantially increased urine excretion of inorganic mercury (Table 4 and Table 5 ). In addition to these lab findings, within 8 months of the removal of her amalgams, the patient reported nearly complete resolution of her neuropathy symptoms, and improvements in her energy, short term memory, vision, and abdominal pain.

After her treatment, the patient had some persistent symptoms, including hip pain, some persistent abdominal pain, and a sensation of tension in her bladder. In order to continue the patient’s care and address these lingering symptoms, it was recommended that she begin physical therapy. As a part of this comprehensive integrative approach, the patient was referred for evaluation by a Doctor of Physical Therapy with 16 years of clinical experience and a certification in manual therapy.

At the time of the evaluation, the patient reported right-sided flank pain and longstanding sacral and bladder pain that had started to improve following the mercury protocol. She experienced tension and pain at her left posterior hip region when needing to urinate. Pain was present in her lumbar spine and left posterior hip and extended down her left lower extremity to her foot (5/10 at worst, 2/10 at best on a visual analog scale with 0 indicating “least possible pain” and 10 indicating ”worst possible pain”). The patient also reported unrelated medial knee pain that began during athletic activities two months prior to the physical therapy evaluation and was addressed separately.

Findings from the objective examination included palpable tension and decreased fascial glide in the right upper quadrant of her abdomen that produced pain in her left lower extremity. The patient showed notable restrictions of her C-section scar tissue and fascial restrictions around the region of her bladder. Posterior to anterior pressure at the spinous process of her L5 vertebrae in the prone position also reproduced her left lower extremity pain. She had decreased left hip range of motion into flexion, abduction, and internal rotation, with tightness and tenderness at her piriformis, gluteus maximus, and gluteus medius muscles.

Physical therapy interventions included muscle energy technique to mobilize the lower thoracic spine and lumbar spine as well as mobilizations of her left hip in
Fascial releases were completed to the abdominal right upper quadrant and through her abdomen, targeting restrictions surrounding her liver, gallbladder, common bile duct, and bladder. Releases were completed to her C-section scar tissue and deep endopelvic fascia. Soft tissue mobilization was completed to her iliacus muscle and the abdominal portion of her psoas muscle.

The patient was educated on appropriate stretches to her piriformis and quadratus lumborum, and she was instructed on strengthening exercises for her gluteal muscles. The lumbar “pelvic clock,” a Feldenkrais technique involving supine hooklying lumbar flexion, extension, and diagonal movements, was used to facilitate normalized movement patterns at her lumbar spine and pelvis. She was also instructed in diaphragmatic breathing and gentle self-abdominal releases. Functional retraining was provided, including addressing appropriate muscle activation, positioning and movement patterns during yoga, and activities of daily living.

The patient was seen for 7 visits of physical therapy, at a treatment frequency of once every week to every other week, over the course of 2 months. Each session lasted 60 minutes.

On her last visit to physical therapy, the patient reported full resolution of all right-sided flank pain, bladder pain, and sacral pain. She no longer had pain or an abnormal sensation in her gluteal region when her bladder was full. Her lumbar and left hip pain had decreased from 5/10 to 0.5/10 at worst. She showed an improved lumbar range of motion, normalized hip range of motion, and reduced restrictions throughout her abdomen. Her pain did not exceed 0.5/10 upon waking in the morning, and she no longer experienced pain when sitting or doing yoga.

Discussion

This patient suffered from mercury toxicity resulting from dental amalgams as her primary known source of exposure. Utilizing an integrative/functional medicine approach, the patient's symptoms, which included neuropathy, abdominal pain, memory loss, fatigue, and hypertension, were resolved after safe removal of the amalgams, dietary modifications, the addition of natural supplements, and manual/physical therapy. The integrative approach allowed for a 70% decrease in total blood mercury levels, a 66% increase in urinary excretion, and a 71% increase in excretion through hair follicles over a period of 6 months.

Dental amalgams are the second most common source of mercury exposure in humans, with seafood consumption being the primary source. Over time, vapors from the amalgams are released within the mouth and inhaled, leading to chronic exposure. Once this patient's source of exposure was identified, it was clear that the most important step was to remove the source, as several studies have shown that removal of amalgams significantly improves symptoms, including abdominal discomfort, paresthesia, and fatigue. It is vital to ensure that a well-trained environmental dentist removes the amalgams to prevent further inhalation of mercury vapors. Similarly, in order to prevent additional exposure, the FDA recommends limiting consumption of seafood like shark, swordfish, and tuna, which we also recommended to our patient.

In Western medicine, dimercaptosuccinic acid (DMSA) is often used as a chelating agent for mercury toxicity, and has been shown to increase the amount of mercury excreted in patients with high levels. Some adverse effects of this and similar medications, such as dimercaptopropane-1-sulphonate (DMPS), include removal of important nutrients and minerals, GI discomfort, and elevated liver enzymes. This treatment was considered for our patient only as a last resort if needed. Although the literature on the use of cilantro as a chelating agent is limited, it has been described as one of the few chelating agents which can penetrate the CNS.

Cilantro can be used to displace metals like mercury, aluminum, and lead from CNS cells into the periphery, which allows for more efficient urinary excretion.

While DMPS is known to have high affinity to mercury, its use is limited by frequent intestinal side effects and cost. Compounded cost of DMPS could be $15-20/day versus the above supplement approach, which was around $5/day. While in this specific clinic, one functional medicine provider used a variety of different chelating agents and natural binders, the personal choice of what product(s) to select for a given patient often remains a subtle art rather than a specific evidence based, cost effective approach. As general rule, we use more gentle, non-pharmacological binders with older patients and/or when a slower course of treatment is preferred. It is clear that what is needed is a side by side randomized comparison of different pharmacological and supplements-based chelators. Studies like this may be valuable for the field as it clarifies relative efficacy of these products, and may help to guide clinicians and the public of best practices regarding heavy metal detoxification regimens. Until such time, one can argue that any approach that uses a safe and reasonably efficacious treatment strategy can be applied based on multiple factors outlined above.

While this case presents rather usual practices for functional medicine treatment of neuropathic pain, the addition of manual/physical therapy, which ultimately resolved nearly all remaining pain, adds a unique angle. While the exact etiology of this patient's pain is not clear, we do speculate that mercury toxicity likely caused changes in muscular, nervous, and fascial tissue, as well as in mitochondrial function. These changes likely contributed to restrictions that caused pain, altered movement patterns and increased strain throughout her musculoskeletal system as well as her viscera. The changes likely led to decreased energy production, resulting in weaker muscles that were more prone to micro-trauma and functional
while mercury detoxification certainly improved cellular function in this patient, careful manual evaluation, treatment, and muscular re-education was essential in re-establishing healthy musculoskeletal and nerve function in multiple body areas. 15

One of the limitations of this case is the inability to distinguish the effectiveness of each aspect of the patient’s treatment regimen individually. We do not have numerical values for the decrease in the patient’s blood mercury as a result of amalgam removal compared to the addition of cilantro and supplements. Future exploration may determine the effectiveness of these additional treatments.

The inability to identify which parts of the treatment are most efficacious in a given patient is an issue that is often heavily critiqued by biomedical researchers, often leading to the inability to obtain serious NIH and other grants. In our opinion, this is unfortunate as it leaves patients without possibly effective treatment options that are not only cost effective, but safer than most current treatment options. For example, this patient had been suffering with her chronic pain syndrome for decades, and she was prescribed a variety of medications, none of which were helpful and, at times, caused adverse side effects. While many of her previously prescribed medications were covered by her insurance, the overall cost of her care was substantially more expensive when compared with her integrative medicine treatment. Although the entire course of her integrative medicine treatment cost the patient thousands of dollars, this led to permanent problem resolution in under 12 months, with no further medical care needed.

Patient Perspective

It is also important to note that this patient, prior to her functional medicine and physical therapy regimen, endured years of treatment, with little to no benefit, and quite possibly, adverse effects, despite paying high medical fees with the expectation of improvements in her health. She states, “I am upset because despite the fact that mercury toxicity is a known cause of hypertension, the physicians I saw […] just wanted to me to take pills to mitigate my symptoms without elucidating the cause. I could have lowered by blood pressure symptoms with pills. This would not only have exposed me to severe side effects, but more importantly, would have left unaddressed the underlying cause, mercury toxicity. Had this mercury toxicity continued to be unaddressed, I would have faced numerous health risks… I have concluded that these physicians just treat symptoms and are unwilling to take the time to think of their patients’ health as a whole system. When I look back… I see missed opportunities for those physicians to think a bit out of the box and move beyond their basic checklist. I also see a negative impact on my health and quality of life. Many thanks [to her functional medicine and physical therapy providers] for helping me to restore my health and my quality of life. I feel so much healthier and stronger than I did before…”

Such unfortunate lack of interest from the allopathic profession, despite clear and objective data demonstrating the rationale for treatment of the underlying cause of symptoms such as hypertension, in addition to the patient’s significant improvement, suggests that the amount of bridging education required is large, and likely will not be easy going forward.

Conclusion

The patient discussed here experienced significant improvement in her symptoms and a better quality of life as a result of an integrative medicine approach to her treatment, which occurred after years of unsuccessful allopathic physician visits. This case demonstrates that an integrative approach to treatment of mercury toxicity is an effective way to decrease blood mercury and increase mercury excretion, although additional studies are needed to further explore the impact of cilantro and supplements individually.

References

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