Environmental Medicine Update

by Marianne Marchese, ND
www.drmarchese.com

Heavy Metal Testing Controversies: The Post-Provocative Urine Test

Introduction

Heavy metals such as mercury, lead, arsenic, and cadmium are pervasive in the environment. Some people are exposed to high doses in various occupations, but most are exposed to low doses through food intake, air, and water pollution. Low dose exposure to metals is linked to numerous health conditions. In order to determine if a person's health problem is due to metal exposure, a thorough environmental history is performed along with laboratory testing for the presence of metals in the body. Blood and urine tests are most commonly used, including the controversial post-provocative urine metal test. This column will explore the various methods of heavy metal testing to assess the presence of metal in the body.

Provocative Urine Testing

In the past few years, several organizations have come out strongly against the use of provocative urine heavy metal testing. The American College of Medical Toxicology (ACMT), an association of physicians with recognized expertise in the diagnosis, management, and prevention of human poisoning and other adverse health effects due to medications, occupational, and environmental toxins and biological agents, and the American Academy of Clinical Toxicology (AACT), a multidisciplinary organization uniting scientists and clinicians in the advancement of research, education, prevention, and treatment of diseases caused by chemicals, drugs, and toxins, are two organizations in particular.

Both have publically stated: "Metals are ubiquitous in the environment and all individuals are exposed to and store some quantity of metals in the body. These do not necessarily result in illness. Scientific studies demonstrate that administration of a chelating agent leads to increased excretion of various metals into the urine, even in healthy individuals without metal-related disease. These 'provoked' or 'challenge' tests of urine are not reliable means to diagnose metal poisoning and have been associated with harm."[1]

These are not the only organizations publically against the use of provoked urine metal testing. State and federal government agencies also oppose its use to diagnose metal toxicity. On August 26, 2015, the State of Minnesota Department of Health published information for health-care providers on heavy metal testing and chelation. It states: "The results of provoked urine studies have no role in determining the body's burden of toxic metals, nor the need for chelation therapy."[2] The source of information cited used to make this determination is an article published October 2013 in the *Journal of Metal Toxicology*, the official print journal of the American College of Medical Toxicology (ACMT).[3]

One of the main criticisms of the provoked urine metal test is that there are no standardized reference ranges. It is true that the reference ranges provided by a commonly used lab offering the provoked urine metal test are the same reference ranges found on the unprovoked urine test. In fact, if one reads the reports carefully, it states this on both the unprovoked and provoked test results. All labs offering the provoked urine test use unprovoked reference ranges. So, if there are no set reference ranges for a provoked urine metal test, how does the doctor determine that the level excreted in the urine on a provoked test is elevated? If there are no reference ranges, at what amount is the patient deemed toxic on a provoked test?

Another criticism of provoked urine metal testing is that there is no standardized method of administration. A provoked urine metal test is performed by administering a chelating agent to a person prior to urine collection. There are various chelating agents used for testing and various lengths of time for which the urine is collected. Different doctors use different chelating agents for testing, including dimercaptosuccinic acid (DMSA), dimercaptopropanesulfonate (DMPS), and ethylenediaminetetraacetic (EDTA). These chelators are given by varying routes of administration. Some are given orally, rectally, and intravenously. This varying nature of performing a provocative urine metal test makes it nonstandardized and difficult for a lab to develop provoked reference ranges.

One method commonly used to determine if elevated levels on a provoked urine metal test are significant is to compare the provoked urine test to an unprovoked test

obtained from the same person on the same day. This can be useful if the doctor understands the different effects that each chelating agent has on the body and the different means by which metals are metabolized and eliminated from the body. An ideal chelator has greater affinity for the metal to be bound, low toxicity, water solubility, and rapid elimination from the body. When a chelator forms a complex with a heavy metal, the chemical affinity of the chelator for the metal should be higher than the affinity of the metal for molecules in the body. Heavy metals have different chemical affinities. As a chelator binds metals with the highest affinity, there is an increase in excretion of metals with lesser affinity. Basically, each chelator pulls metals out in a different order.[4] This concept is key in determining if a provoked metal test truly resulted in an increase excretion of metals compared with the patients' unprovoked test. The doctor must chose the correct chelating agent to be administered based on the patient's history of exposure to metals.[4] A 2010 article published in the *International Journal of Environmental Research and Public Health*, "Chelation in Metal Intoxication," provides a great overview of which chelating agents are able to bind metals and form complex structures to be removed from the body.[5]

Does the Post-Provocative Urine Test Have Diagnostic Value?

The state of Minnesota says: "The results of provoked urine studies have no role in determining the body's burden of toxic metals, nor the need for chelation therapy."[2] Many doctors utilize the provocative urine metal test to determine a patient's body burden of metals or long-term past exposure to metals. There are limited data to establish a link between prior metal exposure and provocative test levels.[6] A 2001 study published in *Environmental Health Perspectives* assessed diagnostic chelation challenge with dimercaptosuccinic acid (DMSA) as a measure of mercury body burden among mercury-exposed workers. It concluded that DMSA chelation challenge is not useful as a biomarker of past mercury exposure.[7] This study was done with a population with known mercury exposure. In the studies done utilizing provoked urine testing, reviews show that almost everyone has a rise in urinary metals after a dose of a chelator regardless of exposure history, symptoms, or disease conditions.[8–11]

Diagnosing heavy metal toxicity in a patient typically means that an elevated level found in the body is linked to symptoms and disease. Treatment for these individuals would then involve removing the metal from the body; this is known as chelation therapy. Studies demonstrating a link between metals and disease are mostly done utilizing blood and unprovoked urine tests. In the book *8 Weeks to Women's Wellness*, heavy metals are linked to breast cancer, endometriosis, uterine fibroids, heart disease, infertility, osteoporosis, PCOS, and thyroid disease.[12] All links were made through blood and unprovoked urine tests. Critics of provocative urine metal testing state that there is no research to support its use as an accurate or reliable means of identifying patients who would benefit from chelation therapy.[6]

A study published in 2007 looked at the urine provoked metal test in children with autism compared with controls.[13] The aim of the study was to assess if children with autism are at increased risk of an excess chelatable body burden of heavy metals. Seventeen children with autism and 5 typically developing children were enrolled in a pilot study to test for body burden of arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg) after administration of oral DMSA. Evaluation included a questionnaire regarding potential exposure to heavy metals and diet restrictions. It included a baseline 24-hour urine collection and a DMSA-provoked urine collection. Unprovoked reference ranges were used in the interpretation of all collections including the provoked test. Fifteen autistic children and 4 typically developing children completed the study. Three out of 15 autistic subjects excreted one metal in greater quantity during the provoked excretion than baseline. Two of these were very close to the limit of detection using the unprovoked reference ranges. In the third case, the provoked excretion of mercury was between the upper limit of normal and lower limit of the potentially toxic reference range, again using unprovoked reference ranges. Fish was removed from this child's diet for greater than 1 month and the provoked excretion test repeated. The repeat excretion of mercury was within the normal range. The study concluded that the proportion of autistic participants whose DMSA provoked excretion results demonstrate an excess chelatable body burden of As, Cd, Pb, or Hg was zero. The confidence interval for this proportion is 0% to 22%.The purpose of this study was to assess the presence of metals in patients with autism using a provoked urine and not to evaluate the effects of chelation therapy in terms of improvement of symptoms of autism.

Other Methods to Test for Heavy Metals

Blood and unprovoked urine are the most commonly used methods of testing for heavy metal exposure. Neither of these tests is 100% accurate in detecting low-dose exposure to metals. Many times, this is due in part to the fact that a thorough exposure history was not performed first in order to determine the metal to which the patient was most likely exposed. This is an important part of the assessment process, so the correct method of testing is chosen based on where that metal will most likely be detected, blood or urine. For example, blood lead level (BLL) testing is the most useful screening and diagnostic test for recent or ongoing lead exposure. Lead has a relatively short half-life in the blood; most gets stored in the bone. Bone lead levels are best to assess past exposures.[14] Urine is not the best method to detect lead in the body.[15] If an unprovoked urine test is what's ordered, it may not detect the true level of lead present. The same can be said for various forms of mercury. It is critical to first determine what form of mercury, based on exposure history, that one thinks the person is exposed to before choosing the method of testing. Elevated

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mercury in the blood usually indicates exposure to organic mercury (such as from eating fish containing methylmercury) or recent exposure to a high level of elemental mercury vapor (such as from dental amalgams).[16,17] Urine is not the best method to assess mercury exposure from fish intake or recent exposure from dental amalgams. However, unprovoked urine is beneficial for nonrecent exposure from amalgams. Mercury vapor first enters the bloodstream and is then cleared through the kidney.[16,17] Again, it is important for the practitioner to understand the forms of metal and method of metabolism and excretion in order to choose the best test.

The reference ranges provided by most labs offering blood and unprovoked urine tests often do not detect low levels of metals – levels that are in fact linked to disease. The ranges are set too high and vary from lab to lab. Some labs report levels in terms of grams per creatinine and others in liters per 24-hour urine. Take arsenic, for example. A 24-hour urine adjusted for per gram creatinine is the best method for testing arsenic, but labs report results using different calculations. Physicians ordering these tests need to be aware of this fact to interpret the results properly. Mayo Clinic states that the reference range for a 24-hour urine is 0 to 35 ug/L and < 50 mcg/g creatinine. The Agency for Toxic Substances and Disease Registry (ATSDR) states that urine levels should be < 100 ug/L. LabCorp has different reference ranges for different forms of arsenic: total arsenic 0 – 50 μg/24 hours and inorganic arsenic < 20 μg/L. Quest diagnostic's range is ≤ 80 ug/L. Last checked, Genova Diagnostics urine arsenic normal range was < 50 and Doctor's Data < 80.

Reference Ranges

The Centers for Disease Control and Prevention has established reference ranges for heavy metals based on the National Health and Nutrition and Examination Survey (NHANES), which looked at human exposure to environmental chemicals. The NHANES Fourth Report, which was published in 2009 and looked at 212 chemicals in the blood and urine of over 2500 persons in the US, states that 0 to 46 ug/L of arsenic in a 24-hour urine sample for someone between ages 20 and 50 who smokes is normal, and 0 to 55 ug/L for nonsmokers aged 20 through 50 is normal. NHANES reports the ranges in percentiles, stating that greater than 95th on its ranges is a concern. However, if looking at what level in the body puts the patient at risk for disease, anything over 80th is a concern. For example, arsenic is linked to DMII is with levels over the 80th percentile on the NHANES Fourth Report updates.[18] The Environmental Medicine column in the *Townsend Letter* reviewed the updates to the NHANES Fourth Report in the January 2015 issue. This report provides the most useful reference ranges for hundreds of chemicals detected in the blood and urine.

Summary

People are exposed to low doses of heavy metals daily. These metals can have adverse health effects, which is why a thorough workup is vital to linking exposure to a person's symptom or disease. The most commonly utilized methods of testing for the presence of metals in the body are blood and unprovoked urine. However, most labs reference ranges are set too high to make the link between metals in the body and disease. The CDC's NHANES *Fourth Report on Human Exposure to Environmental Chemicals* provides a guide on how to interpret blood and unprovoked urine tests no matter which lab is utilized. The provoked urine metal test is controversial due to the fact there are no provoked urine reference ranges or standardized means of administering the test. Many medical professional organizations, state health departments, and government agencies advise against the use of provoked urine metal testing to diagnose metal toxicity. Physicians trying to assess if metals in the body are related to a patient's health concerns should be well trained in the pharmacology and toxicology of metals, the most common source of exposure of each form of metal, and best method of detection for that form. This will help the practitioner decide on the best method of testing for heavy metals.

Notes

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Dr. Marchese is the author of *8 Weeks to Women's Wellness.* She received her doctorate in naturopathic medicine from the National College of Naturopathic Medicine in 2002. Dr. Marchese maintains a private practice in Phoenix, Arizona, and teaches gynecology and environmental medicine at Southwest College of Naturopathic Medicine. She was named in *Phoenix Magazine*'s Top Doctor Issue as one of the top naturopathic physicians in Phoenix. Dr. Marchese lectures on topics related to women's health and environmental medicine throughout the US and Canada. www.drmarchese.com.

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