The Benefits of Pre- and Post-challenge Urine Heavy Metal Testing: Part 1

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Abstract

Measuring urine heavy metals is an accepted method for assessing the presence of these toxins in an individual. A random sample (without a flushing agent) is excellent for showing current exposures because it reflects the level of heavy metals in the bloodstream during the hours immediately before bladder voiding. A sample taken after using a heavy-metal-mobilizing agent provides a reflection of total body burden. By utilizing both pre- and post-flush testing, the clinician gains information that cannot be acquired by other means, including identification of current exposures to lead and mercury – critical for proper treatment. Conducting pre-flush testing is also currently the clinician's only means of identifying cadmium toxicity. In addition, pre- and post-challenge testing allows the clinician to identify which chelating agent is the most effective for the patient; and if oral agents are employed, possible absorption problems can be identified. Since these benefits are not realized with only post-flush testing, it is recommended that clinicians test both before and after a chelation challenge.

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Introduction

The adverse effects of heavy metals, including arsenic, cadmium, lead, and mercury, are of great concern to the general public and the medical community. Recent studies have shown that lead exposure can lead to higher rates of parkinsonism[1] and cognitive decline[2] in adults, as well as lower intelligence quotient (IQ)[3] and learning difficulties in children.[4] Mercury exposure is associated with cognitive decline,[5] mood problems,[6] cardiovascular conditions including hypertension,[7] infertility,[8] and immune dysfunction.[9,10] Cadmium has estrogenic activity[11] and is associated with increased risk for osteoporosis,[12] kidney damage,[13] and cancer.[14] Arsenic, a known carcinogen, is present in many municipal and private water supplies and can increase the risk for diabetes.[15]

Many clinicians routinely screen patients for heavy metal presence using hair, urine, or blood testing. Hair testing is a valuable tool to assess methylmercury exposure,[16] but may not reveal a burden of elemental mercury.[17] Blood tests for heavy metals are routinely offered by reference laboratories and are valid for showing current exposure, but not body burden. The reference ranges for blood levels of these heavy metals were set primarily for industrial exposures as a means of determining when a worker was in danger of acute heavy metal poisoning. The current reference range for blood lead in children, 10 mg/dL, has already been demonstrated to be far too high to prevent IQ damage,[3] yet it has not been reduced.

New U.S Reference Ranges

The best methods for measuring the presence of heavy metals in hair, urine, or blood have been published and are followed by laboratories that offer these tests. But, how can clinicians properly interpret what the findings actually mean? The labs that offer such testing provide reference ranges for each heavy metal that differentiate between safe and unsafe levels of these compounds. Until recently, these labs have had no national data points to utilize when setting these values.

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Table 1. Heavy Metal Ranges for U.S. Residents from NHANES

Metal	Sample	Mean	50th%	75th%	90th%	95th%
Cadmium	Blood µg/L	0.412	0.300	0.400	0.900	1.30
Cadmium	Urine µg/L	0.210	0.229	0.458	0.839	1.20
Cadmium	Urine µg/g cr	0.199	0.212	0.404	0.690	0.917
Lead	Blood µg/dL	1.45	1.40	2.20	3.40	4.40
Lead	Urine µg/L	0.677	0.600	1.20	2.00	2.60
Lead	Urine µg/g cr	0.639	0.634	1.03	1.52	2.03
Mercury	Blood µg/L	0.318	0.300	0.700	1.20	1.90
Mercury	Urine µg/L	0.606	0.580	1.37	2.91	3.99
Mercury	Urine µg/g cr	0.620	0.650	1.27	2.30	3.00

cr = creatinine

The Centers for Disease Control (CDC) are funding ongoing studies to properly assess the average burden of toxic compounds in U.S. residents. The CDC's findings are published in a series titled: the *National Report on Human Exposure to Environmental Chemicals*, the most recent being the *Third Report*.[18] This report includes data on blood and urine levels of lead, cadmium, and mercury that can be used to interpret a non-flushed (random) heavy metal urine or blood test. Copies of the *Third Report* are available to be downloaded in pdf form or ordered as a disc or hard copy from: http://www.cdc.gov/exposurereport/. Not yet published data on arsenic levels should be forthcoming.

Blood levels of heavy metals are reported in µg/L (or µg/dL in the case of lead), while urine levels are reported in either µg/L or as a creatinine-corrected level of µg/g creatinine. Table 1 outlines the findings for cadmium, lead, and mercury. The CDC findings are reported for two study periods: data gathered in the 1999-2000 and 2001-2002 U.S. National Health and Nutrition Examination Survey (NHANES). For sake of clarity, only the 2001-2002 numbers are provided.

The CDC reports provide much more detail for each heavy metal, including a variety of findings (e.g., mean and the 50th-95th percentiles) for different age and ethnic groupings. For specific findings the reader is directed to the CDC report (see url above).

The findings in the CDC report came from individuals who provided random samples throughout the day without having taken a heavy-metal mobilizing agent. Therefore, these values primarily reflect the level of heavy metals present in their blood and urine because of current dietary or airborne exposures. Only a small portion of these values are reflective of body buildup of heavy metals as those are in the cells or bound up in tissue, not in circulation.

The CDC lists averages for the 50th, 75th, 90th, and 95th percentiles, providing data on heavy metal levels normally found in 50 percent of all people, as well as levels found in individuals with higher levels – the top 25-, 10-, and 5 percent of the most heavy-metal exposed individuals. With these values a clinician can determine whether a patient's baseline urine test is normal or whether a patient is in the top 25 percent or more for heavy metal load (because their levels were at or above the 75th percentile).

Table 2. Urine Heavy Metal Reference Ranges from Three Labs Compared to CDC Reference Ranges in µg/g Creatinine

Metal	Lab 1	Lab 2	Lab 3	CDC Mean	CDC 50th%	CDC 75th%	CDC 90th%	CDC 95th%
Sb	<1		<0.149	0.126	0.120	0.173	0.265	0.364
Cd	<2	<0.20	<0.64	0.199	0.212	0.404	0.690	0.917
Pb	<5	<0.01	<1.4	0.639	0.634	1.03	1.52	2.03
Hg	<4	<0.015	<2.19	0.620	0.650	1.27	2.30	3.00
Tl	<0.8			0.156	0.156	0.215	0.287	0.348

Sb = antimony; Cd = cadmium; Pb = lead; Hg = mercury; Tl = thallium

When the author compared the values from the 75th to the 95th percentiles against a local reference lab (Sonora Quest), the differences were startling. According to Sonora Quest, any level of mercury in the blood less than 10.0 µg/L is considered within normal limits. Yet, the CDC numbers show that 95 percent of all persons tested (95th percentile) had less than 1.90 µg/L. This author uses the 75th percentile as the cutoff for "normal." When analyzed more closely, the Sonora Quests' level of detection for blood mercury was only 4.0 µg/L. Because the CDC does not note percentiles above the 95th, we do not know what percent of individuals has ≥4.0 µg/L mercury levels. If, for example, only the top one percent has such levels, then everyone with blood mercury below the top one percent for the country would be told their mercury was non-detectable. Thus, by knowing and using the new CDC values, the clinician will be able to help many more patients identify and avoid current toxic exposures.

Identifying Current Exposure

When the CDC values are used instead of typical laboratory reference ranges, it is possible to identify cases of current exposure. In this regard, the availability of the CDC numbers is revolutionary. It is critical that a clinician be able to spot current toxin exposure in addition to total body burden.

Table 2 illustrates the reference values for antimony, cadmium, lead, mercury, and thallium derived from three different labs that perform urine toxic metal testing (not all labs measured thallium and one did not measure antimony). The reader is advised to note the wide range variability among the three labs for each of the heavy metals listed. This wide variance can cause confusion among physicians and patients and may give the impression that reference ranges are arbitrarily set by the labs without any national standardization. Fortunately the CDC values now provide a standardized reference range.

A combination of the CDC values and knowledge of a patient's current lifestyle choices will greatly assist the clinician in determining whether there are exposures that need to be treated. The following are examples from the author's practice.

Patient Cases Illustrate the Importance of Baseline Heavy Metal Testing

The vast majority of current mercury exposure comes from fish consumption. Jane M. Hightower, MD, an internal medicine physician in San Francisco, published findings of elevated blood mercury levels in patients who regularly consume fish that revealed a wide range of 2.0 µg/L-89.5 µg/L.[19] The mean for women was 15 µg/L and for men 13 µg/L, both of which are far above the CDC cutoff for the 95th percentile. Since urine mercury levels are directly proportional to blood levels, the urine levels would also be well above the

CDC's 95th percentile and would alert the clinician to the presence of significant current exposure.

A 46-year-old woman treated by the author had a pre-flush (baseline) level of mercury of 4.2 µg/g creatinine in the first morning urine. When this result was compared with published CDC reference values, this patient was in the top five percent of mercury-loaded individuals, meaning she must be experiencing current exposure and a large post-flush mercury spill would be expected. Dimercaptosuccinic acid (DMSA) was then taken on an empty stomach and bladder at a dose of 30 mg/kg body weight and urine collected for the next six hours. The post-flush mercury level was significantly higher – 50 µg/g creatinine, clearly indicating a high body burden. If the baseline test had not been conducted, the tremendously elevated mercury reflecting current exposure would have been missed and the focus would have been on chronic body load. To begin chelation treatment without detecting and stopping the source of current exposure is analogous to bailing a boat without first fixing the hole in the bottom. Upon questioning it was revealed she ate tuna fish 3-4 times weekly (which she was told to stop). Since the half-life of methylmercury in the blood is 50-65 days,[20] a follow-up random urine test in 10 weeks would reveal whether the patient had avoided the mercury-laden fish.

A 39-year-old male had a pre-flush first morning urine mercury level of 2.9 µg/g creatinine, well within normal limits for two of the reference laboratories (Table 2), yet between the 90th and 95th percentiles according to the CDC reference range. This patient appeared to have malabsorption of DMSA because his urine mercury level after orally consuming 30 mg/kg body weight DMSA was only 9.4 µg/g creatinine. This low level indicates to a clinician only doing post-flush testing that the patient did not have much of a mercury burden. Yet his pre-flush test would indicate he had a high current exposure. On questioning, it was revealed he ate halibut 2-3 times weekly, giving him a high weekly mercury load. Because he did not appear to be absorbing DMSA well, the challenge was repeated using intravenous 2,3-dimercapto-1-propanesulfonic acid (DMPS) and his mercury spill was much higher.

Not all mercury exposure is from fish. The author had a 47-year-old female patient whose baseline urine mercury level was 4.7 µg/g creatinine and whose level increased to 38 µg/g creatinine after an intravenous challenge with DMPS. She denied fish intake but on questioning revealed she had found a broken mercury thermometer in her car a few months before. She used her home vacuum cleaner to get the liquid mercury out of the car and continued to use the vacuum cleaner in her home, spreading mercury throughout her home and increasing her exposure.

The author has also found many patients with current lead exposure from Ayurvedic and Chinese medicines, some of which are known to be common sources of heavy metals. Increased bone turnover in postmenopausal women can also release lead into the bloodstream acting as a source of current exposure.

These above exposure sources were revealed by having the patient complete a pre-flush urine test and comparing the findings with the CDC values.

Identifying Cadmium Overload

As with other heavy metals, no standards are currently in place that allow a clinician to look at only a post-flush urine heavy metal test (no matter what mobilizing agent is used) to determine whether a patient is carrying a toxic level of a particular metal. There is simply no data available to pinpoint such a reference value. This problem is compounded by the fact that there is currently no widely accepted standard for which mobilizing agent to use for post-flush testing or the proper dosage of the chelating agent.

In the case of cadmium, the best mobilization comes from an intravenous dose of calcium disodium ethylene diamine tetraacetic acid (Ca EDTA), as the agents DMPS and DMSA do not mobilize cadmium well. Therefore, depending on the mobilizing agent used, the amount of cadmium flushed into the urine from body stores can vary greatly. How then can one recognize when the cadmium burden has reached a toxic level? The level of cadmium present in the pre-flush urine must be determined.

While lead[21] and mercury[22] are toxic to the kidneys, more research has been conducted on the renal toxicity of cadmium. Research demonstrates urinary cadmium levels (measured as µg/g creatinine) strongly correlate with the renal levels of this metal.[23] Thus, urinary cadmium levels (measured both in µg/L and µg/g creatinine) show significant correlation not only with blood concentrations of the heavy metal but with

urinary indicators of renal disease. The highest correlation is between urinary levels of cadmium and the protein beta-2 microglobulin, a sensitive marker of renal damage.[13]

A Swedish study on the effects of cadmium on kidney function has determined the level of urinary cadmium that correlates with renal disease. In women with no history of significant cadmium exposure (e.g., from smoking or industrial pollution), subjects who had random urinary cadmium levels of 0.6 µg/g creatinine already showed significant renal tubular damage.[24] In this study, baseline (random) urinary cadmium levels of ≥0.5 µg/g creatinine were associated with renal damage, while levels above 2.0 µg/g creatinine were associated with excessive damage.[25]

A Japanese study confirms these numbers, with renal damage observed in women with cadmium as low as 0.5 µg/g creatinine and in men at 0.6 µg/g creatinine.[26] Renal damage was monitored in these studies by measuring levels of very sensitive markers such as beta-2-microglobulin. Like the Swedish study, this study was conducted on individuals with low environmental cadmium exposures, thus reflective of average persons and not individuals with occupational cadmium exposure. In the case of cadmium, if only post-flush testing is utilized, the clinician can never know whether a patient's cadmium level is high enough to cause renal damage.

Cadmium has also been linked to osteoporosis.[27] A recent study utilizing NHANES data revealed that women with urinary cadmium levels from 0.5-1.00 µg/g creatinine were 43-percent more likely to have osteoporosis.[12] When one refers to the CDC reference ranges for cadmium, the critical level of urinary cadmium indicates increased risk for osteoporosis and kidney damage falls between the 75th and 90th percentiles.

Conclusion

Physicians should be aware of the value of conducting a random, or baseline, urine toxic metal test prior to using a chelating agent to check for body burden of heavy metals. While the post-flush test is standard among many alternative and complementary physicians, using a pre-flush test provides valuable information that cannot be obtained by other means. By conducting a pre-flush test and utilizing the values for urinary heavy metal levels published by the CDC and presented in this article, the practitioner can easily identify when a client is being currently exposed to lead or mercury. Utilizing these values with the published values for osteoporosis and kidney disease risk also enables the practitioner to identify cadmium toxicity, a determination that also cannot be achieved by post-flush testing.

In the second part of this article, the benefits of doing both pre- and post-testing in order to find absorption problems and to identify the most effective treatment agent for the patient will be discussed.

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