ACMT Recommends Against Use of Post-Chelator Challenge Urinary Metal Testing

American College of Medical Toxicology

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The Position of the American College of Medical Toxicology Is As Follows

Metals are ubiquitous in the environment and human populations are constantly exposed [1–4]. Detectable levels of lead, mercury, and other metals are found in blood and urine of individuals who have no clinical signs or symptoms of toxicity and thus no indication for intervention. Reference values suggest normal body burdens of these metals [1–5]. Urine testing for various metals, in an appropriate clinical context, using proper and validated methods, is an accepted medical practice. Post-chelator challenge (a.k.a. post-provocation, or provoked) is the practice of collecting specimens immediately or within 48 h of administering a chelating agent. Post-chelator challenge is subject to misinterpretation and misapplication and may result in unnecessary, costly, and sometimes harmful treatment. The American College of Medical Toxicology reaffirms that post-chelator metal testing (1) has not been scientifically validated, (2) has no demonstrated benefit, and (3) may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal exposure or poisoning.

Evidence-Based Urine Testing for Metals

In current evidence-based medical practice, urinary testing is commonly used for biomonitoring and exposure assessment for metals such as arsenic and inorganic mercury. Some

metals, such as chromium, show no clear correlation between urine concentrations and physiologic effects. For some exposure scenarios, such as prosthetic metal-on-metal hips containing cobalt or chromium, urine is not the appropriate testing medium [6].

Twenty-four-hour urine metal testing is appropriate under the following conditions: (1) a known significant acute exposure to a toxic metal, (2) a suspected exposure to a metal and the presence of symptoms consistent with the exposure, or (3) as part of biomonitoring for occupational exposures to toxic metals. If a 24-h urine metal collection following a course of therapeutic chelation therapy is desired, the test should not be performed until sufficient time interval (e.g., 3–5 days) following the administration of the chelating agent.

Post-Challenge Urine Metal Testing Is Not Validated

Normal reference values for non-challenge urine metal test results vary among and within different populations. Ranges for these values have been established in nationally certified laboratories that meet the proficiency standards for urinary metal testing [5]. Chelating agents such as dimercaptosuccinic acid (DMSA), dimercaptopropanesulfonic acid (DMPS), dimercaptol (BAL), and edetate calcium disodium (CaNa₂-EDTA) bind metallic and metalloid elements and increase their urinary elimination from both healthy and metal-intoxicated individuals [4, 7–10]. However, scientifically acceptable normal reference values for post-challenge urine metal testing have not been established [4, 5, 9, 11, 12]. The results of post-chelator urinary metal testing cannot be compared to normal reference values [5, 11]. Attempts to retroactively convert provoked urine testing results to non-provoked concentrations are unproven and misleading.

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Non-Challenge Levels Cannot Be Inferred Using Post-Challenge Levels

Post-challenge specimens expectedly have increased concentrations of many metallic elements, including essential metals for normal physiologic health such as zinc. Scientific investigation to date has failed to establish a valid correlation between prior metal exposure and post-challenge test values. Although some authors have suggested that mercury [metal] concentrations following a single DMPS dose can be back-extrapolated to calculate pre-chelation concentrations, these data come from a small 1991 study and have not been subsequently validated [13]. Given the ease of obtaining non-provoked metal measurements and the error inherent in such back-extrapolation, this practice is not recommended.

In multiple human studies, post-challenge urine testing has failed to distinguish between individuals with and without documented metal exposure, or between those with and without clinical findings of toxicity [9]. Despite the lack of scientific support to do so, some laboratories and care providers erroneously apply non-provoked normal reference values as a comparator for interpreting results of post-challenge urine metal testing [5]. Currently available scientific data do not provide adequate support for the use of post-challenge urine metal testing as an accurate or reliable means of identifying individuals who are suffering from metal intoxication or who would derive therapeutic benefit from chelation.

Post-Challenge Urine Metal Testing Leads to Unnecessary, Potentially Dangerous Treatment

Unfortunately, the practice of post-challenge urine metal testing and its application to assessment of metal poisoning often leads to unwarranted diagnoses of “metal toxicity” and prolonged unnecessary oral and/or intravenous administration of chelating agents. Chelation therapy, based on such laboratory values, is of no benefit and may be harmful [5, 14].

Chelation is not without risk. Catastrophic outcomes such as fatal hypocalcemia have been reported following the improper use of a chelating agent, edetate disodium ($\text{Na}_2\text{-EDTA}$) [15]. In addition, the safer formulation of this agent, $\text{CaNa}_2\text{-EDTA}$, has been demonstrated to increase urinary excretion of essential minerals such as iron, copper, and zinc [7, 16]. Furthermore, there is published experimental evidence that deleterious effects may occur when chelation is applied in the absence of prior lead exposure [17]. Deferoxamine, an iron chelator, may precipitate aluminum encephalopathy as well as death in patients who are dialysis-dependent [18–20]. The act of eliminating the chelated metal through the kidney may increase the nephrotoxicity of certain metals, for example, cadmium [21]. Chelating agents such as DMSA and DMPS may also increase the elimination of certain essential

elements, as well as promote organ redistribution of metallic elements of concern, such as occurs with mercury [22–25]. Other chelators, such as DTPA, not only may deplete essential metals, such as zinc, magnesium, and manganese, but also may be nephrotoxic themselves [26, 27].

It is, therefore, the position of the American College of Medical Toxicology that post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal exposure or poisoning.

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Compliance with Ethical Standards

Conflicts of Interest None.

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