

Review

The Alchemist's Approach to Metal Poisoning: Transforming the Metal Burden

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Received: 21 February 2014; in revised form: 30 May 2014 / Accepted: 18 June 2014 /

Published: 25 June 2014

Abstract: Metal poisoning is a global problem with humans being exposed to a wide range of metals in varying doses and varying time frames. Traditionally, treatment involves removal of the toxic source or chelation therapy. An intermediate approach is needed. This review outlines the argument for the use of essential metal supplementation as a strategy to induce metallothionein expression and displace the toxic metal from important biological systems, improving the metal burden of the patient. Specific recommendations are given for supplementation with calcium, zinc and vitamin E as a broad strategy to improve the status of those exposed to toxic metals.

Keywords: metal poisoning; treatment; zinc; metallothionein

1. Introduction

Metal poisoning is a global problem, with important regional variations in the amount and type of metal exposure (e.g., contaminated wells, urban areas, mining sites; smelting operations). Once clinically important metal exposure has occurred then steps are taken to reduce exposure and treatment is begun. Of all the treatment options available the most important strategy for all types of poisoning is removing the source of the offending substance. In some instances this is fairly simple (for example, replacing lead glazed ceramics); however, in other instances, this is a daunting task (for example, contaminated primary drinking water sources). If the source of metal exposure can be removed, then the treatment of metal exposed individuals may range from no treatment, where time is allowed to remove the low levels of contaminant, to more aggressive approaches in heavily exposed individuals, such as chelation. If the source of exposure is difficult to remove, such as contamination of the only source of drinking water, then treatment takes on an entirely different dimension. In such instances

allowing time to pass is clearly not an acceptable solution. However, repeated treatment with chelators is not only logistically problematic but also carries with it the increased risk of adverse effects, particularly nephrotoxicity.

The development of an intermediate strategy that lies between passive approaches and chelation is clearly needed. Yet, many of the common medical references used by physicians [1,2] mention only aggressive strategies such as chelation and bowel irrigation. These are well suited approaches to significant metal burdens but are not optimal for chronic and ongoing exposure where logistical considerations, such as availability of medical personnel, and the risk of renal damage are problematic. The need for an intermediate strategy also occurs when the source of exposure is incorporated metal fragments or particles. This is often the case of Cd poisoning, depleted uranium (DU) poisoning, and Be exposure where exceptionally small particles of the metal and metal oxides lodge in the alveoli and dissolve over the course of weeks, months, or even years [3]. In this instance repeated chelation may not be the best approach because the large reservoir of metal would be unaffected by the chelator. An approach to treatment that would be suitable for subclinical exposure or chronic low dose exposure would be beneficial.

In the days of old Alchemists sought to transmute metals from those less desired to those more desirable, the proverbial changing of lead into gold. Such efforts made use of a Stygian furnace or the Philosopher's stone where a magical process would change the nature of a metal. In the chemical sense it is not possible to do this, however, it may be possible to take advantage of normal physiological processes to replace undesired toxic metals in the body (e.g., Hg, Pb, U) and replace them with physiologically desirable metals (e.g., Ca, Zn). The process follows our understanding of metal metabolism and pharmacology, would be useful in metal exposure by any route, and has been directly and indirectly suggested previously [4–7]. The purpose of this review is to synthesize the various points of view and strategies into a whole. It is certainly not possible to summarize all knowledge of the topic in the space allotted here, so this review will focus on a few key ideas and the most promising metals for substitution. Chelation is mentioned only in passing and has been reviewed in detail elsewhere [8–11]. The review is organized in the following fashion; proposed mechanisms will be introduced followed by the discussion of several candidate metals and consideration will then be given to vitamins C and E. After considering several other pertinent issues the discussion will close with final recommendations.

2. Mechanisms

The proposed mechanism of treating metal toxicity consists of substituting desirable essential metals for the offending toxic metal [4]. The targets for substitution include any number of cellular proteins such as CuZn-superoxide dismutase (CuZn-SOD), glutathione peroxidase (Gpx), mitochondrial permeability transition pore, mitochondria complex III, aminolevulinic acid dehydratase (ALAD), porphobilinogen synthase (PBG-synthase), as well as gastrointestinal (GI) tract and other proteins involved in the transport and regulation of absorption of essential elements (e.g., albumin, thionein, beta-lipoproteins, ferritin, Ca/Na-ATPase, divalent metal transporter) that are hijacked by toxic metals. For example, that Fe and Cd use the same serum transporter protein transferrin is well understood.

Interestingly, toxic metals may interact with essential metals and gut proteins to cause nutrient deficiency (as seen with Pb producing Cu deficiency) or metal poisoning may be enhanced by a patient deficient in a particular metal, such as Fe [12]. Essential metal deficiency is also produced when toxic metals such as Cd, Hg and Pb increase the excretion of essential elements (e.g., Cu, Fe, Zn) in the urine, probably by damaging the renal tubule [4].

Mechanisms for enhancing the effects of toxic metals in essential metal deficiency include a direct competition of the toxic metal for the carrier proteins found in the gut, increased uptake of the gut's carrier protein which inadvertently increases absorption of the toxic metal, as well as increased reuptake of the toxic metal in the kidney [4]. Metals in which this interplay has been detected includes As, Cd, Cu, Fe, Hg, Pb, Zn. The interplay of metals at this level often involves simple competitive kinetics. Therefore, dietary supplementation with desirable essential metals can blunt the impact of toxic metals by displacing them from cellular proteins, down regulating carrier proteins which would transport toxic metals, and displacing toxic metals from carrier proteins. The idea that competitive mechanisms are at play is illustrated by Cd and Mn where Cd can displace Mn in Mn-superoxide dismutase (MnSOD) and the adverse effects reversed with Mn [13].

It would be remiss not to mention one of the most important mechanisms by which many of these metals would exert their beneficial effects; metallothionein (MT). MT is a cysteine rich protein involved in the regulation of a number of metals, in particular Zn [12]. Many metals compete for the cysteine binding sites on MT, and also actively induce its expression in the cell. MT is inducible by a wide range of metals including Ag, Au, B, Cd, Co, Cr, Cu, Fe, Hg, In, Mn, Pb, Sn, Zn [4] and probably more. MT can bind up to seven divalent cations and 12 monovalent cations [12], although it may bind up to 18 atoms of Ag [14]. MT appears to play a particularly important role in Zn metabolism binding up to 20% of intracellular Zn [15]. The role that MT plays in the sequestration of metals is intertwined with its role in cell signaling where it releases stored Zn, and possibly interloping toxic metals, in response to physiological cues. MT is inducible in response to metals, inflammation, glucocorticoids, and oxidative stress [12,16].

There are four isoforms of MT (MT I, II, III, IV) with MT I and II being expressed in varying proportions in all tissues. Isoform III is important in nervous tissue and isoform IV in epithelia. MT I and II synthesis is enhanced by Zn which binds to the metal responsive element binding transcription factor (MTF-1). MTF-1 then binds to DNA segments referred to as metal responsive elements (MREs). Extensive reviews of the roles of MT and Zn, as well as other important aspects of cellular redox status, have been done by other investigators [17,18]. MT is, as mentioned above, inducible under a variety of conditions that produce oxidative stress and inflammation. MT inhibits the activity of pro-inflammatory cytokines and operates synergistically with anti-inflammatory cytokines [19]. Elevated levels of inflammatory cytokines have been linked to low Zn levels and the induction of inflammation reduces serum Zn. Zn supplementation appears to lower the levels of some inflammatory cytokines, but the relationship appears to be complex [20].

MT induction seems to offer some protection against various types of chemical injury, including that due to CCl₄. The protection of toxicity from CCl₄ appears to be by directly binding CCl₄ to MT [21]. The still broader protective effect from chemical injury appears to be due to MTs scavenging of reactive oxygen species (ROS) [19]. As an illustration of this, MT null mice are more sensitive to Cd toxicity, including nephrotoxicity, indicating that MT-metal complexes are protective

of renal function. Induction of MT by means other than metals, such as with polycyclic aromatic hydrocarbons, also protects against the effects of Cd, at least in the kidney and liver of bank voles [22]. MT, when bound with metals, especially when those metals are toxic (e.g., Cd, Hg, Pb) is more resistant to degradation in the lysosome and more likely to be excreted by the kidney in a nephrotoxic form [21].

The above evidence suggests that administering supplemental essential metals to displace toxic metals would be beneficial. However, essential elements that displace toxic metals from proteins may, at least temporarily, increase the amount of metal in circulation enhancing the toxic effects normally buffered by those proteins. The important mechanism to keep in mind is to use supplementation to induce the expression of MT, as well as other SH containing proteins, to bind excess toxic metal so that it is more extensively buffered and therefore less active. This is seen, for example, for Cd which competes with Zn for MT [4]. The goal of administering Zn (and other essential metals) is to increase the amount of MT available to bind toxic metals.

Further support of the thesis that essential metal supplementation is a viable option for treating metal toxicity is supported by looking at potential metal candidates.

3. Zinc

The literature demonstrating that Zn, a redox neutral metal, has a beneficial effect of the effects of toxic metal poisoning is particularly rich with demonstrations of both competitive and non-competitive mechanisms. Indeed, Maret and others [18,23,24] have referred to Zn as a “pro-antioxidant” because of the role it plays in a number of cellular systems that are involved in maintaining the redox status of the cell. In terms of protecting from toxic metals Zn supplementation has generally favorable effects on Pb toxicity [25]. Zn has a similar chemistry to Pb in terms of the amino acids to which they both bind and their formation of coordinated compounds [26]. Early studies have shown that Zn supplementation inhibits the absorption of Pb, kidney damage from Pb, the effects of Pb on the hematopoietic system, and the tissue accumulation of Pb including bone (in large enough doses) [26]. The competition of Zn with Pb at the level of the gut was nicely illustrated by Cerklewski and Forbes [26] who found diminished beneficial effects when Zn was given intravenously. The importance of Zn on Pb accumulation was examined by Jamieson, Taylor and Weiler [27] who found that rats with marginal Zn deficiency (Zn 8 mg/kg of rat food) had enhanced accumulation of Pb in bone, while Zn supplementation (Zn 300 mg/kg of rat food) reduced the accumulation of Pb. Kalia and Flora [7] suggest that Zn supplementation protects against Pb and As toxicity both in terms of reducing absorption, competing for biologically active enzymes, and the induction of molecules such as MT. Zn has a number of positive impacts on the consequences of Pb poisoning in experimental animals including markers of renal toxicity, serum lipoproteins, and improved Pb excretion [28]. An intriguing study by Moshtaghi *et al.* [29] suggests that the administration of Zn and/or Se provides at least partial protection against the effects of Pb on rat brain catecholamines. MT has been suggested to remove heavy metal from the CNS via the choroid plexus [16].

A number of studies have shown that Zn affords protection from a variety of other metals. Hg can displace Zn from Zn-metalloproteases which are involved in neural development [30] and ZnCl₂ exposure can significantly reduce the effects of HgCl₂ on several biochemical indices for developing

rat pups [31]. Chapman and Chan [6] have shown that Zn and Se decreased the effects of methyl-mercury (MeHg), Cd, Th and Ag toxicity. Zn pretreatment prevents the nephrotoxic effects of HgCl₂ exposure, and maintains renal vitamin E levels [32]. The mechanisms for this effect appear to be the induction of MT, the induction of glutathione (GSH) and GSHpx [33].

In a similar vein the beneficial effects of Zn extend to still more metals. The use of Zn for the treatment of Cd exposure has been suggested by Bernhoft [34] and Klaassen and Liu [4,5,21] as well as others. The importance of MT as protective against metal toxicity was demonstrated by Klaassen and Liu [21] who showed a protective effect of a low dose of Cd that was MT inducing, against the effects of subsequent high dose Cd exposure. In the experiment MT bound to Cd was found in the cytosol presumably preventing toxic activity at the cellular organelles. Presumably, Zn induced MT production protects the cell from toxic metals by a similar mechanism. A study by Amara *et al.* [35] also showed that Zn protected the testes of rats from the effects of Cd exposure. This included a normalization of sperm count as well as an increase in GSH and protection on a variety of markers of oxidative stress as well as increased MT levels. Zn pretreatment assists in the excretion of As [25]. A study by Hao *et al.* [36] found that ZnSO₄ pretreatment produced significant reduction in uranium induced renal toxicity at both the functional and structural level in the rat. Also shown in the study was that MT levels increased with Zn treatment and indicators of oxidative stress were reduced. Serum chemistries were improved and tissue necrosis was much reduced in the U group treated with Zn. Afonne *et al.* [37] demonstrated that Zn at least partially protects the testes of mice from Cr injury.

Zn supplementation does raise the concern that Zn may displace other beneficial metals from normal physiology. This concern was partially addressed when it was shown that Zn seems to provide a degree of protection in the instance of Fe supplementation and the accompanying risk of oxidative damage from Fe. There did not appear to be a clinically significant impairment in Fe uptake due to Zn administration [38]. Zn can interfere with Cu status, via competitive mechanisms, but is typically an issue only if the dose of Zn is excessive or Cu intake is inadequate [15,39].

It is also noteworthy that long term or high dosage treatment with Zn may produce deficiency of Cu [4,39]. Specifically, doses of Zn in excess of 53 mg/day have been shown to impair Cu status and doses of Zn in excess of 80 mg/day may be immunosuppressive [39]. It has been suggested that excessive Zn may even produce oxidative stress [18].

4. Calcium

Zn is not the only metal that can displace toxic metals; Ca also shares this ability. In clinically important trials Ca supplementation seems to protect against the effects of Pb, at least in pregnant women [40,41]. In a review by Kalia and Flora [7] Ca supplementation, even in those with normal Ca status, was found to be beneficial in Pb poisoning. A simply adequate calcium intake has been shown to protect against the effects of Cd on skeletal structures and many of the effects of Pb poisoning [28]. These studies showing a beneficial effect of Ca on the Pb status of humans is a proof of concept that essential metal supplementation can be safely used to improve the toxic metal burden of patients. With an upper tolerable limit of 2500 mg/day Ca has a wide safety margin.

5. Selenium

Evidence also exists for Se being a beneficial trace element with regard to toxic metal exposure. Selenoproteins (Se containing proteins) are various and include glutathione peroxidases, the selenoproteins P, W, R, thioredoxins as well as other proteins and selenocysteine [42]. These molecules have clear antioxidant properties and have been linked to the prevention of a number of pathologies. The capacity of these selenoproteins to bind metals has been shown for Cu, Mo, Zn and has been suggested for Fe [42]. Se supplementation has been shown to reverse the effect of Hg in Se-deficient mice which may have been mediated, in part, by glutathione and MT [4]. One unusual route of action may be that Se forms a biologically inert Se-Hg compound. However, the overall picture of the effect of Se on Hg toxicity is murky and depends on the speciation of Hg and the route of intake [25]. Rooney [43] points out that the activity of Se on Hg toxicity is complex and supplementation should be approached with caution, especially with Se because of its narrow therapeutic window.

Similar effects have been seen with Se administration reducing the effects of Cd nephrotoxicity with glutathione at least partially mediating the effect [4]. Na Selenite was shown to protect the kidneys of rats from many of the adverse effects of CdCl₂ [44]. Se supplementation was shown to reduce the effects of Cd in various tissues, including the brain, in suckling rats. This was especially true if Se supplementation occurred before Cd exposure [45]. Despite its ability to increase MT levels, Se prevents the carcinogenic effects of Cd in a manner independent of MT [46]. Se administration has been shown in a variety of experimental studies to have a positive impact on Pb and As toxicity and probably involves a variety of mechanisms including the production of seleno-proteins, competition at key enzymes, and the formation of selenium-metal complexes [7]. However, excessive Se administration may enhance the toxicity of Pb, or be in and of itself toxic [7]. As mentioned above selenium has a narrow therapeutic window with overzealous supplementation producing selenosis. At least in the United States dietary selenium intake already meets or exceeds the US RDA of 55 mcg/day. Aggressive supplementation with Se may push Se intake above the upper tolerable limit of 400 mcg/day. The already adequate dietary intake of Se combined with the risk of selenosis (selenium poisoning) and the uncertain effects on Hg does not, in the author's opinion, make Se a candidate for metal supplementation at this time. However, the evidence is sufficient that additional research should be pursued to further explore Se and toxic metal interactions with an eye toward a therapeutic application.

6. Iron and Copper

It is tempting to add Cu and Fe to the metals that would provide beneficial effects in the event of metal intoxication. Indeed there is evidence for it, particularly in the Cu or Fe deficient patient where transport mechanisms are up-regulated in an effort to capture as much dietary Fe and Cu as possible [12]. The up-regulation of these transport proteins also captures more toxic metals, such as is the case of Pb [28]. This is clearly the case in Fe anemic children who demonstrate a significantly greater impact of Pb than those with a normal Fe load. It is also clear that Fe deficiency anemia is a special instance worth considering Fe supplementation. However, supplementation above the level needed to normalize Fe and Cu levels may be problematic. Both Cu and Fe have redox properties that

make them pro-oxidant in excess, a problem likely to be exacerbated when significant competition with other metals occurs, displacing Fe and Cu from their respective binding sites [47]. Excessive Fe may well displace toxic metals from binding sites and as the body struggles to manage the highly redox active Fe atom there may be an increase in the activity of the toxic metal as well as introducing Fe toxicity. The interaction between Fe and Cu is also an issue and excessive Fe administration after the correction of anemia may produce Cu deficiency. The exact nature, severity, and mechanism of Fe toxicity is much debated (see Stohs and Bagchi [46]). Elevated serum Cu levels are seen in some patients with renal disease, a frequent result of metal poisoning, making routine Cu supplementation inadvisable and limited to those only with demonstrably low blood Cu levels.

7. Ascorbate

Ascorbic acid is a well-documented antioxidant and has been shown to reduce the oxidative damage associated with a wide variety of toxins. However, its use in metal toxicity may have undesired consequences. Ascorbic acid is an electron donor and has been shown to change the speciation of several metals to a more toxic form [13,48]. Yet, in Pb poisoning an inverse relationship has been shown between Pb levels and serum ascorbic acid levels [13]. Several other studies have reported beneficial effects of ascorbic acid on Pb and As toxicity [7,9]. Still again, a study by Khalifa *et al.* [49] found that vitamin C, while protecting against the oxidative stress of Cd, it reduced the Cd induced expression of MT. It is unclear what the mechanism of the inhibition was, or if the long-term effects of reduced MT expression are beneficial or deleterious. Therefore, it is undoubtedly wise to provide those exposed to toxic metals an adequate supply of ascorbic acid to prevent deficiency however, an excess may prove counter-productive. There is also some suggestion that mixing chelators and antioxidants may reduce the efficacy of one or the other, or even both, a caution against over-zealous polypharmacy [42].

8. Vitamin E

Vitamin E has been shown to protect against the effects of MeHg, but perhaps not inorganic Hg [6]. There appears to be some protective activity of vitamin E in Pb poisoning [13]. Kalia and Flora [7] review several studies that suggest vitamin E, alone or in combination with chelation, may interact synergistically in treating Pb and As toxicity. Still other researchers argue that vitamin E is not specific in its activity toward metals but its general antioxidant and membrane stabilization chemistry is the beneficial aspect [25]. Some evidence suggests that cellular stores of vitamin E, particularly membrane stores, need to be depleted before metal induced oxidative damage can occur [46]. The toxicity of vitamin E is low with an upper tolerable intake in adults of 1000 mg (1500 IU) daily it seems prudent to use this to advantage [9].

9. Dietary Manipulation

In many regards metal supplementation is dietary manipulation. It may be possible to extend this manipulation further. The selection of specific foods may improve the patient's ability to deal with toxic metals. In particular sulfur containing foods may aid in providing the substrates allowing the formation of proteins with metal binding sulfhydryl groups. Sulfur containing compounds are widely

available in the diet in the form of milk, cheese, garlic, eggs, vegetables in the *Allium* family, and cruciferous vegetables [42]. In terms of specific substances there are some key amino acids that play a role in handling metals. Methionine is the primary dietary source for sulfur and has been shown to prevent MeHg transport into the brain by blocking transport of the MeHg-cysteine complex into the brain [25].

Cysteine contains a free sulfhydryl group and is capable of binding metals; it is also the limiting substrate for glutathione synthesis [12]. Cysteine may form coordinated metal compounds possibly aiding in the removal of metals [42]. Quig [50] argued that cysteine should be provided to patients undergoing metal exposure in the form of a well-balanced protein adequate diet. Yet, to make note of the complexity of poisoning by this metal, cysteine may enhance the toxicity of MeHg [6]. Indeed, given the complexity of MeHg poisoning nutrition may be a special case (see the review by Chapman and Chan [6]) where the interplay between specific dietary factors, including milk, is very important.

10. Important Considerations

If the idea of essential metal supplementation as a strategy to displace toxic metals is to be seriously considered, then several important ideas must be brought to light. For instance, in the case of toxic metals that are irreversibly bound to cellular proteins then competitive displacement is not possible. However, the availability of sufficient nontoxic essential metals will allow the desirable metal to bind to newly synthesized proteins when the toxic metal occupied proteins are eventually degraded by the cell.

Not well considered in the literature is the issue of inorganic *vs.* organometallic *vs.* metallic exposure to the toxic metal in question. The exact metal species may be important for some metals. For instance MeHg is well removed by some substances that do not remove inorganic sources of Hg intoxication. A review by Chapman and Chan [6] outlined the rather inconsistent effect of dietary strategies on MeHg toxicity. They also point to the paucity of data on the issue. In some instances the metal may have an internal reservoir that slowly releases metal into systemic circulation. Such appears to be the case for DU exposure where the metal oxides are lodged in the alveoli and undergo gradual dissolution over the course of weeks, months, or perhaps years [3] or the well-known release of Pb from bone. As mentioned above essential metal supplementation will still be of value for inducing MT and competing for other cellular proteins.

Because the competition between metals for various carriers and other proteins will often be stochastic a sufficient dose of the essential elements (e.g., Ca, Zn) must be sufficient to displace the toxic metal. However, the dose must not be so large that it is wasteful or even toxic, as may occur with Se, or that desired elements may compete with each other for important carrier molecules proteins. For example, Cu and Zn compete for the same binding site on albumin [47].

In another vein displacing a metal from one tissue may increase its concentration in another. Displacing MeHg from liver may make more available for the brain. Most, if not all metals, once displaced from a tissue will need to be excreted by the kidney exposing the kidney to greater amounts of the substance. If the metal is bound to an organic molecule the toxicity may be decreased, and in the long run removing the toxic metal may be beneficial for several organ systems. However, in the short term there may well be a change in kidney function.

Combining approaches to metal toxicity is not new and vitamins, amino acids, chelators, and metals have all been combined in various manners with varying degrees of success [13]. If a combination of metals are administered at the same time (e.g., Zn and Ca) care must be taken that the formulation is such that chemical interactions do not occur rendering one or more of the compounds bio-unavailable. The same is true for any of the molecules administered. For instance the administration of Zn simultaneously with a thiol chelator would be counterproductive, producing an inert and bio-unavailable Zn-chelator complex.

Adequate nutrition should be established in all cases of suspected metal poisoning. To illustrate this point a study by Solon *et al.* [51] described a significant relationship between general nutritional status as measured by Fe and folate status and the likelihood that Pb exposure would have a negative impact on the cognitive development of children. A negative Ca balance also negatively affects the dynamics of Pb [40,41].

11. Conclusions and Recommendations

Prevention is always the best medicine. However, if that were easy there would be no need for metal toxicologists. Because the exposure to toxic metals does occur there needs to be a wide range of approaches suited to the exposure, dose and the time frame of exposure.

It makes good scientific and clinical sense that all patients would benefit from a sound nutritional status with an adequate intake of calories, proteins, lipids, carbohydrate, vitamins and essential elements provided in a diet that is suited to local dietary custom. Malnourished or essential metal deficient patients are at a distinct disadvantage for dealing with a variety of pathologies, and metal intoxication is no different.

It is also clinically and scientifically important to take all possible steps to remove the patient from the source of the toxic exposure. This may mean covering Pb contaminated yards and playgrounds with a layer of clean earth, or painting old houses with peeling Pb paint. Switching the sources of dietary seafood to a less contaminated source may reduce MeHg intake. Changing the mining practices of artisanal gold mining operations to reduce the exposure to metallic Hg would be another strategy. Unfortunately, the elimination of exposure may not be economically possible, such as contamination of primary drinking water supplies.

The evidence outlined above suggests that specific supplementation with Zn and Ca salts and with vitamin E would be prudent and of broad benefit and low risk. Ettinger *et al.* [41] used 1200 mg/day of Ca carbonate in their trial with positive results on Pb toxicity. This dose is in alignment with the US RDA for pregnant and lactating women. If a similar logic is followed, then elemental Zn supplementation at 13 mg/day as the sulfate or gluconate and vitamin E at 19 mg (28.4 IU) (ZnCaE supplement) would provide substrates that induce MT synthesis and compete with the toxic metal in question for a variety of carrier proteins, cellular enzymes, cellular structural proteins, and provide antioxidant protection. The risk of adverse effects from these metals is minimal with little chance of overdose, negative impact on the redox balance of the cell, or hepatic toxicity. This dose of Zn is below the maximum of 20 mg/day that can be administered without medical supervision provided there is an adequate dietary intake of Cu [38] and below the 53 mg/day of Zn that can interfere with Cu status. Higher doses for Zn may be possible in individuals under oxidative stress. For example, type I

diabetics were administered 30 mg/day of Zn with no adverse effects on Cu status and an improvement in indicators of oxidative stress [39]. Nephrotoxicity would be a concern, however, the protection of induced MT on the kidney [22], and the antioxidant effects of vitamin E and Zn [23,25], as well as a slow mobilization of metals should mitigate this risk. Renal compromised patients would need additional supervision. It is also unlikely that allowing the toxic metal to reside in the body for long periods of time would be of benefit to the kidney. The duration of supplementation would vary significantly depending on the type of metal and the progression of clearance from the body.

Additionally, the ZnCaE supplement would be easy to manufacture, distribute, administer, and have a long shelf life. With the exception of administration during chelation, this therapeutic approach would be useful in a wide variety of toxic metal exposures ranging from the acute to chronic, for a wide variety of routes of exposure, and for a wide variety of metals. Clearly research needs to be expanded in this area to demonstrate safety, effectiveness, and to optimize the dosage of each element, as well as to consider the addition of other essential metals, such as Se.

Acknowledgments

The author wishes to thank Ms. Albracht for her patience and consideration during the preparation of this manuscript.

Conflicts of Interest

The author declares no conflict of interest.

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