

Zinc and Multi-Mineral Supplementation Should Mitigate the Pathogenic Impact of Cadmium Exposure

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Abstract

High-level cadmium (Cd) exposure has long been known to induce nephropathy, severe osteoporosis, and fractures in humans. More recent epidemiology, however, reveals that, in populations not known to have important industrial exposure to this heavy metal, high-normal blood or urine Cd levels correlate with increased risk for vascular disorders, cancers, diabetes, and total mortality, as well as osteoporosis and nephropathy. Since these disorders appear unlikely to expedite Cd absorption, and since Cd has promoted these pathologies in rodent studies, it seems reasonable to conclude that Cd is an important mediating risk factor for these disorders in humans. Avoiding tobacco smoke or frequent ingestion of shellfish or organ meats can lessen humans exposure to Cd, but the chief dietary sources of Cd are plant-derived foods – green leafy vegetables, whole grains, tubers, and root vegetables – typically recommended for their health-supportive properties; indeed, among non-smokers, vegans tend to have the highest Cd body burden. Fortunately, iron sufficiency and ample dietary intakes of calcium, magnesium, and zinc can impede absorption of dietary Cd, both by down-regulating intestinal expression of mineral transporters, and by directly competing with Cd for access to these transporters. Correction of iron deficiency appears to be of particular importance for controlling Cd absorption. Moreover, zinc supplementation can counteract the toxicity of Cd already in the body via induction of metallothionein, which binds Cd avidly via its sulfhydryl groups; so long as it remains sequestered in this form, Cd is innocuous. Zinc supplementation may in any case be recommendable, as optimal zinc status exerts protective anti-inflammatory, antioxidant, and immunosupportive effects. Inasmuch as the toxicity of Cd appears to be mediated in large part by oxidative stress, ingestion of spirulina, lipoic acid, melatonin, and N-acetylcysteine may also have potential for mitigating the risk associated with Cd exposure, as suggested by rodent studies. Hence, although Cd may prove to be a major risk factor for morbidity and mortality in humans, practical strategies for limiting its absorption and pathogenic impact are at hand.

Cadmium Emerges as a Human Toxin

Humans are exposed to cadmium (Cd) primarily via absorption from food and tobacco smoke. Its half-life of residence in the body is on the order of 10-30 years, reflecting the absence of physiological mechanisms for excretion of this heavy metal.^{1,2} The toxicity of Cd has long been appreciated, but its potential for harming humans did not gain much attention until the outbreak of Itai-Itai (ouch-ouch) disease in Japan in the 1960s.³ This syndrome afflicted elderly Japanese women who had consumed rice grown in fields recently contaminated with industrial Cd. It manifested as nephropathy, osteomalacia, osteoporosis, and painful fractures. Cd accumulates in the kidney, most notably in the proximal tubules, whose function it impairs, leading to beta-2 microglobulinuria and hypercalciuria.² At slightly higher levels of exposure, glomerular function is also compromised. Cd also accumulates in bone, and can act directly within the bone to promote osteolysis while simultaneously impairing new bone formation;⁴

hypercalciuria stemming from renal tubular damage is not the chief mechanism responsible for Cd-linked osteoporosis.

Although high-level Cd exposure can clearly give rise to nephropathy and osteopathy, recent epidemiological studies suggest that levels of Cd body burden occurring commonly in the general population – among people not known to have suffered industrial exposure – can significantly increase risk for renal tubular damage and osteoporosis. Such studies typically estimate body Cd levels by measuring Cd in spot urine (mcg Cd per g creatinine), which is thought to provide a reasonably accurate assessment of body Cd content during chronic low level exposure; blood Cd, which can reflect more acute exposure, is also employed.¹ In the NHANES III cohort, a cross-section of the non-institutionalized entire U.S. population, urine Cd averaged 0.28 and 0.40 mcg/g in men and women, respectively.⁵ In the CadmiBel study of Belgium, where industrial contamination of soils with Cd is more common, urine Cd averaged 0.74 mcg/g in a less polluted region, and 1.03 mcg/g in a region closer to the source of pollution.⁶ In Swedish post-menopausal women, not known to be at risk from industrial exposure, urine Cd averaged 0.67 mcg/g.⁷ Yet recent assessments, examining the most sensitive markers for tubular dysfunction, show that people with urinary Cd levels in excess of 0.6 mcg/g are at increased risk for discernible renal tubular damage; above 1.1 mcg/g, risk for a decline in glomerular filtration rate increases.⁷ Within the NHANES III population, adjusted odds ratios for albuminuria or reduced glomerular filtration were 1.92 and 1.32 in the upper quartile of urinary Cd relative to the bottom quartile.⁸ Within this same population, after appropriate statistical adjustments, urinary Cd in the range 1.00-1.99 mcg/g was associated with 49% increase in risk for osteopenia, and a 78% increase in risk for osteoporosis, relative to those with lower Cd levels.⁹ Among a cohort of non-smoking Swedish women, adjusted odds ratios for fracture were roughly twice as high among those with urinary Cd greater than 0.5 mcg/g, relative to those with lower Cd levels.¹⁰ Clearly, even in populations not known to have industrial Cd exposure, Cd levels in the high-normal range are associated with poorer bone health and greater risk for nephropathy.

High-Normal Cadmium is Linked to Vascular, Cancer, and Diabetes Risk

Moreover, epidemiologists are now starting to focus their attention on associations of body Cd level with with risks for vascular diseases, cancer, diabetes, and total mortality – and their findings, while not entirely consistent in their details, incriminate Cd in all of these respects. Indeed, it may be reasonable to conclude that, with the exception of cigarette smoke (itself a major source of Cd exposure!), Cd is the most consequential of all environmental contaminants.

One of the first pertinent studies, a cross-sectional analysis of the NHANES III cohort (1988-1994), found that the adjusted odds ratio for myocardial infarction in women was 1.80 in the upper tertile of urine Cd vs. the lower tertile; the results were similar when only never-smoker women were analyzed.¹¹ In the men, the comparable figure was 1.26, which however missed statistical significance. In another cross-sectional analysis based on NHANES III, this time cumulating data from 1999-2006, adjusted odds ratio for prevalent cardiovascular disease (including stroke, angina, heart attack, coronary disease, and congestive failure) was 1.44 in the top quartile of urine Cd, vs. the bottom quartile.¹² In a South Korean population, in which Cd levels tend to be somewhat higher, an interquartile range increase of blood Cd was associated with an adjusted odds ratio of 2.1 for ischemic heart disease.¹³ The association of cadmium status with risk for atherosclerotic thickening of carotid arteries was assessed in 195 healthy

young women; the multivariate-adjusted odds ratios over the tertiles of urine Cd were 1.0, 5.2, and 6.4.¹⁴ With respect to these cross-sectional studies, it should be borne in mind that, owing to fact that Cd accumulates gradually in the body throughout a lifetime, and turnover of this Cd is on the order of 10-30 years,² it is highly unlikely that a cardiovascular disorder of recent onset could have notably influenced urine Cd level. Hence it is much more likely that elevated Cd played a role in the genesis of vascular disease, rather than vice versa. Also speaking for a causative role of Cd in vascular disease are studies showing that Cd accumulates in the human vascular wall (most notably the media), that it disrupts adherence junctions in endothelial cells *in vitro* and in rodents, and that Cd exposure exacerbates atherogenesis in rodents prone to this disorder.^{15, 16}

Cd also has clear carcinogenic potential. Indeed, the International Agency for Research on Cancer has classified Cd as a carcinogen since 1993, in light of its carcinogenic activity in rodents, as well as strong evidence that workers in industries entailing Cd exposure are at increased risk for lung cancer.^{17, 18} Cell culture studies reveal several mechanisms whereby Cd might increase cancer risk, including induction of pro-mutagenic oxidative stress, inhibition of DNA repair mechanisms, and modulation of transcription factor activity.¹⁹⁻²¹

In light of Cd's ability to induce prostate cancer in rodents, epidemiological studies have attempted to correlate Cd body levels with prostate cancer risk, but have yielded inconsistent conclusions²² – albeit one recent study links Cd to risk for advanced prostate cancer specifically.²³ Evidence linking Cd exposure to estrogen-promoted cancers is more compelling. Indeed, studies in rodents and cell cultures demonstrate that Cd can induce estrogenic effects *in vivo* and can directly activate estrogen receptor alpha *in vitro* – suggesting that a pro-estrogenic effects might complement the impact of Cd on DNA integrity in cancer induction.^{24, 25} (There is some doubt, however, that the estrogenic effects of Cd observed *in vivo* are mediated by direct activation of the estrogen receptor.^{26, 27}) Two recent epidemiological studies focusing on breast cancer have been particularly troubling. In a case-control study conducted in Wisconsin, enrolling 246 women with breast cancer and 254 age-matched controls, adjusted odds ratio for breast cancer in the upper quartile of urinary Cd (>0.58 mcg/g) was 2.29 vs the lowest quartile – which suggested that Cd may have been responsible for 45 of the 124 cases of breast cancer per 100,000 population diagnosed annually.²⁸ Subsequent case-control studies targeting women on Long Island and the NHANES cohort (1999-2008) achieved similar results; the adjusted odds ratio for breast cancer in the upper quartile of urinary Cd in the Long Island sample, relative to the lowest quartile, was 2.69; in the NHANES analysis, adjusted odds ratio in the upper two quartiles, relative to the lowest, was 2.50.²⁹ The authors concluded that, if Cd's association with breast cancer was truly causative, about 35% of the breast cancer observed could be attributed to Cd exposure – a finding quite comparable to that of the Wisconsin study. Also speaking in favor of a role of Cd in breast cancer induction is a study correlating urinary Cd with a modest increase in risk for increased mammographic density, a well established risk factor for breast cancer.³⁰ With respect to risk for endometrial cancer, a somewhat atypical prospective Swedish study estimating Cd exposure by food intake found an adjusted odds ratio of 1.39 in the upper tertile; intriguingly, the authors noted that this relationship was strongest in lean subjects expected to have relatively low endogenous estrogen activity – as might have been expected if Cd was indeed exerting estrogenic activity.³¹ Single case-control studies have also linked Cd exposure to increased risk for pancreatic, bladder, and renal cancers.³²⁻³⁴

The association of Cd exposure with risk for overall cancer incidence or mortality has now been examined in several prospective studies – all of which point to a carcinogenic impact of high-normal Cd levels. In the CadmiBel Belgian cohort, a doubling of 24-hour Cd excretion entailed an adjusted hazard ratio of 1.31.³⁵ In the NHANES III cohort, a doubling of urinary Cd was associated with adjusted hazard ratio for cancer mortality of 1.26 and 1.21 in men and women, respectively.³⁶ An analysis of the same cohort, in which urinary Cd was assessed at earlier time points, found adjusted hazard ratios of 1.55 (men) and 1.07 (women, non-significant) for a doubling of urinary Cd.⁵ And in a prospective analysis of the CadmiBel cohort, adjusted hazard ratio for non-cardiovascular mortality (largely cancer) was 1.44 for a doubling of urinary Cd, and 1.33 for doubling of blood Cd.⁶ Although the non-significant risk observed in women in one study is hard to square with compelling evidence linking Cd to breast cancer in other studies, the overall impression is that high-normal Cd exposure is strongly associated with cancer risk and mortality.

Limited evidence also suggests that Cd exposure may pose a risk for type 2 diabetes, and may notably increase risk for nephropathy in diabetics. In a cross-sectional analysis of NHANES III, urinary Cd in the range 1.00-1.99 mcg/g (about one-fifth of the population) was associated with an adjusted odds ratio of 1.48 for prevalence of elevated blood glucose or diabetes; this risk was 2.05 for urinary Cd of 2.00 mcg/g or greater.³⁷ Since diabetic nephropathy might factitiously raise urinary Cd by damaging renal tubules, the authors did an additional analysis that excluded subjects with albuminuria; a similar result was achieved, albeit the magnitude of the association was slightly attenuated. A case-control study in Pakistan likewise linked higher blood and urinary levels of Cd with increased risk for diabetes.³⁸ Rodent studies show that Cd can accumulate in pancreatic islets, and that Cd exposure can increase fasting glucose levels while lowering those of insulin.³⁹ Since oxidative stress appears to be a mediator of the glucolipotoxicity that impairs beta cell function in type 2 diabetes,⁴⁰ and Cd toxicity is mediated in part by oxidative stress,¹⁹ it is reasonable to postulate that Cd exposure might hasten incipient beta cell failure by potentiating this oxidative stress. Furthermore, once diabetes develops, Cd exposure may amplify the risk associated with chronic hyperglycemia; in particular, in several cross-sectional studies enrolling diabetics, markers of renal dysfunction were consistently enhanced in patients with elevated Cd levels.³⁹

Association of Cadmium with Total Mortality

If Cd exposure does indeed increase risk for vascular disease, cancer, diabetes, osteoporosis, and renal disease, it would be reasonable to expect it to have an impact on total mortality. This has now been assessed using data from both the CadmiBel and NHANES III studies. The CadmiBel study reported adjusted risks of 1.20 and 1.25 associated with a doubling of urinary and blood Cd, respectively.⁶ In the NHANES III analysis, a doubling of urinary Cd was associated with a 28% increase in total mortality in men, but a non-significant 7% increase in women.⁵ No such sex differential was noted in the Belgian study. A meta-analysis lumping these two studies calculated a 17% increase in mortality risk associated with a doubling of urinary Cd (both sexes combined).² Further research is evidently needed to clarify the gender-dependence of Cd-related mortality.

As if these findings were not sufficiently troubling, a very recent study suggests that Cd exposure may increase risk for neurodevelopmental impairment in children. In children of age 6-15 enrolled in the NHANES study, the adjusted odds ratios for learning disabilities or enrollment in special education were 3.0 and 3.2 (respectively) in the highest quartile of urinary Cd vs the lowest quartile; on the other hand, a

diagnosis of attention deficit disorder was not linked to Cd.⁴¹ Cd is markedly teratogenic in animals, possibly reflecting the fact that embryos are particularly susceptible to oxidative stress.⁴² Cd also has neurotoxic potential;⁴³⁻⁴⁵ whether Cd exposure might contribute to risk for common neurodegenerative disorders linked to oxidative stress has not been evaluated to date.

It is therefore hard to escape the conclusion that, either high-normal tissue Cd levels play an important mediating pathogenic role in a wide range of disorders, and/or that a metabolic state (or states) which expedites intestinal Cd absorption plays a mediating role in these disorders. (Modulation of Cd egress is not a likely explanation; as noted above, there are no physiological mechanisms for Cd excretion, and the half-life of body Cd is on the order of 10-30 years.) In regard to the latter possibility, since BMI does not correlate with Cd status, it is unlikely that metabolic syndrome increases Cd uptake.

Cadmium Exposure via Smoking and Plant-Derived Foods

What are the determinants of Cd body burden? Smoking is a major source of Cd exposure, and smokers consistently show higher Cd levels than non-smokers; each cigarette contains about 1-2 mcg of Cd, about 10% of which is inhaled when the cigarette is smoked.² It is estimated that, in smokers, the quantity of Cd absorbed from cigarettes is comparable in magnitude to that absorbed from food. (Epidemiologists have of course taken smoking into account when performing multivariate analyses correlating Cd exposure with disease risks.) With respect to food sources, shellfish and organ meats (liver and kidney) tend to be relatively high in Cd, but otherwise the chief dietary sources of Cd are plant-derived.¹ The Cd content of food crops tends to reflect the Cd content of the soil in which they are grown, with the proviso that Cd is more readily taken up by plants grown in acidic soils than in neutral or alkaline soils.² However, some food plants are more adept at assimilating soil Cd than others; green leafy vegetables, whole grains (Cd tends to be higher in the bran), tubers, and root vegetables tend to be relatively high in Cd¹ – ironically, this list includes many foods generally recommended for their health-protective potential! Indeed, a study evaluating vegetarians and semi-vegetarians in the Slovak Republic, the highest blood Cd levels were observed in the vegans, with progressively lower Cd levels in those whose diets included higher amounts of animal products.⁴⁶ As there is a growing consensus that diets rich in whole plant-derived foods impact health favorably in numerous ways, it does not appear that avoidance of specific foods (other than possibly organ meats and shellfish) will be a prudent strategy for minimizing Cd body burden. Furthermore, even though some phosphate fertilizers are contaminated with Cd, there is currently no evidence that organic farming techniques tend to minimize crop Cd uptake.⁴⁷

Essential Mineral Status as a Determinant of Cadmium Absorption

However, it is quite feasible to modulate the efficiency of Cd absorption. Cd transits the intestinal wall by “hitching a ride” on various protein transporters that function physiologically to expedite absorption of essential minerals.⁴⁸⁻⁵⁰ The expression of these receptors is often modulated by nutritional status; a diet rich in a given mineral will typically down-regulate expression of the transporters which mediate its absorption. This is notably true for iron, since iron overload is quite toxic. There is growing evidence that Cd absorption is increased in the presence of iron deficiency; this likely reflects that fact that divalent metal transporter 1 (DMT1), a key mediator of iron absorption whose expression in intestinal epithelium is up-regulated by iron deficiency, can also transport Cd.^{48, 51} Several epidemiological studies have found that estimated body iron content tends to correlate inversely with Cd body burden in pre-menopausal women.⁵²⁻⁵⁴ This also likely explains why, in non-smokers, Cd body levels tend to be higher in women

than in men. The obvious implication is that iron deficiency should be corrected to avoid an up-regulation of Cd absorption. Whether this translates into a recommendation for widespread iron supplementation is more problematic, as elevated body iron stores themselves can exacerbate oxidative stress, and are suspected to increase cancer risk by promoting mutagenic DNA damage.⁵⁵ However, it does seem prudent to employ iron supplementation (at least temporarily) for the correction of iron deficiency.

Intestinal transporters for calcium and zinc, excessive serum or tissue levels of which can be toxic, are likewise regulated by nutritional status. Intestinal Cd absorption is increased up to 8-fold in rats fed diets marginal in calcium, zinc, and/or iron.^{56, 57} It is therefore reasonable to suspect that certain intestinal proteins which mediate calcium and zinc absorption likewise can transport Cd – albeit the specific proteins involved here remain unclear at this time.^{49, 50, 58, 59} In addition, rodent studies reveal that diets enriched in magnesium can blunt Cd absorption.^{60, 61} It seems likely that essential mineral status can influence Cd absorption in at least two ways. In the long term, mineral status regulates intestinal transporter expression. But it is also likely that an essential mineral ingested in a given meal can suppress the absorption of Cd ingested with that meal by competing with Cd for access to its characteristic transporters. An evident implication is that a comprehensive “insurance” supplement rich in essential minerals, ingested with meals on a consistent basis, can be expected to impede Cd absorption. While this strategy could not be expected to impact the pathogenicity of the pre-existing Cd body burden (aside from the impact of zinc, discussed below), a lifelong habit of employing such supplementation would likely confer significant protection from Cd-mediated pathology. Future epidemiology should assess whether consistent use of multi-mineral supplementation is indeed associated with a reduction in Cd body burden.

Furthermore, consideration should be given to the possibility that elevated Cd body levels may to a degree reflect a prolonged suboptimal intake of essential minerals, and that the disease risks associated with elevated Cd levels might be mediated in part by this low mineral status. For example, a low intake of calcium and other minerals might well play some role in the elevated risk for osteoporosis associated with increased Cd levels. If this view is correct, the practical remedy remains the same – an increased intake of essential minerals, via supplementation or improved food choices, is warranted. (By way of analogy, the homocysteine story should be recalled; although elevated homocysteine was linked to increased vascular risk in many prospective studies, it has emerged that systemic inflammation, which can raise homocysteine levels, may be the true mediator of the vascular risk associated with moderate elevations of homocysteine.)

Zinc-Mediated Metallothionein Induction Combats Cadmium Toxicity

A further fruitful strategy for coping with the potential pathogenicity of Cd is suggested by the fact that the protein metallothionein functions to mitigate Cd toxicity by binding it tightly via its sulfhydryl groups, in a manner quite analogous to its interaction with zinc or copper; Cd toxicity is considerably exacerbated in metallothionein knock-out mice.^{62, 63} It appears that Cd is innocuous as long as it remains bound to metallothionein. This finding is particularly intriguing in light of the fact that cellular expression of metallothionein tends to increase with increased zinc exposure.⁶⁴⁻⁶⁶ This phenomenon likely explains why zinc administration has provided a measure of protection from parenteral or dietary Cd in a number of rodent studies.⁶⁷⁻⁷⁰

Epidemiologists are just beginning to examine the interaction of zinc status and the association of Cd levels with disease states. In the study correlating carotid artery thickness with Cd status mentioned above, the authors did an intriguing sub-analysis. They found that the correlation between serum cadmium and carotid thickness was extraordinarily pronounced in subjects with serum zinc in the lower two tertiles, but that it was absent in subjects with serum zinc in the upper tertile.¹⁴ Furthermore, a study attempting to correlate urinary Cd with serum levels of prostate-specific antigen (PSA) observed no clear correlation in the group overall, but observed a significant direct correlation in men whose daily zinc intake was estimated to be below the median level of 12.7 mg.⁷¹ Further studies of this type are clearly warranted.

Intakes of supplemental zinc in the range of 15-50 mg daily have been shown to markedly boost the protein or mRNA of metallothionein in the monocytes and erythrocytes of healthy young men.⁶⁴⁻⁶⁶ Although relatively few epidemiological studies have focused on associations between zinc supplementation and health outcomes, a recent Canadian case-control study has linked prolonged zinc supplementation with reduced risk for breast cancer in both pre-menopausal and post-menopausal women.⁷² Moreover, an international ecologic analysis by Grant has linked increased dietary zinc intake to decreased risk for 12 types of cancer.⁷³ It should be noted that supplemental zinc can exert antioxidant and anti-inflammatory effects, as yet poorly understood, that conceivably could influence cancer risk independent of any impact on metallothionein expression. Indeed, one recent clinical trial demonstrates that 45 mg zinc daily exerts a systemic anti-inflammatory effect – significant reductions in C-reactive protein, interleukin-6, and circulating markers of endothelial activation – suggestive of anti-atherogenic potential.^{74, 75} Supplemental zinc can also aid immune function, particularly in the elderly.^{76, 77} And zinc may have played a key role in the improved control of macular degeneration noted in the AREDS1 study.⁷⁸ Little noticed is the fact that total mortality during 6.5 years of follow-up was significantly lower (RR =0.73) in the AREDS participants randomized to receive zinc.⁷⁹ It is quite conceivable that further clinical and epidemiological studies will demonstrate that supplemental zinc has considerable potential for health promotion, only part of which might be attributable to Cd sequestration. However, it should be cautioned that zinc intakes in excess of 100 mg daily can suppress HDL cholesterol levels; moreover, high zinc intakes can impede copper absorption.^{80, 81} Hence, it is probably prudent to keep daily supplemental doses of zinc moderate (e.g. not more than 50 mg), and to include a small amount of supplemental copper to avoid copper depletion; the 80 mg of zinc daily provided in the AREDS study was complemented with 2 mg of copper.⁷⁸

Supplemental Antioxidants as Antidotes to Cadmium Toxicity

Finally, in light of the fact that much of the pathogenicity of Cd in animal studies is mediated by oxidative stress, the ingestion of foods or supplements rich in antioxidants may have potential for mitigating Cd's adverse health impact.^{19, 82-85} Indeed, the diverse range of pathologies which Cd appears to promote may reflect the fact that oxidative stress is a key mediator of many disorders, including those linked to Cd. Particularly notable is a recent study showing that spirulina ingestion dose-dependently alleviates the teratogenicity induced by parenteral Cd administration to pregnant mice.⁴² The marked antioxidant activity of spirulina may be largely attributable to its primary phycochemical phycocyanobilin, which appears to mimic the physiological role of its chemical relatives biliverdin/bilirubin as an inhibitor of certain NADPH oxidase complexes.⁸⁶ Activation of NADPH oxidase, as well as mitochondrial damage, is believed to play a role in Cd-induced oxidative stress.^{19, 43, 87,}

⁸⁸ Other nutraceutical antioxidants, such as astaxanthin, lipoic acid, melatonin, N-acetylcysteine, and phase II inducers, may likewise have potential for mitigating Cd's pathogenic impact⁸⁹⁻⁹⁹ – though it should be acknowledged that oxidative stress is unlikely to be the only mechanism mediating Cd's adverse effects. The researchers who reported high Cd levels in vegans, also note that whole plant-based foods tend to be rich in phytochemical antioxidants which might to some degree offset the toxic impact of Cd.⁴⁶

Chelation Therapy May Have Limited Potential in Chronic Cadmium Toxicity

There do not appear to be any clinical studies demonstrating that drugs approved for chelation therapy of heavy metal toxicity, such as dimercaptosuccinic acid (DMSA¹⁰⁰), can be useful for meaningfully lowering Cd body stores, except when Cd exposure has been acute and recent. This may reflect the fact that such drugs have poor access to the interior of cells where most Cd is stored during long-term exposure.⁸² In one recent study, mice were exposed to Cd for 8 consecutive weeks, and, immediately following cessation of this exposure, DMSA was administered orally for 5 days.¹⁰¹ This therapy notably diminished the vascular dysfunction and oxidative stress induced by Cd exposure, and also reduced kidney and liver Cd levels by over 50%. The authors suggest that their findings may be clinically applicable for reducing Cd body burden. This conclusion might be more convincing if they had administered the DMSA a number of months following Cd exposure, so that the Cd in the mice had had time to be fully sequestered in the intracellular pools (largely metallothionein-bound) where most Cd is found during chronic low-level exposure. In any case, it would probably be appropriate to conduct clinical studies to assess whether prolonged oral protocols of DMSA (or perhaps other orally administrable agents capable of chelating Cd¹⁰²) might have a worthwhile impact on Cd body burden in patients with excessive Cd levels. Certain ester derivatives of DMSA (such as the monoisoamyl ester) have greater cell permeability, and can promote excretion of metallothionein-bound Cd in mice,^{103, 104} unfortunately, these agents have never been approved for clinical use, and may have more toxic potential than well-tolerated DMSA.¹⁰⁵

Practical Conclusions

In summary, both cross-sectionals and prospective epidemiology now links high-normal Cd body levels with increased risk for osteoporosis, nephropathy, vascular disease, cancer, diabetes, and total mortality. With respect to each of these disorders, animal and cell culture studies suggest that this association may well be causative. The long half-life of Cd in the body renders unlikely the possibility that, in cross-sectional studies, the disorder under consideration is in fact the cause of the elevated body Cd. Aside from poor dietary mineral status, researchers are currently unaware of any pathogenic metabolic state which might boost Cd absorption and concurrently induce the disorders linked to elevated Cd levels. Hence, it is prudent to conclude, at least at present, that elevated body Cd levels, within the high-normal range, are in fact responsible for a vast toll of human morbidity and mortality.

Avoiding cigarette smoke is the most obvious way to limit Cd exposure. Excessive intake of shellfish or organ meats may also be inadvisable in this regard. However, some of the most health-supportive plant-derived whole foods can be rich in Cd (contingent on their soil of origin) – indeed, vegans tend to have the highest body levels of Cd – so it does not seem prudent to avoid Cd exposure solely via food choices. If and when the risk associated with Cd exposure is more fully appreciated, adoption of certain

agricultural measures – avoiding the use of Cd-rich soils in farming, and raising the pH of acidic soils – may enable a reduction in the Cd content of the food supply.

Multimineral supplements, ingested with meals, have the potential to suppress absorption of dietary Cd, both by down-regulating the expression of certain intestinal mineral transporters, and by competing with Cd for access to these transporters. Correction of iron deficiency appears to be especially important in this regard. Supplemental zinc is of particular interest in that it can act acutely to mitigate the pathogenicity of the Cd already in the body via induction of metallothionein, a protein which binds and sequesters Cd. Effective antioxidant measures also have the potential to limit Cd's pathogenic impact, in light of evidence that oxidative stress may be a key mediator of this pathogenicity. It is not clear that any current pharmaceutical measures for heavy metal chelation have important potential for decreasing Cd body burden, save in cases where Cd exposure has been recent and acute; nonetheless, clinical studies evaluating the impact of long-term oral administration of chelating drugs such as DMSA on Cd levels might be warranted.

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