BioMetals **17:** 543–547, 2004.

Nutritional interactions in intestinal cadmium uptake - Possibilities for risk reduction

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Key words: Cadmium, diet, intestinal uptake, iron, trace element status, risk reduction

Abstract

Effects of dietary composition and trace element status on fractional intestinal cadmium uptake is reviewed below. Fractional cadmium uptake is of fundamental importance for internal dose, related individual susceptibility to cadmium, induced renal damage and eventually bone disease. Diet composition with regard to macronutrients has some effects on cadmium bioavailability. Major determinants of intestinal cadmium uptake are however diet composition with regard to crude fibres and trace elements, especially iron. Deficiencies may increase intestinal cadmium uptake 5–8 times. Ultimate risk management would be not to raise crops on cadmium polluted soil. Provisionally, assurance of optimal trace element status in persons exposed to cadmium is essential for risk reduction.

Introduction

Food contamination with cadmium can be a considerable health risk in areas, where industrial activities have resulted in high soil levels of cadmium (Järup *et al.* 1998). Estimation of population risk associated with dietary cadmium exposure on a regional basis requires knowledge about the external dose, while individual risk depends also on individual susceptibility, including factors affecting intestinal cadmium uptake, which can vary extensively. Below, factors influencing the bioavailability of cadmium in dietary components are reviewed. Accordingly focus is mainly on the fractional intestinal cadmium uptake, which may be estimated directly or indirectly in humans and experimental animals using one of four experimental designs: 1. Single dose or prolonged feeding of ^{109}Cd labelled food items, followed by gamma-counting of whole animals or organs; 2. Single dose or prolonged feeding of 'cold' Cd labelled food items followed by measurement of organ Cd levels by atomic absorption spectroscopy; 3. Chemical balance methods quantifying intake and elimination of Cd; 4. Stable isotope methods calculating uptake of added ^{106}Cd by mass spectroscopy or neutron activation analysis. The whole-body retention (WBR) expressed as per cent of the initial dose is considered a valid estimate of the fractional intestinal uptake (Andersen 1989). In experiments where the whole-body burden (WBB) of cadmium cannot be measured, the fractional uptake can be estimated from the combined hepatic and renal deposition, which is more than 70% of WBB in most situations (Andersen 1989). Due to the very low intestinal Cd uptake in humans and experimental animals, isotope methods are more accurate than methods based on chemical balance or organ accumulation of unlabelled Cd. Due to the high precision of the isotopic analyses, a very low dose, 'spike', not influencing the homeostasis of endogenous cadmium can be employed, and human experiments can be performed with an ethically acceptable dose.

Effect of dose size and dosing regime on intestinal cadmium uptake

Many experimental animal studies have employed doses larger than doses received by humans, even

those living in Cd polluted areas. Daily human intakes are from 10 ug Cd/kg bw (high exposures) and downwards to 0.1 ug/kg (WHO 1992, Järup *et al.* 1998). The tolerable daily cadmium intake can be estimated to be 1 μg/kg bw from the Provisional Tolerable Weekly Intake of 7 μg/kg body weight, recommended by WHO/JECFA (2003). Daily dietary cadmium intake in unpolluted European areas vary from 0.1 to 0.45 μg/kg bw, in more polluted areas the total intake may be significantly more than the tolerable daily cadmium intake and reach several hundred ug/day (WHO 1992, Järup *et al.* 1998; Nordberg *et al.* 2003). The critical effect is renal tubular dysfunction leading to proteinuria with increasing incidence at renal cortex cadmium levels beyond 140 ug/g. The question of dose in animal experiments is important as studies have demonstrated quite different toxicokinetics at high and low dose – especially the fractional intestinal uptake depends on dose size (Engström & Nordberg 1979; Andersen 1989; Goon & Klaassen 1989; Andersen *et al.* 1992).

Lind *et al.* (1997) investigated whether intestinal cadmium uptake depends on the dosing regime, eg single dose versus chronic exposure, by administering similar doses of diet incorporated cadmium to groups of mice, either during the entire exposure period of 5 weeks or to a 7 $\times$ higher dietary concentration during 24 h one day per week. The dietary concentrations resulted in average cadmium doses of 38.8 and 44.6 ug/animal. These data indicate that single dose experiments may slightly overestimate the uptake. Our data indicate that dose size is a much more important parameter. Based on these considerations, single dose administration of extrinsic cadmium at dose levels below 10 umol/kg bw will offer data relevant for evaluating effects of diet composition on cadmium availability.

Uptake of extrinsic and intrinsic cadmium

Due to limitations in performing human uptake studies, animal experimentation is important, and most often the kinetics of added cadmium (extrinsic label) is studied. Knowledge about the bioavailability of ionic cadmium compared to that of cadmium incorporated during the growth of dietary components is therefore of major interest for validating experimental data. Andersen & Nielsen (unpublished) incorporated ^{109}Cd into algae that were fed to blue mussel that were homogenised and given as a single oral dose to mice by stomach tube. Similarly, liver homogenate from ^{109}Cd laden mice were administered orally to mice. Other groups were given the same dose of ^{109}Cd by stomach tube, either mixed with non radioactive mussel or liver homogenate or in pure water. The intestinal uptake estimated from WBR was similar in all groups. Sullivan *et al.* (1984) fed ^{109}Cd labelled plankton to oysters, that were lyophilized and incorporated into high-zinc (167–179 mg/kg) and low-zinc (106–114 mg/kg) diets which were given to mice, Cd levels 300–460 ug/kg diet. The WBR of oyster-incorporated ^{109}Cd was similar to that of inorganic ^{109}Cd added to a diet without oyster added. The intestinal uptake estimated from WBR was increased at the lowest zinc level.

Welch *et al.* (1978) compared the intestinal uptake of ^{109}Cd incorporated into lettuce during growth with that of ionic ^{109}Cd in rats using whole-body counting. Cadmium incorporated into lettuce was slightly more bioavailable than ionic cadmium, but there was no major difference in uptake. McKenna *et al.* (1992) included lettuce and spinach labelled with ^{109}Cd during growth at high or low Zn levels in feeds given to Japanese quail. Control groups received feeds with similar Zn and ^{109}Cd levels. The resulting ^{109}Cd levels in kidney and liver indicated that vegetable associated Cd was less bioavailable than ionic cadmium, with spinach incorporated cadmium having the lowest bioavailability. Cadmium in vegetables grown at high zinc level was slightly less bioavailable than cadmium from low zinc vegetables, however, similar addition of zinc to the control diet did not influence cadmium uptake. The reductions in uptake were modest, up to 60% (spinach/high Zn compared to control).

Wagner *et al.* (1984) labelled wheat during growth with ^{109}Cd to 0.1 ug Cd/g grain (10–25 times the average concentration in American wheat). Mice were given about 1 ug/kg Cd either incorporated into wheat or as ionic cadmium. The intestinal uptake estimated from the combined liver and kidney deposition was very similar, indicating equal availability of cadmium incorporated into wheat and ionic cadmium. Chan *et al.* (2000) compared the bioavalability estimated from combined hepatic and renal deposition of simiar doses of cadmium administered either incorporated into wheat during growth, added to wheat or as a single oral dose to mice. Extrinsic cadmium was only slightly (nonsignificantly) more bioavailable than intrinsic cadmium, but less absorbed than cadmium administered by gavage.

Lind *et al.* (1995) found that the biovailability of intrinsic cadmium in hepatopancreas from crab *Can-*

cer pagurus and mushroom *Agaricus augustus* was similar to that of ionic cadmium, estimated from the combined hepatic and renal deposition after 9 weeks of feeding semisynthetic diets with the various sources of cadmium added. Also, Lind *et al.* (2001), compared the intestinal uptake in mice of intrinsic cadmium in fresh or broiled horse kidney to that of ionic cadmium by adding horse kidney or $CdCl_2$ to diets fed to mice resulting in Cd levels of 0.05 or 3 mg/kg. Soluble horse liver cadmium was mainly present as metallothionein (MT) complex. The intestinal uptake estimated from liver and kidney cadmium levels was similar in all groups.

These studies comparing extrinsic and intrinsic labelling indicate that most often intrinsic Cd is slightly less available than extrinsic Cd, however, the bioavailability of intrinsic cadmium is not very different from that of extrinsic cadmium, and thus, experiments studying the bioavailability of added cadmium are valid for understanding effects of diet composition and individual dietary status.

Effects of diet composition on intestinal cadmium uptake

Andersen *et al.* (1992, 1994) gave either 5 umol/kg or 0.5 nmol/kg single oral doses of ^{109}Cd to mice fed either rodent pellets or semisynthetic diets for several weeks before dosage. These doses correspond to very high or very low doses to humans, corresponding to either heavily or non-polluted areas. The semisynthetic diets contained refined materials, had a low dietary fiber content and standard trace elements and vitamins at 2× the marginally sufficient levels for each compound. Thereby they were much closer to a 'western human diet' than standard rodent pellets. The same type of carbohydrates was used in all diets, but the amount was adjusted to allow variation in energy contribution from lipids and proteins. Mice fed the semisynthetic diets retained 5–8 times more cadmium than mice fed standard rodent pellets, wich is a complex diet rich in natural fibres, vitamins, and trace elements. This agrees with classical studies of Engström & Nordberg (1978) and Kello & Kostial (1977). High dietary concentrations of lipid and protein increased the net intestinal uptake of cadmium, but far less than the difference between a crude and a refined diet. A high concentration of wheat bran in the semisynthetic diet reduced the net intestinal cadmium uptake, but it was still significantly higher than in mice eating the standard mouse diet. Andersen & Nielsen (unpublished) gave groups of mice fed similar diets as in the single-dose experiments mentioned above ^{109}Cd-labelled $CdCl_2$ in drinking water for a prolonged time period. The WBR of cadmium was reduced by a high dietary concentration of wheat bran, in agreement with results of the single-dose experiments.

Iron status has been demonstrated in several studies to be an important determinant of intestinal cadmium uptake. Flanagan *et al.* (1978) administered ^{115}mCd to human voluteers and estimated the intestinal uptake by whole-body γ-scanning: The WBR at about 25 days postdosage was about 2.6% in 10 males and 7.5% in 12 females. The WBR was inversely correlated with serum ferritin levels. Thus, 8 women with serum ferritin levels between 0 and 20 ng/ml on an average absorbed 10% (highest absorption 22%), while 4 men with serum ferritin levels between 40 and 100 ng/ml absorbed only about 2% on an average. Shaikh & Smith (1980) administered ^{109}Cd labelled $CdCl_2$ in beef kidney homogenate followed by 450 ml of milk to human voluteers. The WBR was calculated to be 1.1–3% in men and 1.4–7% in women, the high value measured in a woman with low serum ferritin. Animal experiments have demonstrated increased intestinal Cd uptake during trace element deficiency (Fe: Flanagan *et al.* 1978; Schäfer *et al.* 1990; Groten *et al.* 1992; Zn: Waalkes 1986; Ca: Reviewed by Brzóska & Moniuszko-Jakoniuk 1998). Reeves & Chaney (2001, 2002) fed female rats rice diets or sunflower kernel diets with proficient or marginal levels of Ca, Zn or Fe in all combinations. A single dose (1 g of the feed extrinsically labelled with ^{109}Cd) given after 5 weeks of feeding was consumed within 2 h after overnight fasting. The extensive data indicate, that marginal status for each trace elements increased cadmium uptake. More importantly, a combined effect (additive or more than additive) was observed, as groups marginal for two metals absorbed more cadmium than groups marginal for only one metal, and groups marginal for all 3 trace elements absorbed the largest fraction of the dose. Comparison of the different uptake rates indicated, that iron was the most important determinant of intestinal cadmium uptake.

These data together indicate that dietary trace element status is a major determinant of individual risk during dietary cadmium exposure. While diet composition with regard to protein and lipid type and amount only slightly influences cadmium uptake, very crude diets with a high content of natural fibres and a high content of trace elements significantly reduce intest-

inal cadmium uptake, up to a factor of 8 times, while trace element deficiency increases cadmium uptake.

Discussion

The brief review above demonstrates that dietary composition and status may extensively affect the fractional intestinal cadmium uptake. Dietary factors increasing intestinal cadmium uptake are refined, low fibre diets low in iron, calcium and zinc. Hence, individuals with one or several deficiencies involving these nutrients may be at higher risk for cadmium induced adverse health effects than individuals with a sufficient dietary supply of and a proficient status with regard to these essential metals. The ultimate risk management of cadmium polluted agricultural soils is restriction of raising crops based on a WHO issued TDI as criterion. Due to the very large cadmium contaminated agricultural areas in some countries, there are situations where the use of cadmium-contaminated soils cannot immediately be completely avoided. In this situation, fortification of key dietary items with micronutrients could offer a means of reducing the risk associated with increased dietary cadmium intake. It is important that assessment factors in risk management of dietary cadmium exposure are based on high quality data. In this respect, good exposure data can be achieved, however, the question of individual susceptibility in relation to diet composition needs further investigation.

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