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Review

Role of diet in absorption and toxicity of oral cadmium-A review of literature

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The role of diet or its components in the absorption, distribution and toxicity of cadmium (Cd) has received attention in recent times. Experimental evidence in literature strongly suggests that the absorption of Cd is dependent on factors such as age, pH, diet and intestinal metallothionein (MT) production. The chemical forms of Cd such as Cd-MT in foods or inorganic Cd administered directly in foods or drinking water have also been considered in literature. The bioavailability or absorption of Cd as Cd-MT in foods has been shown in many reports to have decreased in relation to Cd administered directly as inorganic Cd in drinking water or foods. However, some other studies have reported contrary findings. Although research evidence has indicated that the type or components of a diet may also influence the absorption or toxicity of Cd irrespective of the chemical form involved. Diets low in proteins, minerals and certain vitamins have been reported to increase Cd absorption and toxicity. Conversely, diets rich in fibres have the reverse effect. The lack of conclusive information on the availability of Cd in Cd-MT for intestinal uptake in relation to that of ionic Cd is noticeable, and as a result there is a great need for further studies in this area. Also, since humans are usually exposed to Cd-MT in foods and rarely to inorganic Cd, the toxicity of food-incorporated Cd deserves further investigation, in view of the observed differences in tissue accumulation from these forms of Cd.

Key words: Cadmium, cadmium-metallothionein, cadmium absorption, diet components.

INTRODUCTION

The possible effects on the general population of long-term low–level exposure to cadmium (Cd) have been of concern in recent times. This is because the element is readily distributed to tissues after exposure, where it inhibits antioxidant enzymes (Gupta et al., 1991; Bagchi et al., 1996; Asagba and Eriyamremu, 2007; Chater et al., 2009). This inhibition can lead to increased oxidative stress which may result in membrane damage and loss of membrane bound enzymes such as the ATPases (Figueiredo-Pereira et al., 1998; Asagba et al., 2004; Asagba and Obi, 2005; Galazyn-Sidorczuk et al., 2009). Tissues in which these effects have been reported are the liver and kidney which are considered the main target organs in acute and chronic cadmium exposure (Sarker et al., 1995; Asagba and Obi, 2000). Other tissues involved in Cd toxicity include the testis, heart, bone, eye and brain (WHO, 1992; Pal et al., 1993; Lall et al., 1997; Asagba et al., 2002; Eriyamremu et al., 2005; Asagba, 2007).

Contamination of the environment by Cd may occur through anthropogenic and natural sources (WHO, 1992). The metal enters the human body through the two main routes of inhalation and ingestion. For the general population, ingestion is the major route of intake, with food being the main contributor. Knowledge of the absorption of Cd from experiments with human subjects is very limited, but a considerable body of animal experiments is available in literature (Ohta and Cherian, 1991; WHO, 1992; Andersen et al., 1992). These experiments indicate that different factors seem to affect the degree of absorption and toxicity of cadmium. Besides age, intestinal absorption of cadmium is influenced by a variety of factors including its chemical form, dose and route of exposure, environmental matrix in which it is contained, intestinal content, diet composition, nutritional status and interactions of cadmium with other nutrients (Kello et al., 1979; WHO, 1996; Diamond et al., 1998; Bhattacharyya et al., 2000).

According to Andersen et al. (1992), the two aspects of intestinal cadmium uptake that have been studied mainly

in experimental animals are: (1) the effects of dietary components on the intestinal uptake of ionic cadmium administered after mixing with the diet in drinking water or given as a single oral dose, and (2) the bioavailability for intestinal uptake of cadmium incorporated into various foodstuffs. Besides these two aspects, the present review will also be focused on the relationship between diet components and the bioavailability, uptake and toxicity of oral cadmium.

MECHANISMS OF ABSORPTION OF CADMIUM

Several reports of single exposure studies show that the individual absorption of cadmium nitrate or chloride ranges from 0.5 to 8% (Friberg et al., 1974). However, limited observations in humans given radioactive cadmium indicate that the average absorption is about 5% (Flanagan et al., 1978; Reilly, 1980).

Although food intake is among the most important routes of Cd exposure, not many details are known about the intestinal absorption mechanisms of Cd. Available research evidence (Foulkes et al., 1981; Foulkes, 1989) indicates that the mechanism of cellular Cd uptake in the rat jejunum consists of non-specific binding to anionic sites on the membrane, followed by a temperature-dependent and rate-limiting internalization step which is probably related to membrane fluidity. Completion of the absorptive process is by transport across the basolateral membrane into serosal fluid. This step proceeds at only l - 2% of the rate of uptake from the lumen. The major site of cadmium uptake in the intestine is not certain, however a low pH of the gastric content emptied into the duodenum is thought to contribute to improve uptake (Andersen et al., 1992). Beyond the duodenum, the pH increases and cadmium will rapidly be chelated by various dietary components and therefore be less bio-available. Transport of cadmium from the small intestine is also thought to be facilitated by other possible mechanisms, including metal transport proteins such as Divalent metal transporter 1 (DMT1), calcium ion channels, amino acid transporters (as cysteine–cadmium conjugates) and by endocytosis of cadmium-metallothionein (Cd-MT) complexes (Leazer et al., 2002; Park et al., 2002). In oral cadmium exposure, cadmium can be rapidly taken up and distributed to the liver and kidney, and the degree of uptake is largely dependent on factors such as age, pH, diet type and metallothionein production (Andersen et al., 1992). The gastro-intestinal tract produces metallothionein (MT) which can sequester cadmium. The role of MT in the absorption of Cd has not been fully elucidated. Earlier studies have shown that the ability of the intestine to produce MT is limited but increase from the proximal to the distal small intestine (Elsenhans et al., 1994; Elsenhans et al., 1999). This would improve the ability of the distal small intestine to handle Cd and thus make the metal less bio-available in this region (Eriyamremu et al., 2005). Similarly, the findings of Min et al. (1992) suggest that mucosal MT in the small intestine might trap Cd absorbed from the intestinal lumen. However, the report by Lind and Wicklund (1997) does not support the hypothesis that intestinal Cd absorption is increased when the Cd-binding capacity of intestinal MT is saturated.

MTs are a family of low molecular heavy weight metal binding proteins, which are unique in their high cysteine content (Chang et al., 2009). These proteins are widespread in eukaryotes and plants, and are also found in prokaryotes (Manuel et al., 1992). After absorption of cadmium, it is delivered to the liver by endogenous intestinal MT. It is assumed that hepatic Cd-MT then gradually redistributes the metal to the kidney which is the main target organ for chronic Cd toxicity (Elsenhans et al., 1997). The foregoing reports are also in consonance with the report of Min et al. (1991) which also showed that MT in intestinal mucosa plays a significant role not only in the absorption of Cd but also in its transport to the kidney. Thus, cadmium absorption and transport to the kidney is dependent on MT because it aids these processes. Nevertheless, it is apparent that toxic forms of the metal other than Cd-MT exist in the target sites, cells and organs (Suzuki, 1992). The chemical forms of cadmium have therefore been divided essentially into two groups namely, non-toxic MT-bound and toxic non-MT-bound (Suzuki, 1992).

ABSORPTION AND TOXICITY OF CADMIUM-METALLOTHIONEIN IN RELATION TO INORGANIC CADMIUM

The chemical form of Cd is an important factor on its gastrointestinal absorption. It has been reported that Cd in foods such as meat, sea foods and vegetable exists mainly as Cd-MT or MT-like Cd binding proteins (Ohta et al., 1993). As is already well known, MT is induced in the intestinal tissue by oral Cd administration, and the mechanism of gastrointestinal absorption of Cd has mainly been on Cd ion (Kikuchi et al., 2003). However, the chemical forms of Cd such as Cd-MT in foods or Cd bound by MT induced in the intestinal tissue have also been considered in literature (Muller et al., 1986; Groten et al., 1991; Groten et al., 1994).

It has been shown that during dietary, Cd exposure may be absorbed as complexes with MT or other dietary constituents which may be soluble or insoluble. There is conflicting information in literature on the availability of Cd-MT for intestinal uptake in relation to that of ionic Cd. Cherian (1983) administered five weekly doses of 20 µg ^{109}Cd-labelled Cd-MT or cadmium chloride in mice. Two weeks after the last dose, the whole body retention of Cd was about four times lower in the group fed Cd-MT than in that fed ionic Cd. Similarly, the findings of Ohta et al. (1989) suggest that the uptake of Cd from $CdCl_2$ and Cd-

MT is different. These workers studied the gastrointestinal uptake and transport of cadmium (Cd) and the role of metallothionein (MT) in everted sacs of rat intestine (ESRI). Although Cd-MT was taken up intact by everted sacs, the uptake was slow as compared to Cd salts. The intracellular presence of MT had little effect on the uptake of $CdCl_2$ but the Cd was sequestered by MT in the intestine.

In another study, by Sugawara and Sugawara (1991), $CdCl_2$ or Cd-MT was given orally to mice which were sacrificed at 30 min and 2 h after intubation. Although the Cd in Cd-MT was secreted rapidly into the urine, its absorption was found to be significantly less than that of $CdCl_2$. The authors attributed the poor absorption to a decrease uptake of Cd-MT. They also found that $CdCl_2$ taken up into the mucosa could stimulate MT synthesis even 30 min after its intubation. However, the percentage of MT-bound Cd in the Cd of intestinal supernatants was lower with $CdCl_2$ than with Cd-MT. They suggested that the transport mode of lumenal Cd-MT to mucosal cells is different from that of luminal $CdCl_2$. It was hypothesized that lumenal Cd-MT was probably internalized into intestinal cells in an intact form. Furthermore, the Cd-MT may pass through the basolateral membrane in this form. It was therefore concluded that the different distributions of Cd in liver and kidney after intubations with both forms of Cd is in support of the hypothesis. The intestinal uptake and transport of Cd to different organs were also studied by Ohta and Cherian (1991) in control and oral zinc pretreated rats using an *in situ* intestinal loop model. Intestinal loop was incubated with either $CdCl_2$ or Cd-MT for 30 and 60 min in rats under anaesthesia. The results suggest a slow uptake of exogenous Cd-MT from the intestine and transport to the kidney in contrast to deposition of Cd in the liver from $CdCl_2$.

The distribution of Cd was examined by Groten et al. (1991) in rats fed diets containing either Cd-MT or $CdCl_2$ for 4 weeks. The results obtained indicate that there is a relatively higher Cd accumulation in the kidneys after oral exposure to Cd-MT in the diet. In a further study by Groten et al. (1994), the dose-dependent Cd disposition and differences in renal toxicity after long-term dietary exposure to Cd-MT or $CdCl_2$ were examined. Male Wistar rats were fed diets containing 0.3, 3, 30, or 90 mg Cd/kg either as Cd-MT or as $CdCl_2$ for 10 months. In rats fed 30 and 90 mg/kg Cd as $CdCl_2$, the Cd concentrations in intestine, liver and kidneys were all higher than in rats fed the same doses in the form of Cd-MT. In consonance with their earlier findings (Groten et al., 1991), the kidney/liver Cd concentration ratio was higher with Cd-MT than with $CdCl_2$. However, at the lower Cd concentrations (0.3 and 3 mg/kg), no differences in Cd accumulation between Cd-MT and $CdCl_2$ groups were observed and the kidney/liver Cd ratio was also similar. When based on the amount of Cd-MT per milligram Cd in the tissue, rats fed Cd-MT and those fed $CdCl_2$ had a similar relative Cd-MT concentration in liver and kidney. Biochemical and histopathological changes in the kidney were observed in rats fed 90 mg/kg as Cd-MT but the effect was less pronounced than that of $CdCl_2$. It was therefore concluded that the health risk of dietary intake of Cd at low doses does not seem to differ between Cd-MT and $CdCl_2$.

Similar uptake of cadmium acetate and Cd-MT has been found by Muller et al. (1986) when these different forms of Cd^{2+} were exposed to rats by gavage. Other reports also indicate no difference in the bioavailability of Cd incorporated into dietary components in relation to inorganic Cd. For example, Wagner et al. (1984) exposed mice to Cd either incorporated into wheat during growth or as ionic Cd. The intestinal uptake, as estimated from the combined liver and kidney deposition, was very similar, indicating equal availability of Cd incorporated into wheat and ionic Cd. In another study by Sullivan et al. (1984b), Cd labeled plankton were fed to oysters which were then lyophilized and incorporated into a diet given to mice. The whole body retention of oyster-incorporated Cd was similar to that of inorganic Cd added to a diet without oyster, and even slightly larger when the intestinal Cd content was subtracted from the whole-body retention. In contrast, in a similar comparative study (Asagba, 2002), less Cd was accumulated in the tissues of rats fed fish-incorporated Cd in diet relative to those exposed to the metal in drinking water. This disparity was attributed to the inability of Cd to be easily released from the Cd tainted diet; hence it is less available *in-vivo* relative to its fate when given in drinking water. This interpretation agrees with the view expressed by Lind et al. (1995) based on the results they obtained when female Balb/C mice were fed a diet containing 0.4 ppm Cd from either boiled crab (*Cancer pagurus*) hepatopancrease or dried mushroom (*Agaricus augustus*) or as in organic cadmium ($CdCl_2$). Using Cd accumulation in the liver and kidney as a measure of Cd absorption, it was demonstrated that bioavailability of Cd from boiled crab hepatopancreas is slightly lower than that of Cd from mushroom and inorganic Cd. Fractionation of Cd in boiled crab hepatopancreas and mushroom revealed that Cd in crab hepatopancreas is mainly associated with denatured proteins with low solubility, whereas a large fraction of Cd in dried mushroom is associated with soluble ligands.

In a related study by Groten et al. (1990), the toxicity of cadmium was examined in rats fed diets containing either tissue-incorporated cadmium or cadmium salt for 4 wks. The test diets contained 30 mg cadmium/kg either as $CdCl_2$ or as Cd incorporated in pigs' livers; the control group was fed a diet containing liver from a pig not treated with cadmium. Over 90% of the cadmium present in the livers of the pigs was bound to metallothionein. Analysis of the diet and determination of the food consumption revealed that both cadmium-fed groups were exposed to similar dietary cadmium levels. There was no adverse effect on general health or survival. Feeding cadmium resulted in growth retardation and slightly

decreased water intake. Moreover, both cadmium-treated groups showed clear signs of anaemia and increased plasma aspartate and alanine aminotransferase activities. For the group fed cadmium chloride, all of these effects were more pronounced than for the group fed cadmium incorporated in liver. Microscopic examination of the liver and kidneys, however, did not reveal any lesion that could be attributed to the cadmium treatment. After exposure to cadmium the spleen showed decreased extramedullary haematopoiesis, an effect that was also more pronounced after feeding of the cadmium chloride than after feeding liver-incorporated cadmium. The differences in the extent of the toxic effects between the inorganic and the tissue-incorporated cadmium were accompanied by differences in the cadmium concentrations in liver and kidneys: the feeding of cadmium incorporated in the livers of the pigs resulted in about half the accumulation of cadmium in the livers of the rats that took place after intake of a diet containing cadmium chloride. In contrast, a much less marked difference in cadmium accumulation was observed in the kidneys.

EFFECTS OF DIET COMPONENTS ON THE ABSORPTION AND TOXICITY OF CADMIUM

There are several studies in literature which indicate that the uptake, distribution and toxicity of Cd are influenced by the type or composition of the diet of a population. The present review will be focused mainly on the effects of dietary fibers, proteins, minerals and vitamins on the absorption, distribution and toxicity of Cd.

Dietary fibers

The studies of Andersen et al. (1992) indicate that semi-purified diets (low in fibre content and were very much closer to a western human diet) result in increased Cd uptake in mice compared with unrefined whole diets rich in natural fibers, chelating agents and trace elements. Phytic and alginic acids increased the combined liver and kidney deposition of cadmium in rats fed diets containing cadmium and supplemented with phytic acid or different types of dietary fibres such as pectin, agar or glucuronic acid (Rose and Quarterman, 1984, 1987). Cadmium exposed rats fed a Nigerian-like diet (NLD) had a significant decreased Cd accumulation in the organs as compared to Cd exposed rats fed a control diet (Asagba et al., 2004; Asagba and Eriyamremu, 2007). The decreased accumulation of Cd can be attributed to the high fiber content of the NLD.

The gastrointestinal absorption and organ distribution of Cd after exposure for 9 weeks to three fibre-rich foodstuffs (wheat bran, sugar-beet fibre and carrots) were determined in mice by Lind et al. (1998). After 9 weeks, significantly lower fractional Cd accumulation (% total Cd intake) in the liver and kidneys was observed in the group receiving the wheat-bran diet than the other groups, indicating a lower fractional absorption of Cd. The wheat-bran diet had markedly higher levels of inositol hexa- and pentaphosphates (phytates) and a Zn level that was twice as high as those in the other diets. The authors made the following conclusions: (1) The higher levels of myo-inositol hexa- and pentaphosphates in the wheat-bran diet most probably contributed more to the lower fractional absorption of Cd than the elevated Zn level, due to the formation of insoluble Cd-phytate complexes, (2) Compared with the wheat-bran diet, the sugar-beet-fibre and carrot diets contained very low levels of myo-inositol penta- and hexaphosphates and consequently the fractional Cd absorption from these diets was higher.

Little is known about the influence of dietary fibres and nutritional status on metal absorption in human subjects. However, the study of Berglund et al. (1994) also indicates that absorption of cadmium in non-smoking women of 20 - 50 years depends on intake of dietary fibers. These workers measured the intake and uptake of cadmium in relation to diet composition in these women. A vegetarian/high-fiber diet and a mixed-diet group were constructed based on results from a food frequency questionnaire. There were no differences in the intake of nutrients between the mixed-diet and the high-fiber diet groups, except for a significantly higher intake of fiber ($p < 0.001$) and cadmium ($p < 0.002$) in the high-fiber group. Fecal cadmium corresponded to 98% in the mixed-diet group and 100% in the high-fiber diet group. No differences in blood cadmium (BCd) or urinary cadmium (UCd) between groups could be detected. There was a tendency toward higher BCd and UCd concentrations with increasing fiber intake; however, the concentrations were not statistically significant at the 5% level, indicating an inhibitory effect of fiber on the gastrointestinal absorption of cadmium. A similar work in rats also showed that wheat phytate and/or fiber contributed to reduced absorption of Cd (House et al., 2003)).

Proteins

The role of proteins in the absorption and toxicity of cadmium has also received attention in biological literature. Fox et al. (1979) fed groups of Japanese quail low level of Cd in diets supplemented with soy protein, casein or gelatin for 14 days. The whole body retention of Cd was three times higher in the group fed diets containing soy protein than in that fed casein or gelatin. The effect of glycinin, ovalbumin and gelatin on the absorption of cadmium was studied by Kojima et al. (1985). All three proteins were found to reduce intestinal Cd uptake which might suggest a protective effect of these proteins against Cd toxicity. Low protein diets generally enhance Cd toxicity while high protein diets reduce the toxicity (Fox, 1979; Revis, 1981). This is not surprising since low protein diets enhance the uptake of Cd (Suzuki et al., 1969), while the reverse effect is observed with a high

protein diet (Revis, 1981).

The study of Tewari et al. (1986) lends further credence to the effect of a low protein diet on the toxicity and intestinal absorption of Cd. Their reports indicate that feeding of Cd administered rats with a low protein diet not only increased Cd accumulation in the liver and kidney, but also enhanced the susceptibility of these organs to cadmium intoxication. These authors attributed the enhanced susceptibility to Cd intoxication to decreased availability of MT occasioned by low dietary proteins. MT not only aids in the absorption and distribution of Cd, but also ameliorates its toxicity. This is because it is a free radical scavenger (Szczurek et al., 2009). Conversely, our studies (Asagba et al., 2004, 2006) revealed that the concomitant exposure of rats to Cd and a Nigerian-like diet (NLD) which is low in proteins and high in carbohydrate and fibres for 16 weeks decreased Cd accumulation in the organs. However despite the decrease in Cd accumulation, the NLD predisposes rats to Cd toxicity, and this was attributed to decreased MT production occasioned by low availability of dietary proteins as postulated by Tewari et al. (1986).

From the foregoing reports, it is conceivable that a high protein diet should decrease Cd absorption, as a low protein diet has the reverse effect. However, contrary to the general trend in literature, the study of Revis and Osborne (1984) showed that the intestinal absorption of ionic Cd was increased by high dietary protein. These workers studied the relationship of dietary protein to cadmium absorption and tissue deposition in male Sprague-Dawley rats exposed to different levels of cadmium in the drinking water. In animals fed a high-protein or low-protein diet and drinking water containing 25 or 50 ppm cadmium, liver and kidney Cd and MT were both significantly higher in rats fed the high-protein diet for 2 to 4 months. These differences were explained by the concentration of cysteine observed in these two diets. When cysteine was added to the low-protein diet to the level observed in the high-protein diet and fed to rats receiving 25 ppm cadmium in the drinking water, significant dietary differences in liver and kidney cadmium and metallothionein were not observed. As observed in our studies (Asagba et al., 2004, 2006) and that of Tewari et al. (1986), the animals fed the low protein diet were more susceptible to Cd toxicity. Metallothionein concentration in the lung and liver from low-protein-fed rats was approximately half the level observed in rats fed the high-protein diet, which suggests a relationship between cadmium-induced toxicity and metallothionein concentrations. These results illustrate the importance of considering dietary protein (and possibly cysteine) when studying cadmium metabolism in experimental animals.

Minerals

It is well known that many toxic effects of Cd arise from interactions with essential elements, such as zinc (Zn). These interactions can take place at different stages of absorption, distribution in the organism and excretion of both metals and at the stage of Zn biological functions. Exposure to dietary Zn intake has an important effect on Cd absorption, accumulation and toxicity (Brzóska and Moniuszko-Jakoniuk, 2001). The Zn status of the body is important in relation to development of Cd toxicity. Numerous studies show that enhanced Zn consumption may reduce Cd absorption and accumulation and can also prevent or reduce the adverse actions of Cd, whereas Zn deficiency can intensify Cd accumulation and toxicity (Brzóska et al., 2008; Roqalska et al., 2009). Studies have shown that the nutritional status of animals or humans with regard to zinc (Zn), iron (Fe) and/or calcium (Ca) can have a profound effect on the rate of Cd absorption from the gut. If the long-term intake of one or more of these minerals is low, the nutritional status is reduced and Cd absorption increases; by contrast, if long-term intake is high, nutritional status is enhanced and Cd absorption is decreased (Reeves and Chaney, 2001; Brzóska and Moniuszko-Jakoniuk, 1998; Fox, 1988). Thus, the mineral nutrient status resulting from the mineral composition of the diet could be an important factor that controls the extent of food Cd absorption and tissue accumulation. However, this factor generally has not been taken into account when interpreting the potential risk of food Cd to humans.

A study on the effect of marginal nutritional status of Zn, Fe and Ca on the bioavailability of Cd in sunflower kernels (SFK) demonstrated a much higher rate of absorption and organ retention of Cd in rats given a marginal supply of these mineral nutrients than in those receiving an adequate supply (Reeves and Chaney, 2001). In addition, it was shown that the intrinsic, natural concentration of Zn, but not Ca and Fe, was enough to reduce the absorption and organ retention of dietary Cd supplied by the SFK. Foods such as rice, on the other hand, contain a very low intrinsic amount of Zn, Fe, or Ca (Pedersen and Eggum, 1983). Previous studies conducted to assess the risk of food chain Cd indicated that rice, because of its poor supply of Zn, Fe and Ca, could have caused populations of subsisting rice consumers to suffer a high incidence of Cd-induced renal tubular dysfunction. These individuals consumed rice raised in soils that were contaminated by a mixture of ore wastes of Cd and Zn in a ratio of 0.5 - 1:100 µg. These populations seem to be more susceptible to Cd poisoning than those who consume more nutritious diets but with similar intakes of Cd (McKenzie-Parnell et al., 1988; Tachechi, 1978). It has therefore been hypothesized that the low nutritional status of rice consumers, which results from an inadequate supply of these minerals from rice, could contribute significantly to a higher apparent susceptibility to soil Cd contamination from rice than the higher nutritional status of those who consume other grains with higher mineral content.

To test this hypothesis, Reeves and Chaney (2002) conducted a study in which rats were fed diets with adequate or marginal amounts of dietary Zn, Fe, or Ca. The basal diets contained 40% low quality, milled rice fortified with 0.62 mg of Cd/kg as $CdCl_2$ (0.25 mg of Cd/kg diet). Rats consumed the diets for 5 weeks and then were fed 1 g of a similar diet containing ^{109}Cd labeled rice. The results obtained from this study support the hypothesis that populations exposed to dietary sources of Cd and subsisting on marginal mineral intakes could be at greater risk than well-nourished populations exposed to similar amounts of dietary Cd. It was concluded that different food crops can cause unequal Cd risk at equal Cd concentration if diets containing the food are not balanced to provide adequate interacting mineral concentrations.

In another study conducted by Reeves et al. (2005), the role of certain minerals in the accumulation of duodenal Cd was determined. In the first experiment of the study wild-type and MT-null mice were fed 40% rice diets containing marginal or adequate amounts of Fe, Zn and Ca and 240 µg Cd/kg. Duodenal Cd was 10 times higher in both wild-type and MT-null mice regardless of their mineral status. In the second experiment, one group of rats was fed 40% rice diets in which Cd was incorporated into the rice during growth and maturation and another group was fed 40% rice diets in which Cd was incurporated into the rice during cooking. Each group also was fed either marginal or adequate amounts of Zn, Fe and Ca. After 5 week, rats were given a single meal labeled with ^{109}Cd and the amount of label retained after 7 d was determined by whole-body counting. Rats with marginal mineral status retained 10 times more ^{109}Cd than those with adequate status; however, there was no difference between rats fed endogenous or exogenous Cd rice. Although duodenal Cd concentration was 8 times higher in the marginally fed rats, MT concentration was unchanged. These two experiments indicate that MT induction is not involved in duodenal Cd accumulation in animals with marginal dietary status of Fe, Zn and Ca. In addition, they support the hypothesis that marginal deficiencies of Fe, Zn and Ca, commonly found in certain human populations subsisting on rice-based diets, play an important role in increasing the risk of dietary Cd exposure.

It is known that during the suckling period, gastrointestinal absorption of mineral is very high due to increased nutritional requirements during the period of rapid growth and development (Kostial, 1983; WHO, 1996). This applies not only to the essential minerals such as calcium, but also to the toxic metals such as cadmium or lead. The effect of calcium supplementation on absorption and retention of cadmium in the suckling period was evaluated in Wistar rat pups of both sexes by Sarić et al. (2002). Animals were maintained in the litters with the mother rats and supplemented with 1, 3 or 6% calcium (as $CaHPO_4.2H_2O$) in cow's milk by artificial feeding. All rats were exposed to cadmium (as $CdCl_2.H_2O$) either orally or perinatally. Results showed that after oral exposure, cadmium concentrations in all calcium-supplemented groups were significantly decreased in the organs and carcass, and that the effect was dose-related. No such effect of calcium was found after perinatal cadmium exposure. Calcium supplementation *per se* significantly increased calcium concentration in the carcass and had no effect on iron in organs and zinc in carcass. The authors concluded that calcium supplementation during the suckling period could be an efficient way of reducing oral cadmium absorption and retention without affecting tissue essential trace element concentrations.

Studies on the influence of various types of minerals on the intake and uptake of Cd in human subjects are scanty in the literature. However, Vahter et al. (1996) studied the dietary intake and uptake of cadmium (Cd) in non-smoking women (20-50 years of age) consuming a mixed diet low in shellfish or with shellfish once a week or more. The shellfish diets contained twice as much Cd as the mixed diets. The results obtained by these workers indicate a lower absorption of Cd in the shellfish group than in the mixed diet group or a difference in the kinetics. It was therefore concluded that the bioavailability and/or kinetics of dietary Cd is not only related to the type of diet but also to the body iron store.

Very few reports are available on the mechanisms by which dietary minerals influence absorption of Cd. It was shown that Cd and Fe use the same enterocyte apical membrane transporter, divalent metal transporter-1, to transport Cd into cells; thus, the two minerals compete with each other for uptake (Park et al., 2002; Bannon et al., 2003). When dietary Fe intake is low relative to Cd, enterocyte uptake of Cd would be favored. Similarly, it was suggested that Cd and Ca use the same Ca channel in the liver (Blazka and Shaikh, 1991); however, Lecoeur et al. (2002) blocked the Ca channels of an intestinal epithelial cell model, HT-29, with verapamil and no effect on Cd uptake occurred. In addition, Hoadley and Johnson (1987) concluded that the two elements did not share a common carrier in rat intestine. Conversely a recent report by Min et al. (2008) suggests that CaT1, a Ca transporter, may stimulate the intestinal absorption of Cd and this may account for the inhibition of intestinal Cd uptake by Ca. However, the findings of Toraason and Foulkes (1984) suggest that cadmium and calcium do not interact specifically at a 1,25 $(OH)_2$ D_3-dependent transport site. Excess dietary Zn was also shown to reduce Cd absorption (Hoadley and Cousins, 1985; Jacobs et al., 1978); perhaps these two minerals also act through specific and common transporters.

Vitamins

Dietary vitamins can also markedly influence the absorption

of Cd from the gastrointestinal tract. The effect of dietary vitamin C supplement on cadmium absorption and distribution was evaluated in an animal model by Grosicki (2004). The results obtained indicate that the vitamin C supplement decreased the carcass Cd burden and the Cd content in the liver, kidneys, testicles and muscles; the highest decreases were found in the testicles and the lowest ones in the muscles. In addition, the rats supplemented with vitamin C revealed an improved body weight gain during the experimental period. Similarly Sauer et al. (1997) observed a significant attenuation of cadmium-induced tissue injury in retinol-pretreated rats, possibly because of a 7-fold increase in MT production in the liver and less cadmium accumulation in the lung, kidney and testis.

Another study by Prasad et al. (1982) indicates that vitamin B_6 and B_1 deficiencies in rats resulted in a non-specific increase in Cd ions. The authors concluded that altered metal uptake rates were probably not a result of hormonal disturbances due to vitamin deficient state.

SUMMARY

The mechanism of Cd absorption consists of non specific binding to anionic sites on the membrane, followed by a rate-limiting internalization which is temperature dependent. Completion of the absorption process is by transport across the basolateral membrane into serosal fluid. The degree of absorption of Cd is largely dependent on factors such as pH and MT production, amongst others. The chemical form of Cd is an important factor on its gastrointestinal absorption. It has been reported that Cd in foods such as meat, sea foods and vegetables exists mainly as Cd-MT or MT-like Cd binding proteins. There is conflicting information on the availability Cd in Cd-MT for intestinal uptake in relation to that of ionic Cd added to diet or drinking water.

Available information from animal and human studies indicates that diet type or composition may influence the absorption of Cd from the intestine irrespective of the chemical form involved. Diets low in proteins, minerals and certain vitamins have been reported to increase Cd absorption and toxicity. Conversely, diets rich in fibers have the reverse effect. The lack of conclusive information on the availability of Cd in Cd-MT for intestinal uptake in relation to that of ionic Cd is noticeable, and therefore there is a great need for further studies in this area. Also, since humans are usually exposed to Cd-MT in foods and rarely to inorganic Cd, the toxicity of food-incorporated Cd deserves further investigation, in view of the observed difference in tissue accumulation from these forms of Cd.

Abbreviations

Cd, cadmium; **MT,** metallothionein; **Cd-MT,** cadmium-metallothionein; **DMT1,** divalent metal transporter 1; **ESRI,** everted sac of rat intestine; **NLD,** Nigerian-like diet; **UCd,** urine cadmium; **BCd,** blood cadmium.

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