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Study of the influence of the ph of water in the initiation of digestive tract injury in cadmium poisoning in rats

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ABSTRACT

Cancer has genetic and environmental causes, one of which is the ingestion of heavy metals such as cadmium.

Objective: To evaluate the lesions caused by cadmium poisoning in the digestive tract and the possible effect of the drinking water pH in the initiation of these lesions.

Methods: 90 male Wistar rats were used, divided into six groups ($n = 15$): A – received 400 mg/l cadmium chloride (CdCl2) in drinking water at a neutral pH of 7.0; B – received CdCl2 (400 mg/l) in drinking water at an acidic pH of 5.0; C – received CdCl2 (400 mg/l) in drinking water at a basic pH of 8.0; D – received water at an acidic pH of 5.0; E – received water at a basic pH of 8.0; and F – received water at a neutral pH of 7.0. Animals were euthanized after 6 months. Samples of the esophagus, stomach, small intestine and large intestine of each rat were removed for microscopic analysis.

Results: There were no microscopic changes in either the esophagus or small and large intestines. Only cadmium-exposed animals showed mild dysplasia of the gastric mucosa ($p = 0.012$), regardless of the pH ($p > 0.05$).

Conclusion: Cadmium exposure led to the formation of dysplastic lesions in the gastric glandular epithelium, regardless of the water pH.

1. Introduction

In most developed countries, cancer is responsible for an important proportion of the national health expenditure [15]. Although the incidence rates have been decreasing for many types of cancer due to changes in the prevalence of risk factors and prevention efforts, the absolute number of patients with newly diagnosed cancer is expected to increase because of population growth and aging [27,17]. Cancer has genetic and environmental causes, one of which is heavy metal intake [14].

Cadmium (Cd) is a heavy metal that is carcinogenic to humans [11,26]. It has been widely discarded into the environment as a result of industrial waste and agriculture [1]. People are mainly exposed to cadmium by smoking or through the intake of contaminated grain, some vegetables, and seafood [29,24]. Diet is the main source of cadmium exposure among nonsmokers [14]. Drinking water contributes only a very small percentage to the total consumption of cadmium per person [23].

Based on the estimates for cadmium intake, more than 80% of cadmium comes from foods like vegetables and cereal [23]. The average amount of cadmium ingested from foods generally ranges between 8 and 25 μg/day [14]. Nevertheless, few studies have evaluated the direct impact of heavy metals in the mucosa of the digestive tract [4].

The gastrointestinal tract is one of the main targets of cadmium [22]. There is evidence of the resilience of gut in balancing the various chronic effects of cadmium and lead in the intestinal mucosa [4]. Moreover, the intestinal microbiota plays an essential role in limiting the body's burden of heavy metals [3].

Studies have shown that the microenvironment of tumors is usually more acidic than in normal tissues [30,2,25]. The study by [21] reported an increased incidence of preneoplastic lesions in the prostates of animals exposed to high concentrations of cadmium that were administered in the drinking water at acidic pH.

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No previous studies have evaluated the effect of the pH of drinking water in cadmium toxicity in the digestive tract. The objective of this study was to evaluate the lesions caused by cadmium poisoning in the digestive tract and the possible effect of the drinking water pH in the initiation of these lesions.

2. Materials and methods

2.1. Ethical approval

This study was approved by the Ethics Committee on Animal Use at the Universidade do Oeste Paulista (CEUA – UNOESTE) (Protocol 2202).

2.2. Animal Protocol

In our study, we evaluated 90 male adult Wistar rats (*Rattus Norvegicus Albinus*), weighing 200–250 g. The rats were divided into groups of four and placed in large rectangular boxes (measuring 49 × 34 × 16 cm) that could accommodate up to five adult rats. The animals were maintained under a controlled temperature of 25 ± 2 °C, relative humidity of 50 ± 15% and a normal photoperiod (12–12 h light-dark cycles).

The cadmium source was cadmium chloride ($CdCl_2$ – Sigma Chemical Company, St. Louis, MO, USA) with a hydration of at least 98% and water content of approximately 2.5 mol / mol. For 6 months, the animals were treated with $CdCl_2$ in their drinking water on a daily basis at a concentration of 400 mg/L (adapted from [20]. The pH of the water was adjusted using hydrochloric acid or sodium hydroxide. The drinking water was changed three times a week to maintain the pH. Any wastewater containing cadmium was sent to the central reservoir of the Universidade of Oeste do Paulista (UNOESTE) and neutralized for disposal. The amount of water remaining in the rat troughs was measured every time the solution was changed to estimate the average intake for each animal. Additionally, the pH of the remaining water was measured to ensure that the pH remained the same.

The animals were divided into the following six groups: group A – 15 rats that received cadmium chloride in their drinking water at a neutral pH 7.0; group B – 15 rats that received cadmium chloride in their drinking water at an acidic pH 5.0; group C – 15 rats that received cadmium chloride in their drinking water at a basic pH 8.0; group D – 15 rats that received drinking water at an acidic pH 5.0; group E – 15 rats that received drinking water at a basic pH 8.0; and group F – 15 rats that received drinking water at a neutral pH 7.0. Animals from all groups received water and food *ad libitum*.

The animals in all groups were euthanized 6 months after the beginning of the experiment. Euthanasia was performed by intraperitoneal injection of thiopental (Syntec, USA) at a dose of 100 mg/kg. Necropsy was performed and samples of the esophagus (proximal, medium and distal), stomach, small intestine and large intestine from each rat were removed for microscopic analysis.

2.3. Histopathological analysis

The tissue samples were fixed in 10% formalin (Chemical Kinetics, São Paulo, Brazil) for 24 h, processed with standard histological procedures, and paraffin embedded (Dynamic Analytical Reagents, São Paulo, Brazil). Sections with a 5 μm thickness were obtained and stained with hematoxylin-eosin (HE) (Dolles, São Paulo, Brazil).

Histopathologic analysis was blinded and performed by a single experienced observer (GAN) using a conventional optical microscope (NIKON Labophot, Japan). The following parameters were evaluated with the respective scoring scheme: interstitial inflammatory infiltrate (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) and inflammatory cell-type present (polymorphonuclear and/or monuclear); tissue congestion (0 = absent, 1 = mild, 2 = moderate, and 3 = severe); non-neoplastic changes in the mucosa (atrophy, necrosis, and hyperplasia); dysplastic lesions (0 = absent, 1 = mild dysplasia, 2 = moderate dysplasia, and 3 = severe dysplasia) and benign and malignant neoplastic lesions (0 = absent and 1 = present). The lymphoid hyperplasia (0 = absent and 1 = present) was evaluated in the small and large intestines. Measurements of the thickness of the esophageal mucosa were performed for two areas from each fragment, using an image analysis system Leica Application Suite 4.2.0 LAS (Microssistems Leica, Switzerland) (Fig. 1).

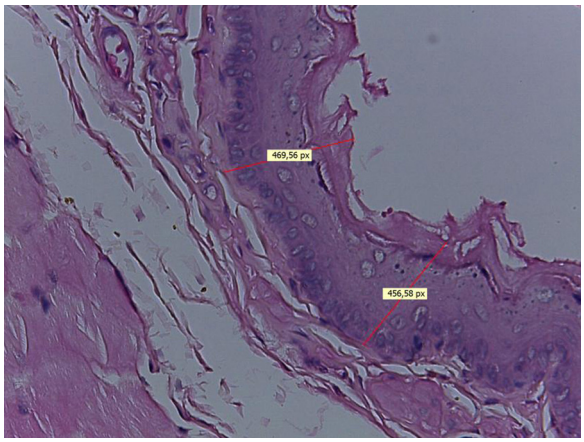

Fig. 1. Esophageal mucosa microscopy showing the standard for measuring the thickness of the epithelium (animal from Group A; hematoxylin-eosin, 200× magnification). px: pixel.

2.4. Statistical analysis

To evaluate the variable thickness of the esophageal epithelium, we used the nonparametric Kruskal–Wallis, followed by multiple comparison of the posts by Dunn's test.

For other parameters, the likelihood ratio (LR) test and Fisher's exact test were used to compare the groups. Statistical tests were performed at a significance level of 5%.

3. Results

3.1. Mortality

Five animals died during the course of our study (one rat each from groups A, C, and D and two rats from group E). The cause of death for the animals in groups A and C was acute pulmonary edema, a complication that is associated with cadmium exposure [14]. It was not possible to establish the cause of death for the rats from groups D and E.

3.2. Water intake

The average water intake per animal per day was 55 ml for group A (approximately 22 mg of cadmium), 57 ml for group B (approximately 22.8 mg of cadmium), 52 ml for group C (approximately 20.8 mg of cadmium), 60 ml for group D, 70 ml for group E and 73 ml for group F. There was no significant difference between the groups with respect to the cadmium and water intake ($p > 0.05$).

3.3. Histopathological analysis of the esophagus

There were no signs of interstitial inflammatory infiltration, tissue congestion, non-neoplastic changes in the mucosa (atrophy,

Table 1
Median thickness of the esophageal mucosa in each group ($n = 85$).

Groups*	Thickness of the esophageal mucosa (px#)
A	459.96[a]
B	493.44[a]
C	476.38[a]
D	445.56[a]
E	438.34[a]
F	453.65[a]

*Group A: cadmium in water at pH 7.0; Group B: cadmium in water at pH 5.0; Group C: cadmium in water at pH 8.0; Group D: water at pH 5.0 only; Group E: water with pH 8.0 only; Group F: water with pH 7.0 only.
#px: pixel. Lowercase letters indicate groups that were compared at the same time. Different lowercase letters: $p < 0.05$.

Table 2
Mild dysplasia frequency in the gastric mucosa of animals in the study groups ($n = 85$).

Groups*	Mild dysplasia
A	1/14 (7,1%)[a]
B	2/15 (13,3%)[a]
C	4/14 (28,6%)[a]
D	0/14 (0%)[b]
E	0/13 (0%)[b]
F	0/15 (0%)[b]

*Group A: cadmium in water at pH 7.0; Group B: cadmium in water at pH 5.0; Group C: cadmium in water at pH 8.0; Group D: water at pH 5.0 only; Group E: water with pH 8.0 only; Group F: water with pH 7.0 only. Lowercase letters compare groups at the same time. Different lowercase letters indicate $p < 0.05$.

necrosis, and hyperplasia), dysplastic lesions or benign or malignant neoplastic lesions in any of the esophageal segments in any of the evaluated groups.

Histomorphometric analysis of the thickness of the esophageal mucosa was not significantly different between the groups ($p > 0.05$) (Table 1).

3.4. Histopathological analysis of the stomach

There were no signs of tissue congestion, non-neoplastic changes in the mucosa (atrophy, necrosis, and hyperplasia) or benign or malignant neoplastic lesions in the stomach in the groups evaluated.

Mild interstitial inflammatory infiltrate in the gastric mucosa was observed in one group B animal, two group E animals and three group F animals ($p > 0.05$).

Only animals that were exposed to cadmium showed mild dysplasia of the gastric mucosa ($p = 0.012$) (Fig. 2), but there was no significant effect of the water pH ($p > 0.05$) (Table 2).

3.5. Histopathological analysis of the small intestine

There were no signs of interstitial inflammatory infiltration, tissue congestion, non-neoplastic changes in the mucosa (atrophy, necrosis, and hyperplasia), dysplastic lesions or benign or malignant neoplastic lesions in the small intestine in the evaluated groups.

Although there was a lower incidence of lymphoid hyperplasia in the small intestine of group C, there was no statistically significant difference between the study groups for this parameter ($p > 0.05$) (Fig. 3A and 3B and Table 3).

3.6. Histopathological analysis of the large intestine

There were no signs of interstitial inflammatory infiltration, tissue congestion, non-neoplastic changes in the mucosa (atrophy, necrosis, and hyperplasia), dysplastic lesions or benign or malignant neoplastic lesions in the large intestine in the assessed groups.

Table 3
Frequency of lymphoid hyperplasia in the small and large intestine of the animals in the study groups (n = 85).

Groups*	Lymphoid hyperplasia	
	Small intestine	Large intestine
A	7/14 (50%)[a]	1/14 (7,1%)[a]
B	7/15 (46,6%)[a]	2/15 (13,3%)[a]
C	4/14 (28,6%)[a]	2/14 (14,3%)[a]
D	10/14 (71,4%)[a]	2/14 (14,3%)[a]
E	9/13 (69,2%)[a]	2/13 (15,4%)[a]
F	5/15 (33,3%)[a]	3/15 (20%)[a]

*Group A: cadmium in water at pH 7.0; Group B: cadmium in water at pH 5.0; Group C: cadmium in water at pH 8.0; Group D: water at pH 5.0 only; Group E: water with pH 8.0 only; Group F: water with pH 7.0 only. Lowercase letters compare the groups at the same time in the same column. Different lowercase letters indicate $p < 0.05$.

There was a slightly lower incidence of lymphoid hyperplasia in the large intestine of the group A animals, but there was no significant difference between the study groups for this parameter ($p > 0.05$) (Fig. 3C and D and Table 3).

4. Discussion

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization (FAO) and World Health Organization (WHO) established that the provisional tolerable weekly intake (PTWI) of cadmium is 7 μg/kg of body weight [5,6]. Only approximately 5% of the cadmium dose is absorbed from the gastrointestinal tract, while the pulmonary absorption is approximately 90% of the dose inhaled into the lungs [10]. Although the absorption from the gastrointestinal tract is lower, exposure to cadmium can occur from eating food (e.g., shellfish, organic meats, leafy vegetables, and rice from certain areas of Japan and China), water (closed water pipes or industrial pollution) or contamination of drugs, and it may affect long-term health [1]. In spite of this, there are fewer studies on ingested cadmium than on inhaled cadmium.

One of the main factors affecting the availability of heavy metals for plants is the soil pH, which is generally inversely related to the availability of these elements [7]. In this study, the use of pH, at different concentrations of cadmium, was evaluated in animals to determine whether the pH could affect the toxic effect of cadmium on the digestive tract, which could be an alternative to prevent or minimize the cadmium toxicity.

The study by [19], which also evaluated the influence of the pH on cadmium poisoning, albeit in the oral mucosa and salivary glands, reported no changes in buccal mucosa and tongue mucosa, despite direct contact, or salivary glands, even with exposure to high concentrations of cadmium in drinking water, regardless of the water pH. The same was observed for the esophageal mucosa in this study. Therefore, the squamous epithelium is likely resistant to the direct effect of cadmium.

Gastric cancer is one of the leading causes of cancer mortality, which is second only to lung cancer IARC, 2003. Generally, stomach cancer has environmental and behavioral factors that serve as predisposing characteristics of their incidence [32]. In the present study, cadmium led to the formation of dysplastic lesions in the gastric mucosa, showing that the ingestion of cadmium is a predisposing factor for gastric cancer. In addition, unlike the esophageal epithelium, which is a squamous epithelium, the gastric epithelium is glandular tissue that was injured perhaps by direct cadmium contact. The study by [21] reported the formation of glandular preneoplastic lesions in the prostate of animals exposed to high

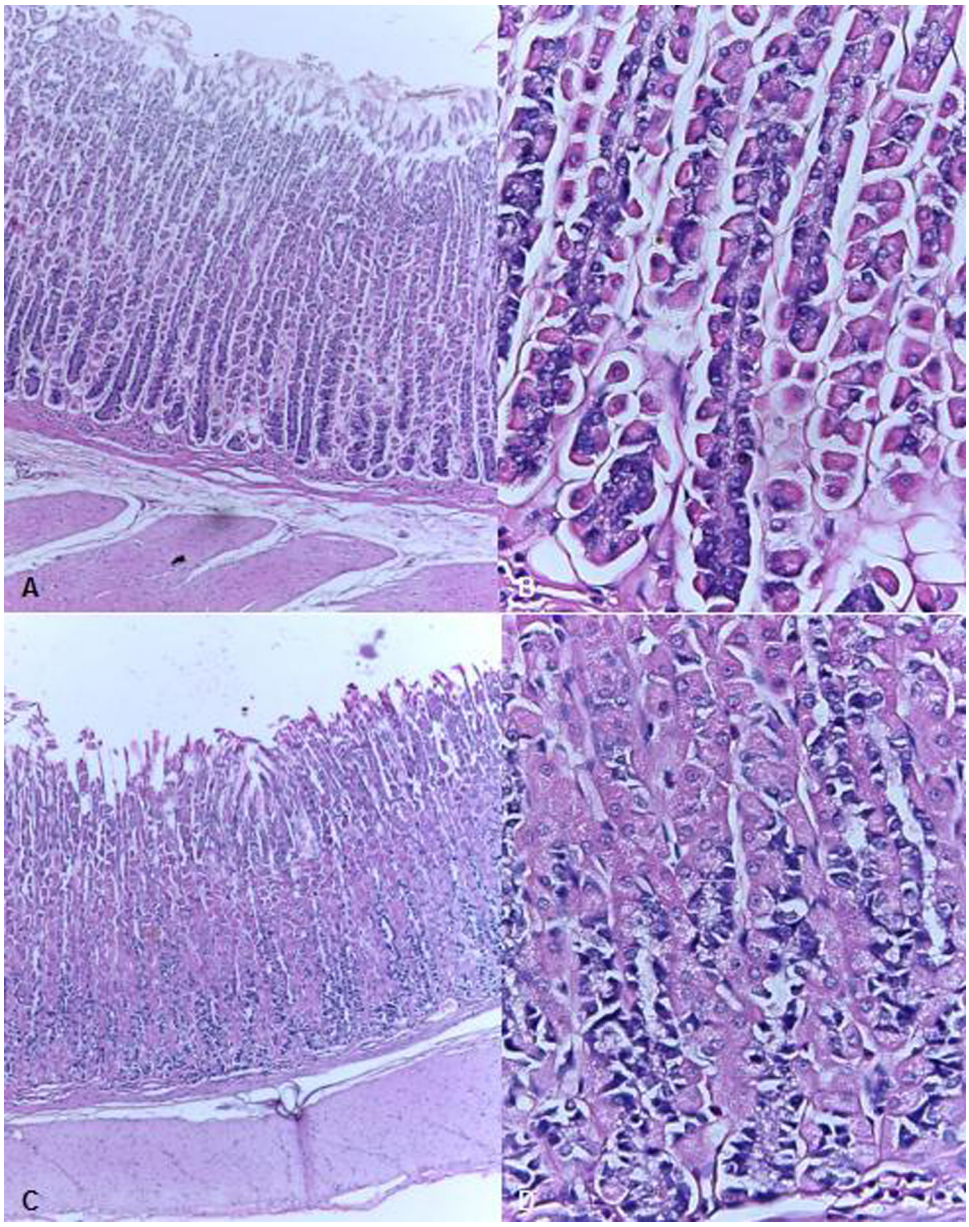

Fig. 2. Light microscopy of the stomach. A and B – Normal mucosa (animal from group B). C and D – Mucosa with mild dysplasia. Note the architectural remodeling and hyperchromatic nuclei (animal from group A). (Hematoxylin-eosin, 100× magnification in A and C and 400× magnification in B and D.)

concentrations of cadmium in drinking water, confirming that the glandular epithelium is more susceptible to the toxic effect of cadmium. However, the study by [21] reported an increased incidence of precancerous lesions in the prostate when the animals were exposed to cadmium, in acid pH; however, in this study, the pH did not influence the incidence of these lesions in the stomach. The pH likely influences cadmium absorption, which in turn influences its access to the prostatic epithelium, but the gastric epithelium seems to be affected by direct contact.

It is noteworthy that one of the main factors affecting the toxicity of cadmium is the exposure time [14]. In this study, the exposure to cadmium for six months (chronic exposure) may have also contributed substantially to the appearance of gastric lesions.

The pH is a relevant factor in both gastric and intestinal phases of digestion and should be taken into consideration when analyzing the results from *in vitro* digestions [34].

In the circulation, cadmium is mainly bound to metallothioneins (MT) [33]. In chronic intoxication, cadmium stimulates de novo synthesis of metallothioneins. Toxicity in the cells starts when loading with cadmium ions exceeds the buffering capacity of intracellular metallothioneins [28]. In the *in vitro* study by [16], above pH 3.5 nearly all cadmium remained bound to the metallothionein and Cd-MT was resistant towards proteolysis. At pH values of 2.5 and 1.7 the protein was digested to 80% and 100%, respectively. Cadmium is poorly absorbed in the stomach [14], but considering that the pH of the stomach varies between 1.5 and 2.0, it is possible that also *in vivo* Cd-MT proteolysis maybe occurs and can affect cadmium absorption by intestine [16].

Cadmium is absorbed by enterocytes, mainly in the duodenum and proximal jejunum [28]. Some essential metal transport proteins such as divalent metal transporter 1 (DMT1) transport cadmium in the intestine [18,28,33]. DMT1 appears to be a key transporter involved in cadmium toxicity. Free cadmium may be

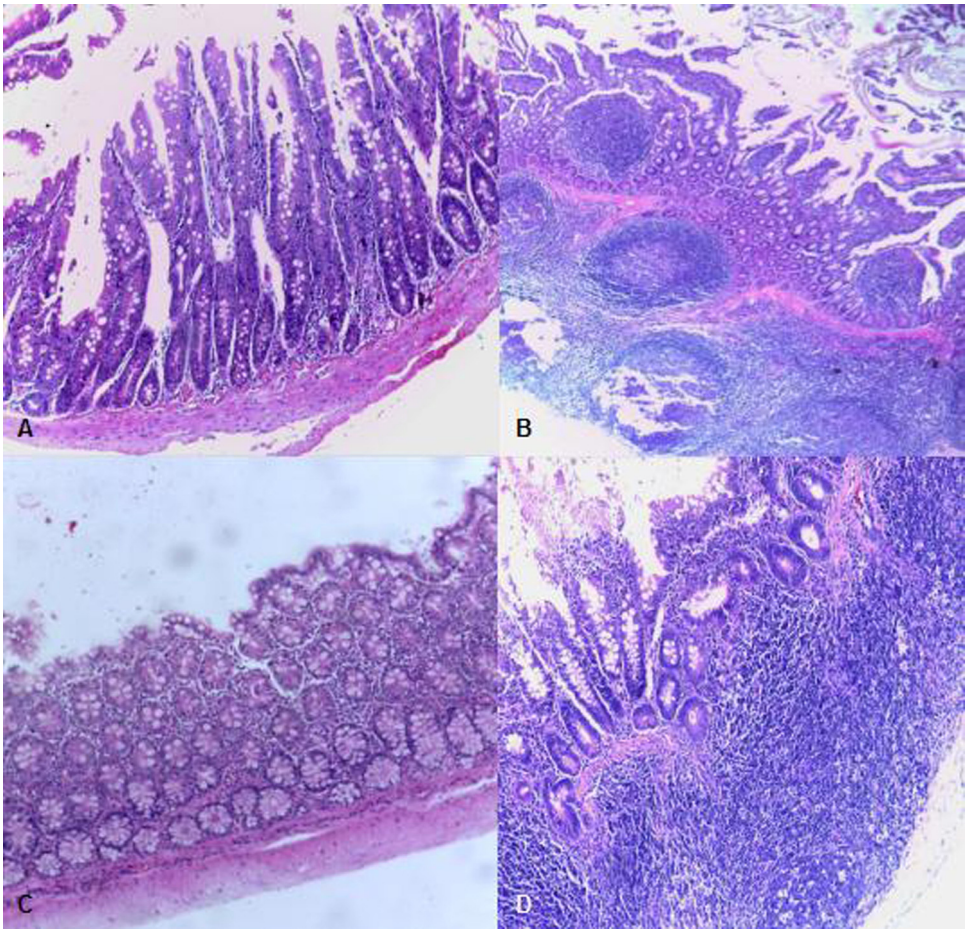

Fig. 3. Light microscopy of the intestine. A – Normal small intestine mucosa (animal from group C – hematoxylin-eosin, 100× magnification). B – Mucosa of the small intestine with lymphoid hyperplasia (animal from group B – hematoxylin-eosin, 40× magnification). C – Normal mucosa of the large intestine (animal from group F – hematoxylin-eosin, 100× magnification). D – Mucosa of large intestine with lymphoid hyperplasia (animal from group D – hematoxylin-eosin, 40× magnification).

taken up from the gut lumen into enterocytes via DMT1-mediated transport [31].

The zinc/bicarbonate sympoters (cotransporters) ZIP8 and 14, expressed at the apical membrane of enterocytes also can transport cadmium into cells [31,33]. Transient receptor potential cation channel subfamily V (TRPV) 5 and 6, that are major transporters for calcium in intestine and kidney, may be involved in cadmium transport in these tissues [33]. A possible role of metallothioneins in cadmium absorption at the enterocyte luminal domain is unclear [28].

DMT1/SLC11A2 transporter is a Cd^{2+}/H^{-} cotransporter [8]. ZIP8/SLC39A8 transporter has also been demonstrated to be a Cd^{2+}/HCO^{3-} symporter (cotransporter) [18], as well as ZIP14/SLC39A8 [9]. ZIP8 [18] and ZIP14 [9]-mediated Cd^{2+} uptake is dependent on extracellular HCO^{3-} levels. Perhaps the acidic or basic pH in which cadmium is carried may interfere with the absorption due to the fact that cadmium transporters also are cotransporters of H^{-} and HCO^{3-} ions. Also, the *in vitro* study by [34] found that there is an increased binding of cadmium at pH values above 3 during the intestinal phase of digestion, when they investigate the effect of pH on the adsorption of this metal to lettuce.

Although, the study by [22] reported that cadmium consumption resulted in tissue damage and intestinal inflammation, in our study, the intestine, both small and large, was not altered by cadmium exposure even though it has a glandular pattern of mucosa like the stomach. Our data corroborate the findings of other studies about the resilience of the intestine to heavy metals [4]. It is likely that in addition to limiting the body's burden of heavy metals [3], the intestinal microbiota can protect the intestinal mucosa against heavy metals. The pH of the water did not contribute to the toxicity of cadmium on the intestine, despite of the possibility of influence of this on cadmium transporters in the enterocytes, but this can justify dependent pH changes in prostate observed in the study of [21].

5. Conclusion

Chronic exposure to cadmium in drinking water led to the formation of dysplastic lesions in the gastric glandular epithelium, but not in esophageal and intestinal epithelia. However, the pH of the water seems to have no influence on the digestive tract lesions.

Conflict of interest

The authors declare that they have no conflicts of interest.

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