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IMPACT OF HEAVY METAL EXPOSURE ON KIDNEY CANCER PROGRESSION

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ABSTRACT

Exposure to heavy metals, even at relatively low concentrations, poses a significant risk to human health due to the physiological inability to metabolize and excrete these elements efficiently. Among the diseases associated with this exposure, kidney cancer stands out for its aggressiveness and the difficulty of early detection. The main heavy metals linked to carcinogenesis are cadmium, arsenic, lead, and mercury, which tend to accumulate in tissues, causing oxidative stress, mitochondrial dysfunction, and DNA damage, creating an environment conducive to carcinogenesis. Pathological mechanisms, such as interference in the expression of the tumor suppressor gene p53 and activation of hypoxia-induced factor (HIF-1), favor tumor progression, especially in clear cell carcinoma, a subtype with a strong correlation with metal toxicity. Chronic exposure to these elements compromises

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essential cellular functions and is associated with non-specific signs such as proteinuria and high blood pressure, making clinical diagnosis difficult. From a diagnostic point of view, techniques such as urinalysis after administration of chelating agents and detailed laboratory tests, combined with imaging methods, are essential for the early detection of heavy metal poisoning and its complications. In cases where renal carcinogenesis is advanced, renal biopsy reveals characteristic alterations such as tumor necrosis and fibrosis. The research used bibliographic methodology, reviewing the literature of the last five years in databases such as PUBMED and Google Scholar. Occupational exposure in sectors such as the battery industry and mining raises important legal questions about corporate liability and worker protection. Strict surveillance and control policies are essential to prevent contamination and reduce the incidence of neoplasms associated with chronic exposure to heavy metals.

Key words: Occupational Exposure. Renal toxicity. Chelating agents. Carcinogenesis and Clear Cell Neoplasia.

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INTRODUCTION

Relatively low concentrations, due to the physiological weakness of the body to effectively metabolize and excrete this type of material, which progressively accumulate in tissues and cause significant physiological and pathophysiological dysfunctions and disorders in humans. Acts 1, 2.

Its pathological capacity has been widely recognized as an important risk factor in various diseases, such as hypertension, proteinuria and abdominal cramps, among which kidney cancer stands out as a particularly worrying condition, not only because of the aggressiveness of this form of cancer, but also because of the difficulty of its early detection 1, Acts 2, 3.

According to the report of the European Association of Urology in 2020, renal cell carcinoma represents approximately 2% of all cases of carcinomas reported worldwide, with a prevalence of 1,793 cases per 100,000 European inhabitants, occupying the seventeenth position of lethal cases due to malignancies in general [4].

Exposure to heavy metals are triggers of carcinogenesis, although there are no studies to date that quantify this interaction [5]. Heavy metals such as cadmium, mercury and arsenic tend to accumulate chronically in tissues due to the body's physiological inefficiency in eliminating them and the natural biological resistance of these materials, triggering toxicological processes that compromise normal cellular functions [1, 2].

Exposure to these metals compromises fundamental biological processes, favoring both pathogenesis and the appearance of mutations[2]. One of the most relevant pathophysiological mechanisms is oxidative stress, which results in imbalance between antioxidant systems and free radicals [5, 6]. In addition, these metals compete with ions essential for critical cellular functions, such as DNA repair and cell signaling, creating an environment conducive to carcinogenesis6.

For example, exposure to cadmium interferes with the cellular expression of the tumor suppressor gene p53, which is essential for cell cycle control and prevention of tumor cell formation [1, 7]. Another mechanism affected is cell signaling, such as hypoxia-induced factor (HIF-1), which promotes local angiogenesis, favoring the progression and invasion of renal neoplasms, especially the clear cell subtype, which has the highest correlation with metal toxicity [1, 8].

Clinically, exposure to heavy metals presents signs and symptoms that vary depending on the metal involved in the poisoning [8]. For example, arsenic tends to cause

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respiratory symptoms due to its frequent exposure to aerosols and gaseous form, while mercury usually exhibits digestive symptoms due to its form of contamination, which is normally found in water and soil [9, 10].

However, with the advance of chronicity, exposure to different metals such as arsenic, mercurium, cadmium and lead tend to present non-specific and generic signs, in case of acute poisoning or exposure to small amounts over a short period of time, such as proteinuria and arterial hypertension, which can make clinical diagnosis difficult without detailed knowledge of the patient's occupational environment [9, 10].

The evolution of intoxication promotes underlying renal dysfunction due to the high filtering capacity of the kidneys, which exposes them to greater contact with metals, intensifying oxidative stress [7]. Frequently, this dysfunction progresses to an asymptomatic and prolonged phase of cancer [1, 8]. However, as the neoplasm progresses, pronounced symptoms emerge, such as hematuria, low back pain, and palpable abdominal mass, indicating tumor progression [11].

The diagnosis of chronic heavy metal poisoning combines a detailed analysis of the patient's work history and specific laboratory tests [2, 8], such as urinalysis 24 hours after administration of chelating agents, substances responsible for binding to the binding sites of metal particles and forming stable, water-soluble complexes with metals [2].

Together with blood tests, which help detect the presence and load of heavy metals contained in the systemic circulation, although it is not the determining diagnosis in chronic poisoning and is commonly used in cases of acute poisoning, it is supported by auxiliary imaging techniques such as tumography and X-rays, which look for any mass, deformity or gross alteration in the kidneys [12, 13].

Biopsy of renal tissue can also be used, although it is used in cases where renal poisoning has progressed to carcinogenesis, presenting specific histological alterations, such as tumor necrosis and peritumoral fibrosis [6, 8]. In addition, this procedure allows the degree of cell differentiation and the extent of tumor invasion to be assessed, providing key information for therapeutic planning and prognosis [6].

Therapeutic intervention is carried out by chelating drugs, a fundamental approach to mitigate and prevent the toxicological effects of heavy metals [2]. These compounds have the ability to bind to metal ions, forming stable complexes that inhibit the binding of heavy metals to cell surfaces, increasing their water solubility and facilitating their description by

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the renal urinary route. This significantly reduces the toxicity of metals and promotes their effective elimination from the body [12].

Antagonists such as dimercaprol and drugs derived from it are widely used in the treatment of arsenic, mercury and cadmium poisoning, playing a crucial role in reversing toxicity [1, 12]. However, the use of dimercaprol is usually accompanied by notable adverse effects, such as nausea, vomiting, headache, burning sensation in the lips, throat and mouth, as well as a generalized feeling of constriction [12].

Occupational exposure to heavy metals occurs mainly in industrial sectors, such as battery factories and mines, which raises important legal questions, especially when recurrent renal neoplasms are identified among workers [14, 15]. These cases lead to investigations and expert reports to identify possible failures in safety control, in addition to quantifying the clinical damage caused to those affected [15].

Proof of death by autopsy can be challenging, as the disease does not present obvious physical features due to intracellular accumulation [15]. Tests are usually performed when there is a suspicion or request, but in cases of death from complications of kidney cancer, a complete autopsy is usually not considered necessary, as the cause of death is confirmed as renal carcinoma [14, 15].

Another obstacle to quantifying this damage is that the population at risk, such as industrial workers, usually does not have sufficient economic resources to pay for clinical studies aimed at early diagnosis, treating only the symptoms [15]. Concern increases in the case of miners and prospectors, as they often lack formal documentation from a legal point of view, which makes their work careless and illegal [14,15].

Reducing occupational and environmental exposure to heavy metals is a major public health challenge [14]. Rigorous health surveillance policies are essential to reduce the incidence of neoplasms related to these metals, together with regular monitoring of renal function, especially in the population at risk such as workers exposed to metals and the population living near industries, is essential to prevent renal carcinoma and ensure the health of these professionals [14, Question 15].

The objective of this research is to critically evaluate the influence of chronic exposure to heavy metals on the progression of carcinogenesis, exploring the pathophysiological mechanisms involved, the anatomopathological alterations presented and the pharmacological, semiological and legal behaviors involved in the subject.

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MATERIALS AND METHODS

The bibliographic method was used to collect data from scientific medical sources in Portuguese, Spanish and English, on the following platforms: Scielo, Google Scholar and PUBMED in the last five years, searching for keywords such as (Occupational exposure), (Renal toxicity), (Chelating agents), (Carcinogenesis) and (Clear cell neoplasia).

The study includes a table detailing the clinical manifestations of the main heavy metals related to human poisoning, including arsenic, lead, mercury and cadmium, in addition to presenting the main means of poisoning and the anatomical area of kidney involvement, also exposing their relationship with renal carcinogenesis.

To support this information, reference books on the subject were consulted, such as Porth CM. Pathophysiology. 9th ed. Rio de Janeiro: Guanabara Koogan; 2014, "Pathological Basis of Diseases" by Robbins & Cotran Pathology (9th edition; Rio de Janeiro: Elsevier; 2016), and Harrison's Internal Medicine (19th ed. Porto Alegre: AMGH Editora; 2017). As well as relevant articles available on the websites of global kidney cancer support organizations such as the International Kidney Cancer Coalition (IKCC) and institutional ones such as the report "Heavy Metals, Cancer and Environmental Risks" of the National Cancer Institute; 2023.

THEORETICAL FRAMEWORK

Heavy metal poisoning is of extreme concern in humans, mainly due to the physiological weakness of the body to metabolize and excrete substances effectively [1, 2]. These accumulate chronically in tissues, triggering toxic processes that result in major cellular dysfunctions [1].

Oxidative stress plays a significant role in the progression of heavy metal poisoning to kidney cancer[7]. This mechanism creates an oxidative environment that results in an imbalance between antioxidant systems and free radicals, compromising cellular integrity [5, 6].

Chronic exposure to heavy metals such as lead, cadmium, mercury and arsenic interferes with the expression of the tumor suppressor gene p53, which is essential for cell cycle control and tumor cell prevention, resulting in a progressive increase in abnormal cells, favoring carcinogenesis [1].

In addition, cell signaling is impaired by the increased metabolic demand of cancer cells and by the hypoxic environment resulting from reactive oxygen species, which

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promotes the formation of hypoxia-induced factor, which induces local angiogenesis, facilitating the spread of cancer cells and harmful agents [5, 6].

In chronic cases, where signs and symptoms are nonspecific and general, such as the presence of proteinuria and hypertension, the key to diagnosis is urine analysis 24 hours after administration of chelating drugs, together with blood tests for the detection of circulating metals, combined with auxiliary imaging techniques that check for any macroscopic abnormalities in region [9, Acts 10, 12].

In cases where poisoning has already progressed to renal carcinogenesis, biopsy may be used, especially to detect the most common form of carcinoma associated with exposure to heavy metals: clear cell neoplasia [6, 8]. Robbins & Cotran, in "Pathological Basis of Diseases", describe the pathological alterations in the kidneys, with enlarged cells and cytoplasm rich in glycogen and lipids, resulting in a whitish coloration under hematoxylin and eosin[6].

Treatment with chelating agent drugs is based on their ability to form stable binding complexes with heavy metals, neutralizing their toxicological effects and facilitating their excretion from the body via the urinary tract [1, 2]. These compounds are responsible for competing for cell binding sites with heavy metal ions, preventing metals from binding to vital cellular components such as enzymes and proteins, preserving and ensuring normal cellular function [12].

The chelation process involves the formation of a heterocyclic ring between the metal and the ligands of the chelating agent, which stabilizes the complex and allows its excretion, mainly by the renal route [12]. An ideal chelating agent should be highly soluble, facilitating its elimination, resistant to metabolic degradation and have the ability to penetrate the storage sites of heavy metals in tissues, promoting their effective elimination [2, 12].

Among the chelating agents, dimercaprole derivatives stand out for their effectiveness in the treatment of arsenic, mercury and cadmium poisoning. This drug, administered intramuscularly, acts by antagonizing the biological actions of metals that form mercaptides with essential sulfhydryl groups, neutralizing their toxic effects. Its absorption is rapid, with maximum concentrations reached between 30 and 60 minutes, and its short half-life allows complete elimination in about four hours, making it effective in removing heavy metals from the body [12].

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In 2021, the State University of Western Paraná conducted a population-based study between 2005 and 2017 entitled "Mercury and lead poisoning with the highest prevalence in children and workers in Paraná", where the result of prevalence of affectation was presented, exposing the prevalence in ages from 20 to 59 years, mainly due to exposure in their work environment such as electrochemical industries, laboratory and electromechanical tests, due to the lack of correct handling of safety equipment, which can influence renal carcinogenesis [16].

Another study conducted in 2022, researchers from Fiocruz Minas Gerais and the Federal University of Rio de Janeiro (UFRJ) carried out a longitudinal study, which began in 2021 and continues to the present, addressing the living, working, and health conditions of the victims affected by the Brumadinho dam collapse disaster in Minas Gerais. entitled "Brumadinho Health Project", which aims to demonstrate that the consequences continue to this day, despite the fact that the catastrophe occurred five years ago. [Question 17].

The study involved 2,805 adults over 18 years of age affected by heavy metal poisoning, suitable for working age. The studies were found to be comparative with the researchers' suspicions, finding high proportions of increased levels of total arsenic in urine (33.7%) and manganese in blood (37%), highlighting the environmental risk beyond the workplace. [Question 17].

As discussed in previous reports, exposure to heavy metals in the environment, and especially in the industrial environment, which comes into contact with metals more easily, raises health and legal issues, especially the occurrence of carcinogenesis in the population at risk. This leads to investigations into potential failures in security controls and their impacts.

RESULTS AND DISCUSSION

Meticulous research on renal cancer progression revealed significant results consistent with the literature and epidemiology, providing a deep understanding of the complex pathological relationship between heavy metal poisoning and renal cancer progression [7, 8].

The findings were systematically organized into a table that explored the following topics: heavy metals that cause poisoning, contamination pathways, structural alterations in different locations of renal anatomy, main signs and symptoms, and their relationship with cancer development.

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Table 1- Profile of heavy metal poisoning: contamination routes, structural alterations and relationship with cancer [1, 8, 13].

Heavy metal	Pollution Medium	Buildup in the body	Initial clinical presentation	Relationship with Cancer
Cadmium (Cd)	Industry, batteries, pigments	Kidneys, liver	Proteinuria, hypertension, edema	Strong
Arsenic (As)	Contaminated water, pesticides, industries	Kidneys, skin, lungs	Weight loss, hypertension, proteinuria	Strong
Mercurius (Hg)	Mining, contaminated fish	Kidneys, central nervous system	Fatigue, loss of appetite, kidney dysfunction	Possible
Lead (Pb)	Old paints, batteries, flooring, fuel	Bones, liver, kidneys	Anemia, fatigue, abdominal cramping	Possible

Exposure to cadmium is most common in industrial settings, especially in battery and pigment industries that use cadmium as a raw material [12]. The metal, when absorbed by the body, binds to metallothionein, a low molecular weight protein synthesized in the liver [1].

This cadmium-metallothionein complex circulates in the blood and in the proximal tubules, where the complex is reabsorbed, causing oxidative stress and DNA damage, compromising the capacity for cellular repair at that site, with a strong relationship with renal carcinogenesis [12].

Cases of arsenic poisoning occur mainly in industrial areas and regions with contaminated water, where arsenic is used in the manufacture of pesticides and in processes of physical extraction of the metal [8, 9]. When absorbed into the body, arsenic accumulates in the renal tubular series, causing oxidative stress and interfering with cell signaling pathways, such as apoptosis and the cell cycle, causing DNA damage and being strongly carcinogenic [5]. In addition, arsenic inhibits enzymes essential for cellular respiration, such as pyruvate dehydrogenase, leading to mitochondrial dysfunction and chronic inflammation, resulting in interstitial fibrosis [5, 9].

Mercury exposure occurs primarily in industrial settings, such as mining, and from consumption of contaminated fish [10, 14]. After being absorbed, mercury binds to proteins with sulfhydryl groups, which facilitates its distribution in organs such as the kidneys. In the proximal tubules and nephron, it accumulates causing oxidative stress, DNA damage, apoptosis, and a possible relationship with neoplasms, although this association is not yet widely studied and its complications are usually related to non-renal neurological damage[19].

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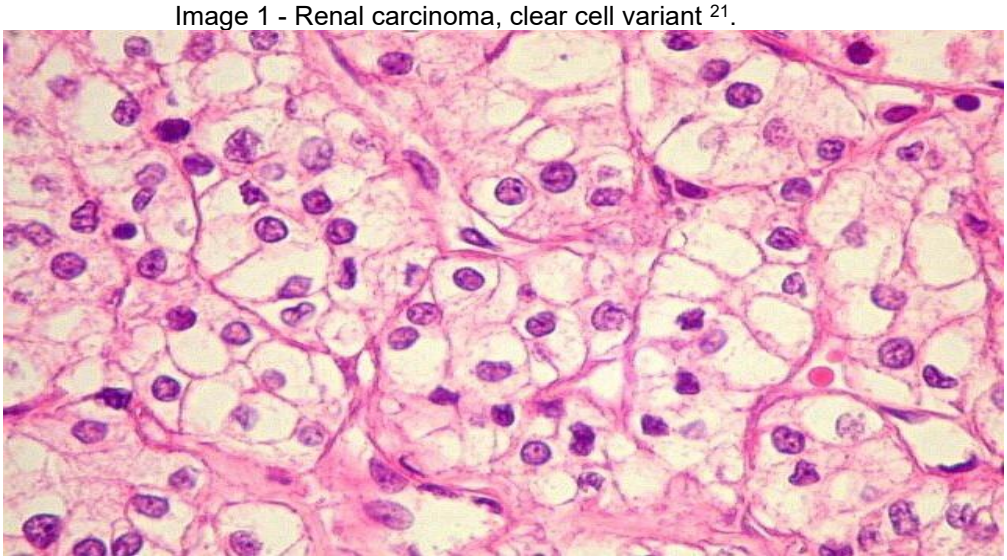
Lead poisoning is common in industrial settings, such as the paint, battery, and fuel industries, as well as in areas with environmental contamination[1 8]. After absorption, lead binds to plasma proteins and is distributed throughout tissues [18, 20]. In renal glomeruli, it causes oxidative stress, DNA damage, mitochondrial dysfunction and chronic inflammation, interfering with the regulation of intracellular calcium and inhibiting enzymes essential for energy metabolism [20]. Although it is associated with an increased risk of renal cancer, its main condition is neurological [13, 20].

Clinically, these poisonings present non-specific symptoms and signs that make diagnosis difficult without knowing the work and home history, such as, for example, renal alterations represented by proteinuria, being a common complication in all the heavy metals mentioned above [8, 13].

Hematological alterations, such as anemia, are typical of lead contamination, while cardiovascular manifestations, such as hypertension, are frequent in cadmium and arsenic poisoning [19, 20]. Therefore, the use of diagnostic aids, such as urinalysis 24 hours after administration of chelating agents, detailed blood tests, and imaging techniques, such as tomography and radiography, is necessary [10, 12].

In cases where poisoning has evolved into renal carcinogenesis, biopsy is an important resource, being performed by collecting a sample of tissue suspected of injury. This sample is then analyzed with the hematoxylin-eosin staining technique, which helps detect the most common type of carcinoma associated with heavy metal exposure: clear cell carcinoma[6].

Image 1 - Renal carcinoma, clear cell variant [21].



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When clear cell carcinoma is observed under a microscope, it is noted that the tumor cells have a pale and prominent cytoplasm, resulting from the accumulation of glycogen and lipids [6, 8]. In addition, cell nuclei are atypical, varying in size and shape, with dense chromatin and prominent nucleoli [5, 6]. The architecture of the tumor is characterized by alveolar or nest arrangements, often surrounded by a delicate network of capillaries [6]. However, pharmacological treatment of heavy metal poisoning is not sufficient to delay cancer, so a combination of chelating agents, radiotherapy, and immunotherapy is used [8, 12].

Chelating agents such as DMSA (meso-2,3-dimercaptosuccinic acid) and DMPS (2,3-dimercapto-1-propanesulfonic acid) are substances that bind to metal ions, forming soluble complexes that can be excreted by the body, playing a crucial role in the treatment of metal ions [22, 23]. First, chelating agents bind to heavy metals in the body, reducing their availability to interact with tissues and cells; then, they increase the solubility of metal-chelating complexes, facilitating their elimination by the kidneys through urine [12, 23].

Full recovery usually takes up to three weeks, depending on the severity of the condition and the organs affected [12]. However, the incidence of adverse effects such as nausea, tachycardia, and local reactions highlights the need for careful follow-up of patients [12, 24]. Approximately 50% of patients experience side effects after intramuscular administration, which may limit their use in certain situations [12].

Despite these limitations, the positive effects outweigh the negative ones, and dimercaprol and drugs derived from this component, such as medo-2,3-dimercaptosuccinic acid and 2,3-dimercapto-1-propanesulfonic acid, remain an indispensable tool in the fight against heavy metal toxicity, providing important benefits in the recovery of intoxicated patients. especially in cases related to arsenic, mercury and cadmium [12].

Forensic medicine plays a crucial role in medico-legal investigations, mainly to determine the causes or circumstances of suspicious deaths. In this field, there is the subspecialty of forensic toxicology, which is responsible for analyzing chemical biological samples in cases of unexpected deaths, using systematic methods to identify toxins or substances that may have contributed to the death of the victim.

Autopsies are not always considered necessary in cases of death due to complications of kidney cancer, for example [14]. This is due to the fact that, in many of these cases, the cause of death is already confirmed and supported by medical records as due to a malignant renal neoplasm, which may limit the need for further investigation [14, 15].

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However, there are additional challenges when it comes to relating and identifying other diseases or conditions that are triggered by continued exposure to any toxic substance, especially if it is in small amounts in the long term, since the agent may no longer be present in the body [14]. Continuous exposure to heavy metals that do not present obvious morphological changes is noteworthy, which makes a conclusive diagnosis difficult [15].

Another major obstacle to the control and early diagnosis of the damage caused by heavy metal toxicants is the lack of access to adequate clinical diagnostic tests, as suffered by the inhabitants of underdeveloped countries such as those in Latin America who have less access to medical advances, but above all the population of workers in risk areas such as miners, Industrial workers and gold prospectors [14].

These populations often do not have economic resources or formal documentation to support the company and support the medical history, as is the case of illegal miners who cannot report where they work for fear of reprisals from their bosses, which makes a definitive diagnosis difficult, which leads to a palliative approach, treating only the symptomatological manifestation [15]. This legal and social precariousness aggravates the situation, increasing the risks of exposure and complications from substances harmful to human health [14].

Reducing occupational and environmental exposure to heavy metals is a major public health challenge. Rigorous health surveillance policies are essential to decrease the incidence of neoplasms related to these metals, along with regular monitoring of kidney function, which is critical, especially for the population at risk, including workers exposed to heavy metals and people living near industries.

FINAL CONSIDERATIONS

The results of this study reinforce the strong relationship between heavy metal exposure and renal carcinogenesis, especially in industrial workers. Epidemiological evidence shows that regions with high exposure to metals such as cadmium, arsenic and mercury have a significant increase in the incidence of poisoning by metals promoting renal neoplasia, which corroborates the chronic toxicity of these elements.

From a legal point of view, susceptibility to renal neoplasia among exposed workers highlights the urgent need for stricter regulation and effective enforcement in industries. Companies that fail to protect their employees from heavy metal contamination could face

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serious legal repercussions, especially in situations where exposure has been a determining factor in the development of the disease.

The implications for public health and occupational safety are clear. Preventive measures and strict enforcement of legislation are critical to prevent not only kidney cancer, but any type of carcinogenesis related to this exposure and ensure a safer environment for workers.

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