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Cadmium Chloride-Induced Hepatotoxicity: Molecular Mechanisms, Oxidative Stress, and Histopathological Alterations—A Comprehensive Review

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ABSTRACT

Cadmium chloride (CdCl) is a highly dangerous heavy metal commonly used in electroplating, pigment production, battery manufacturing, plastic stabilization, and other laboratory settings. Due to the speed of industrial growth and human activities, cadmium levels in air, water, and soil have gone up dramatically, This way the compound is a leading reason for environmental and occupational contamination of health. Essential trace elements are those the body relies on but with cadmium, the body does not. In fact, its biological half-life is up to forty years, making the chemical progressively accumulate in tissues. Although the kidney has long been known as the prime organ involved in chronic lead poisoning, cadmium absorption actually causes rapid damage to the liver due to this organ's primary role in metabolism and detoxification of foreign substances (xenobiotics). CdCl liver accumulation initiates many pathological responses including overproduction of reactive oxygen species (ROS), exhaustion of the cell's antioxidant systems, mitochondrial malfunctions, release of inflammatory cytokines, cell death, and fibrosis. At a larger level of tissues and functions, all these changes cause disturbances in liver structure and function leading to hepatocellular injury. Oxidative stress and disruption of calcium homeostasis are just two mechanisms of cadmium toxicity besides other effects like antioxidant enzyme inhibition, DNA and membrane (lipid) damage, and activation of several intracellular signaling pathways such as NF-B, MAPK, and Nrf2. From a histological standpoint, changes include liver cell (hepatocyte) alterations, widened blood sinuses, cells of the immune system coming into the tissue, blood vessels in a state of congestion, spots of necrosis (cell death), and fibrosis. From a clinical point of view, liver damage caused by CdCl is seen as an increase in the levels of some biomarkers, viz. alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin, as indicators of disease state changes and alteration of enzyme activities for antioxidant defense (e.g. glutathione peroxidase).The article reviews the present state of knowledge on cadmium environmental exposure sources, toxicokinetic pattern of CdCl, mechanisms responsible for cadmium-induced liver damage, and the corresponding histopathological and biochemical manifestations. Comprehending the molecular events involved is a crucial step toward the designing of strategies aimed at preventing cadmium-induced liver injuries identification of biological indicators of exposure, and formulation of new ways of treatment that will lessen liver damage caused by cadmium exposure.

Keywords: Cadmium chloride, Hepatotoxicity, Oxidative stress, Liver injury, Reactive oxygen species, Toxicokinetics, Heavy metals, Histopathology, Inflammation, Apoptosis.

INTRODUCTION

Heavy metal pollution has become a major environmental issue of the current century largely due to the rapid progress in the industry cities minerals, and the lack of proper treatment of industrial byproducts to the environment. Of all the toxic metals cadmium (Cd) has been the topic of considerable discussion because it is highly persistent in the environment, tends to build up in bio systems, and can Quite a bit damage the human as well as animal health. Cadmium is classified as a non-essential, transition metal of Group 12 in the periodic table, and is acknowledged as one of the most hazardous polluters by numerous health organizations at international level. Really, unlike iron, zinc, and copper which are essential metals, cadmium neither serves a beneficial

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purpose nor its toxic influence even when present as small quantities. Cadmium chloride (CdCl2[1-4]) is one of the highly water-soluble forms of cadmium and it can be widely used as an industrial electroplate agent, production of pigments, creation of batteries, plastic items catalysts stabilizers, photographic chemicals, and chemical analytical instruments. Due to extremely high solubility in water CdCl2 quickly contaminates the aquatic environments and the cropland soils, and from that point it gets into the food chain easily. Containing foodstuffs, drinking water, cigarette smoke, occupational situations and general environmental polluting activities are the primary ways of human contact. As the industries are constantly running more and more people are experiencing the toxicity of cadmium at low levels continuously so this form of contamination is turning out to be a serious health matter. After uptake by the body cadmium is carried and other blood components and initially collects in the liver before being moved into the kidney under chronic exposure. The liver is a key organ in carrying out the detoxification and metabolism of foreign chemicals, and is So Mainly vulnerable to damage by cadmium. Numerous liver damage pathways which are interlinked and may include oxidative stress inflammation mitochondrial failure, programmed cell death/apoptosis, change in cellular-signalling, and a breakdown in the regulation of metals. And, cadmium may be causing an overproduction of reactive oxygen species (ROS) as a result, which then, attacking the membrane lipids proteins nucleic acids, organelles can bring breakdown of the liver tissue.

Experiments carried out show that the use of cadmium greatly changes the antioxidant system and this is mainly through lowering the levels of glutathione (GSH) and inhibiting antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). As a result, the oxidative damage will lead to membrane lipid peroxidation, protein oxidation, mitochondrial injury, DNA fragmentation, and release of inflammatory mediators like tumour necrosis factor-alpha ((TNF-), interleukin-1 (IL-1), and interleukin-6 (IL-6). This inflammatory processes worsen liver damage and promote fibrosis and chronic liver disease. Cadmium-induced toxicity also results in disturbance of body calcium homeostasis and mitochondrial respiratory chain enzymes which then cause a significant fall in ATP levels and initiate apoptotic (programmed) cell death[5-6]. Data shows both intrinsic mitochondrial apoptosis and inflammatory pathways are involved in the hepatocyte depletion if cadmium exposure. The common histological changes observed are swelling of hepatocyte, vaculopatric degeneration, sinusoid congestion, inflammatory cell infiltration, necrosis, and fibrosis. Clinically, the impairment of the liver is evidenced by increased levels ofALT AST ALP, gamma-glutamyl transferase (GGT), bilirubin, and a reduced ability to synthesize albumin.

In fact, the (IARC) classified cadmium and its compounds as Group 1 human carcinogens (IARC), meaning that they can cause cancer. Besides liver injury, many studies have reported chronic cadmium exposure as a cause of renal failure, male reproductive toxicity osteoporosis cardiovascular complications, immune system dysfunctions, and cancer. Modern toxicology based upon molecular methods has, in turn, brought a substantial improvement to our knowledge of cellular damages caused by cadmium. Research into signaling pathways of NF-B MAPK PI3K/Akt, Nrf2/Keap1, mitochondrial apoptosis etc. has revealed new ways how diseases develop and what treatments could help. In addition, various naturally derived antioxidants phytochemicals vitamins and chelating compounds are considered as potentially effective ways to counteract the oxidative liver injury[7-8].Generally, this paper reviews different environmental sources of cadmium, the features related to CdCl in the body, and molecular mechanisms that underlie-induced (hepatotoxicity). However, this paper also discusses how such features as oxidative stress inflammation apoptotic process, mitochondrial disruption and histopathology of the liver contribute to hepatic injury and in doing so, also summarizes the state-of-the-art about biochemical biomarkers that are utilized to monitor liver damage. If the molecular basis for this liver damage can be clearly understood, then this could bring new means, including prevention and treatment, to tackle-induced (hepatotoxicity).

Objective

The objective of this review is to comprehensively summarize the current evidence regarding the sources, toxicokinetics, molecular mechanisms, oxidative stress pathways, histopathological alterations, biochemical biomarkers, and potential therapeutic approaches associated with cadmium chloride-induced hepatotoxicity.

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Justification

A comprehensive understanding of cadmium-induced liver toxicity is essential because increasing environmental and occupational exposure continues to pose significant public health concerns. Integrating current mechanistic and pathological evidence may facilitate early diagnosis, preventive interventions, and future therapeutic development.

Review Questions

This review addresses the following questions:

1. What are the major sources and toxicokinetic characteristics of cadmium chloride?
2. Which molecular mechanisms contribute to cadmium-induced hepatotoxicity?
3. What histopathological and biochemical alterations occur following cadmium exposure?
4. What research gaps remain for future investigations?

REVIEW METHODOLOGY

Study Design

This study is a narrative review of published scientific literature on cadmium chloride-induced hepatotoxicity.

Data Sources

Relevant articles were identified through electronic databases including PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect.

Literature Search

Searches were conducted using combinations of keywords including "cadmium chloride", "hepatotoxicity", "oxidative stress", "liver injury", "histopathology", and "molecular mechanisms".

Selection Criteria

Peer-reviewed English-language articles focusing on cadmium-induced liver toxicity, molecular mechanisms, oxidative stress, histopathology, and biochemical biomarkers were included.

Data Analysis

Information from eligible studies was critically reviewed and synthesized narratively according to major thematic areas.

Data Collection Tool

The primary tool used for data collection was a structured electronic literature search of peer-reviewed scientific databases using predefined search terms and eligibility criteria.

Sources of Cadmium Exposure

Cadmium happens to be a mineral element that appears in the ground naturally, which is not something you can see in the ground but it is there. Human activities, Then again, have caused a significant increase in environment cadmium levels. Mechanism-wise, industrial releases, minerals extraction refining coal burning and waste

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disposal are all the main factors leading to cadmium pollution together with phosphate fertilizers. Cadmium is known for not being digestible by microorganisms and that means on cadmium that is already in the environment, the cadmium remains and will not disappear easily[9]. As a result, cadmium can slowly build up within living systems and the environment, which can have serious health implications after long exposures.

Occupational Exposure

Work-related exposure is arguably the most crucial way cadmium poisoning can occur. It is Mainly risky for battery makers, those who electroplate goods welders metal refiners, people who produce pigments and alloys, plastic producers and all kinds of recyclers. When exposed to the inhalation of cadmium-laden dust and fumes during these jobs, the cadmium gets quickly absorbed through the lungs, enters the blood circulation and accumulates in our most important organs. People whose jobs involve a lot of exposure to cadmium and other similar metals have very likely to have chronic liver disease, loss of kidney function, weakened bones, lung problems, as well as a higher cancer risk[10-11]. It is, That means, very important for industrial hygiene measures, personal protective equipment, and regular biological monitoring to be employed correctly.

Environmental Exposure

Poisoning the environment comes from industrial discharges, tailings from mines, sludge generated from wastewater, leachates of landfills, and deposition from atmosphere. Cadmium when released into the environment gets the agricultural field soils as well as water bodies contaminated and then the metal gets into the crops and aquatic organisms[12]. Research shows that rice, leafy vegetables cereals shellfish and organ meats are the main sources of cadmium. Humans mostly absorb cadmium in food except for smokers who mainly take cadmium through tobacco. Constant consumption of the dietary sources of cadmium in the form of food that is contaminated by cadmium might increase the level of the metal in the human tissues over time, since the cadmium remains in the body very long.

Cigarette Smoking

Smoking is still one of the biggest non-work-related reasons people come into contact with cadmium. Cigarettes carry much more than just nicotine and they contain traces of lead which are absorbed from the ground by the plants. When people smoke, they inhale cadmium into their lungs from cigarette smoke. Around 40, 60% of this cadmium will be absorbed and That means, the levels of cadmium in the blood and tissues will rise quite Really when it comes to the person who smokes. But, the body of a long-time smoker can become overwhelmed with cadmium that builds up in the liver and kidneys. Such exposure can cause a lot of harmful effects because cadmium can produce free radicals (also known as "oxidative stress") when it interacts with certain biochemical changes in the body. So, the overall picture from long-time smoking is one of severe liver damage and toxic substances being released throughout the body[13-14].

Drinking Water and Food Chain

Cadmium in drinking water mainly comes from industrial waste, mine tailings, improper handling and disposal of waste, and agricultural activities that result in runoff. People who regularly drink contaminated drinking water get chronically exposed mainly to those in highly industrialized areas. In water animals and the crops on the farmland, bioaccumulation of cadmium is happening. As cadmium concentrations increase at each level on the food chain (which is called "biomagnification") the risk of human exposure becomes greater. So, eating contaminated food for many years is another reason for chronic cadmium intoxication across the world[15-16].

$CDCL_2$ TOXICOKINETICS

Toxicokinetics describes the absorption, distribution, metabolism, and excretion (ADME) of toxic substances within biological systems. The toxicokinetic characteristics of $CdCl_2$ largely determine its biological persistence and toxicological effects.

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Absorption

Cadmium chloride gets into the body mainly by being inhaled or swallowed, and less frequently by being absorbed through the skin. When it's breathed in, cadmium can be taken up very quickly by the body and distributed around as well. The level of metal in food is the biggest reason for the variation in cadmium absorption through the digestive system[17]. Cadmium has the ability to hitch a ride on the same transporter metal as say iron, zinc, or calcium like DMT1. Because of that, when there is deficiency or scarcity of these elements, the uptake of cadmium increases.

Distribution

After being absorbed, cadmium first builds up in the liver and there it causes the liver to produce metallothionein, a cysteine-rich metal-binding protein that temporarily reduces the amount of free cadmium toxicity. If cadmium exposure continues over a long time, the Cd-metallothionein complex will travel from the liver to the kidneys where it will be accumulated gradually[18-19].Some other tissues that can be affected include the pancreas, the lungs, the testes, the bones and the heart and blood vessels.

Cellular Uptake

Cadmium gains entrance to hepatocytes mainly through transport systems that were designed originally to handle essential divalent metals like calcium, zinc and iron. Because of its chemical ionic similarity characteristics, cadmium can compete with these essential metals leading thereby to interference with several enzyme systems and cellular signaling pathway[20]s.

Biotransformation

Unlike a number of other xenobiotics, cadmium doesn't get metabolically broken down. It is a very stable metal. Rather, cadmium forms tight bindings at cellular level with proteins like metallothionein and glutathione, resulting in extended staying time within the cells. This feature makes cadmium extremely difficult-to-persistent as well as its toxicity is accumulative.

Elimination

Cadmium leaves the body very slowly. Its presence in the body of a person can stay up to 20-40 years without any major biological changes which explains why chronic exposure to low levels of cadmium is still considered harmful. Cadmium exits the body mainly through urine and feces, but a relatively small share of the body's total content is passed out each year. So, one-time exposure after another leads to more and more buildup, Mainly in the liver and kidneys, which Really raises the chances of getting liver and kidney problems as well as other cancers[21[.

Mechanisms of Liver Toxicity

Cadmium chloride (CdCl) causes liver toxicity by affecting various molecular and cellular mechanisms all working in coordination with each other rather than one. After entering the body, cadmium is quickly carried to the liver where a protein called metallothionein (MT), rich in cysteine, is produced to hold the metal and So reduce its toxicity briefly. But continuous or excessive exposure defeats the body's protective capacity and leads to the accumulation of cadmium within the cell and the start of oxidative stress, inflammation, mitochondrial failure, DNA breaks, endoplasmic reticulum stress, death of the cell (apoptosis) and fibrosis. While metals like transition metals can generate free radicals through Fenton-type reactions because of their redox properties, cadmium is not a redox metal. Rather, it creates an overload of reactive oxygen species (ROS) mainly indirectly. Disrupting mitochondrial electron transport and depleting the levels of intracellular antioxidants, inhibiting antioxidant enzymes, and perturbing vital metal homeostasis all can contribute to ROS production. The created oxidative imbalance is mainly responsible for the triggering subsequent inflammatory, degenerative and cell

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death processes. Biomolecular pathways like NF-B (nuclear factor-kappa B), MAPK (mitogen-activated protein kinase), cAMP response element-binding protein (CREB), PI3K/Akt (phosphatidylinositol-3 kinase/protein kinase B), JNK (the c-Jun N-terminal kinase), ERK (extracellular signal-regulated kinase), p38 MAPK and TGF- (transforming growth factor-beta) as well as Nrf2 (nuclear factor erythroid 2-related factor 2) become active in cadmium-induced liver damage. Through interaction with each other the activation levels of different cascades determine how severe the actual hepatocellular damage has been[22].

Oxidative Stress

Oxidative stress is considered the underlying mechanism for CdCl-induced liver damage. It occurs when cells produce more reactive oxygen species than antioxidant systems can counteract. The resulting imbalance ultimately causes damage to lipids proteins carbohydrates, nucleic acids, and intracellular organelles. Cadmium interferes with the function of respiring mitochondria in liver cells by inhibiting electron transport chain complexes. Electrons leaking from damaged mitochondria cause the generation of superoxide anion (O-), hydrogen peroxide (HO), hydroxyl radicals (OH), and reactive nitrogen species. Such molecules can break down the cell membrane and start the release of lipids through a process called lipid peroxidation.

One of the first biochemical signs of oxidative stress is the depletion of reduced glutathione (GSH), the main intracellular molecule that neutralizes reactive oxygen species. High affinities between cadmium and sulfhydryl (-SH) groups allow it to form complexes with glutathione, metallothionein, and many other antioxidant proteins quite spontaneously. Lack of available glutathione dramatically weakens the cell's antioxidant defence and leads to more oxidative damage. Exposure to cadmium is accompanied by a decrease in the activities of various antioxidant enzymes e g. superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and glutathione-S-transferase (GST). The low levels of these enzymes leave the system more vulnerable to reactive oxygen species and So, the levels of oxidative damage increases. Reduced ability to defend against oxidative stress leaves the body open to a range of oxidative stress-related problems.

Lipid peroxidation is a hallmark of cadmium intoxication. Hepatocyte plasma membranes richly filled with polyunsaturated fatty acids are susceptible to the action of free radicals which leads to the production of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), two commonly used biomarkers for the assessment of oxidative stress. Membrane lipid peroxidation destabilizes the membrane integrity, disrupts membrane fluid property, impairs ion transport mechanism, and increases cellular permeability resulting in swelling and death of the liver cell. Cadmium-induced oxidative damage extends beyond liver cell membranes to cell proteins and even DNA. In the liver cell membrane lipid peroxidation destabilizes the membrane integrity. When it comes to enzymes and other proteins, they become sensitive to change by oxidative modification after the attack by reactive oxidants. For instance, the oxidation of amino acid residues will result in changed enzyme structure and activity. It is well-known that reactive free radicals are the principal mediators of DNA damage and mutation which are the primary causes of carcinogenic effects. The oxidation of DNA produces many types of damaged nucleotides that are not easily repaired like 8-hydroxy-2'-deoxyguanosine (8-OHdG) which is a widely studied marker of oxidative DNA damage. On top of DNA strand breaks and loss in genetic stability, there are also reports of oxidative stress-induced damage to the DNA repair mechanisms in cadmium-treated cells. Genotoxicity can also be attributed in part to mutational load generated as a consequence of persistent exposure to high oxidative stress levels due to cadmium. DNA is another significant molecular target. Oxidative stress induced by cadmium generates oxidized nucleotides like 8-hydroxy-2'-deoxyguanosine (8-OHdG), causes DNA strand breaks, chromosomal instability, and impairments in DNA repair mechanisms. Genomic instability resulting from prolonged DNA damages can promote mutagenesis and carcinogenesis. Protection of the liver against the oxidative damage caused by cadmium exposure has been linked to the activation of the Nrf2, Keap1 signal transduction pathway which is one of the most important pathways that protect the cells against oxidative stresses through gene activation. In regular physiological situations, Nrf2 is anchored to Keap1 while located in the cytoplasm. Yet, oxidative stress will usually cause an unbinding releasing the Nrf2 molecule which then can move into the nucleus and will activate antioxidant response element (ARE)-controlled genes which lead to the expression of various antioxidant and cytoprotective proteins like heme oxygenase-1, NAD(P)H: quinone oxidoreductase 1, glutathione S-transferase and GPx, respectively. But, long cadmium exposures are reported to

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affect Nrf2 pathways So reducing antioxidant gene expressions and making the liver more vulnerable to the effects of oxidant substances.

Experiments have increasingly showed that giving natural antioxidants like curcumin quercetin resveratrol silymarin vitamin C, vitamin E, selenium, and N-acetylcysteine together with cadmium has a preventive effect and Because of this A lot lowers cadmium-induced oxidative stress through increasing antioxidant enzymes activity, reducing lipid deterioration processes, protecting GSH content, and maintaining mitochondrial structure. The results clearly show that oxidative stress is by far the most probable event causing the initial damage to liver via CdCl2-induced toxicity.

Inflammation

Inflammation is one of the two main mechanisms whereby cadmium causes damage to the liver and is closely linked to the process of oxidative stress. The reactive oxygen species that are generated upon cadmium exposure lead to the activation of various signal transduction pathways of the cell which, in turn, lead to the production of multiple inflammatory cytokines and chemokines. If inflammation becomes persistent hepatocyte injury increases, fibrosis is encouraged, and the condition progresses toward chronic liver disease. One of the liver resident cells - specialized macrophages - are called Kupffer cells. These have a very important role in the livers innate immune response and are known for their surveillance capability at the cellular level. Hepatocyte damage and reactive oxygen species can both trigger Kupffer cells. The triggered macrophages then release a cascade of pro-inflammatory mediators: one two three examples, but all together these mediators can be tumor necrosis factor-alpha (TNF- alpha), interleukin- 1beta (IL-1beta), interleukin-6 (IL-6), gamma interferon (IFN- gamma), monocyte chemoattractant protein-1 (MCP-1), and transforming growth factor-beta (TGF- beta) which will attract neutrophils and monocytes from blood to the liver, thereby exacerbating the inflammatory process[23].

Of the inflammatory signal transduction systems, the nuclear factor kB (NF-kB) pathway is regarded as the chief orchestrator of cadmium-induced inflammation. In normal physiological situations, NF-kB is rendered dormant by its association with a group of protein inhibitors called IkBs, all residing in the cytoplasm. Using this oxidative stress cadmium-generated reactive oxygen species activate IKK (IB kinase), the resulting kinase phosphorylates and thereby degrades IB proteins. So, free NF-kB is released and it moves to the nucleus, where it activates the expression of many inflammatory genes among which there are pro-Inflammatory cytokines TNF-, IL-1, IL-6, also enzymes like inducible nitric oxide synthases (iNOS) and cyclooxygenase-2 (COX-2), plus various adhesion molecules. This activation of NF-kB also gives the loop mechanism where inflammatory cytokines stimulate, in the same way reactive oxygen speces, the production thereof, while oxidative stress further activates NF-kB signaling. This cross-talk sustains the inflammatory condition even if the original toxic factor no longer exists! Another mechanism is the cascade of mitogen-activated protein kinase (MAPK). Its a major class of signaling molecules that include the kinase enzymes ERK and JNK. These signals affect not only the expression of the genes which lead to inflammation but also the release of different cytokines, and determine cell death, survival, and change of tissues. Really, the liver cell (hepatocyte) damage caused by JNK activation is quite severe; in addition, such liver cell injury is accompanied by an influx of inflammatory cells. The liver has specialized cells called hepatic stellate cells (HSCs) as its major fibrogenic cells. On top of the other damage mechanisms inflammation also plays a role in the activation of HSCs. When activated, these HSCs turn into myofibroblast-like cells that produce excessive amounts of collagen types I and III plus extracellular matrix proteins. As the liver's structure is taken over one after another by the deposition of collagen the organ develops fibrosis. If this is left untreated cirrhosis is the final outcome. Inflammatory mediators also make the blood vessels of the sinusoids in the liver so thin in their walls that they are easily ruptured and leakage ensues. The consequence here is that liver tissue gets flooded with blood, swollen up, and the circulation at this level becomes impaired. Lack of sufficient supply of oxygen makes worse further oxidative damage and localized deaths of hepatocytes occur.Data that has surfaced recently suggests that another mechanism is the one that causes the NLRP3 inflammasome to be awakened by the presence of cadmium. For our purposes, an inflammasome is a cellular machinery consisting of lots of the structural proteins, which play key functions during the innate immune response. NLRP3 activation via caspase-1 leads to pro-IL-1 beta and pro-IL-18 being processed and So resulting in IL-1beta and IL-18, thereby augmenting the inflammatory reaction. On a broader perspective, excessive

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activation of inflammasomes has long been considered as a main contributor of chronic inflammation fibrosis as well as the development of cancer at the local level (in this case, the liver).

Together, oxidative stress and inflammation can act in a more combined way than separately. In fact, oxidative damage is followed by a signaling inflammatory response while inflammatory mediators further produce reactive oxygen species leading ultimately to the development of a cycle of progressive hepatic lesion that repeats itself. Blocking the loop at different points such as by using antioxidants or anti-inflammatory drugs could be a viable option in the treatment of cadmium-induced liver damage.

Apoptosis

Programmed cell death (apoptosis) is one of the main drivers of CdCl toxicity in the liver. Apoptosis is different from necrosis in that it is a precise and finely tuned pathway marked by features like the shrinking of the cell, condensation of the chromatin, DNA fragmentation, the formation of apoptotic bodies, membrane blebbing, and lack of large inflammatory response, whereas in necrosis the cell is simply destroyed and often it is with the involvement of inflammatory cells. Cadmium leads to both the mitochondrial (innate) and death receptor-mediated (extrinsic) routes of induction of apoptosis, which result in a step-by-step disappearance of liver cells. With the intrinsic path of apoptosis the starting point is the presence of oxidative stress and the damage resulting from these to the mitochondria[24]. The production of reactive oxygen species under cadmium stress alters the dynamics between the pro-apoptotic proteins (i. e. Bax Bak Bad), and the anti-apoptotic ones (Bcl-2, Bcl-xL). An increase of the Bax/Bcl-2 ratio results in more mitochondrial outer membrane permeability, allowing the release of cytochrome c in the cytoplasm. When cytochrome c comes into contact with apoptotic protease activating factor-1 (Apaf-1) and procaspase-9 the apoptosome forms which leads to the activation of caspase-9, and then further the downstream executioner caspases like caspase-3 and caspase-7 are released. Caspases then begin to degrade both nuclear and structural proteins which will definitely lead to complete programmed cell death. Then again, the extrinsic pathway of death through cadmium can also be initiated by the death receptor's activity including Fas (CD95) and tumor necrosis factor receptor-1 (TNFR1). The interaction with the receptors leads to the activation of caspase-8 which can either directly result in the death of a cell (through the activation of the executioner caspases) or indirectly by enhancing the mitochondrial apoptotic signaling via the release of active Bid (tBid).It is also clear that cadmium-induced apoptosis is mainly a combination of different mechanisms. The other important mechanism is the endoplasmic reticulum (ER) stress that the cells undergo during cadmium-induced death. ER has a huge job, among others, of folding the synthesized polypeptides and delivering them for further destinations inside the cell. In cadmium poisoning, there is a great accumulation of ER's unfolded or even misfolded proteins and that triggers a cascade termed the unfolded protein response (UPR). Long lasting and unremitting ER stress causes C/EBP homologous protein (CHOP) to be highly expressed and in turn caspase-12 is activated. When the mechanisms of adaptation to these stresses do not work properly, the cells undergo the death programme called apoptosis. Experimental reports support the idea that ER stress is closely related to two other mechanisms such as oxidative stress and mitochondrial failure and this is one reason for the rapid loss of liver cells. Cadmium has another way to induce apoptosis. That is by causing DNA damage that will lead to an activation of a tumor suppressor protein called p53. The expression of various pro-apoptotic genes like Bax and PUMA can be turned on by the p53 protein and at the same time p53 blocks the expression of the anti-apoptotic factors. So, when there is persistent oxidative damage of DNA, one consequence, among many others, is that the apoptosis-related signaling becomes more active and the number of cells that will survive the death programme diminishes greatly. Overapoptosis diminishes the liver's ability to regenerate and causes malfunction of the liver. Although death of cells by apoptosis seems to be beneficial for removing cells with damage, long-term destruction of the hepatocytes results in the change of the liver tissue, Because of this making it more likely the fibrosis and cirrhosis to develop in the liver.

Mitochondrial Dysfunction

Mitochondria are involved in energy production, calcium homeostasis regulation, reactive oxygen species (ROS) regulation, and apoptosis. Because of this they are amongst the very first intracellular organelles to be disturbed on cadmium exposure. One of the ways that cadmium works is by stopping the functions of complexes I II III,

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and IV of the electron transport chain. Electron transport becoming a slow activity reduces oxidative phosphorylation, limits ATP synthesis, and increases electron leakage, ultimately causing ROS elevation. In a way, ATP insufficiency will lead to the failure of many energy-dependent cellular functions, including membrane transport, protein synthesis, and detoxification. Another characteristic of cadmium toxin is the drop of mitochondrial membrane potential (m). Disruption of membrane potential leads to insufficient ATP production and allows opening of Mitochondrial Permeability Transition Pore (mPTP). Continuous opening of the mPTP will trigger mitochondrial swelling, rupture of the outer mitochondrial membrane, and release of apoptogenic proteins like cytochrome c, apoptosis-inducing factor (AIF), and Smac/DIABLO into the cytoplasm. Cadmium further throws out a major disturbance in intracellular calcium homeostasis. High calcium levels in the cells boost the calcium intake in mitochondria, which in turn lead to mitochondrial membrane permeability transition and the opening of calcium-dependent protease. Mitochondrial DNA[25], or mtDNA, is Mainly fragile to damage caused by the oxidation process, which is because it lacks the protective histones and has limited DNA repair mechanisms Oxidative changes to mtDNA lower the production of respiratory chain proteins, and further mitochondrial dysfunction results. That means, the oxidation process gets worsened because of this vicious cycle of mitochondrial dysfunction and oxidative damage. Mitochondrial dysfunction also affects hepatic (liver cell) metabolism by decreasing fatty acid -oxidation and changing glucose metabolism. This metabolic imbalance leads to the build-up of lipids which are mainly the reason for hepatocellular degeneration and other problems that are characteristic of the liver function impairment that one sees after the body has been subjected to a chronic cadmium exposure.

Summary of Molecular Pathways

CdCl2-induced hepatotoxicity operates mainly through the interaction of various interconnected molecular paths and not through independent pathways. The presence of Cd in the liver cells first gives rise to oxidative stress through overproduction of ROS and the reduction of antioxidant systems. This kind of stress then triggers inflammation and mainly NF-B and MAPK signaling pathways that cause pro-inflammatory cytokines and attract immune cells. Meanwhile, mitochondrial dysfunction, calcium imbalance, DNA damage, and ER stress initiate intrinsic and extrinsic apoptotic pathways culminating in liver cell loss.Continuously active molecular events will be the reason why hepatic stellate cells are activated, ECM is produced, and fibrosis and chronic liver disease happen. As oxidative stress really helps in connecting apoptosis, inflammation, and mitochondrial dysfunction, strategies that aim at normalizing redox balance may be capable of reducing cadmium-induced liver damage effectively.

Transition to Histopathological Changes

Changes on the cellular and molecular levels are accompanied by distinctive structural liver tissue features. Oxidative stress, infiltration of inflammatory cells, damage to mitochondria, and apoptosis together damage the liver structure and lead to hepatocellular degeneration, sinusoidal congestion, inflammatory infiltration, vascular alterations, focal necrosis, and the development of progressive fibrosis. At the same time, these microscopic alterations also correspond very well with biochemical changes; for example, high levels of enzymes like serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin.

Histopathological Changes and Biochemical Markers of $Cdcl_2$-Induced Hepatotoxicity

Histopathological Changes

Histopathological investigation is still among the most trustworthy tools to evaluate CdCl-induced hepatic damage. The visual inspection of microscopic slices enables us to determine if and how the tissue has physically changed after an acute or chronic Cd exposure. The pathological consequences are manifestations of a combination of mechanisms such as oxidative stress, cell inflammation, mitochondrial dysfunctions, cellular metabolism disruption, and programmed cell death. A lot of lab investigations with small animals have proved that cadmium chloride administration causes hepatic lesions that vary as dosage and time. This shows that liver damage gradually escalates as exposure periods continue. The main role of the liver is detoxification and

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metabolism of foreign matter, which the body cannot break down or uses as poison. Cadmium chloride entering our blood stream after absorption is mostly carried straight towards the liver via the portal vein. At first, a protein called metallothionein is made by liver cells to trap any loosely bound cadmium and Because of this prevent it from doing direct damage. A major problem arises when exposure time is so prolonged that metallothionein is no longer capable of effectively handling cadmium, resulting in the cadmium concentration build-up inside cells and Because of this the degradation of hepatocytes[26].

Hepatocellular Degeneration

Early histological evidence of CdCl2 is hepatocellular degeneration. The damage of the membrane leads to intracellular accumulation of water and electrolytes which in turn leads to swelling of the normally polygonal shaped hepatocytes. Lipid metabolism disruption as well as endoplasmic reticulum functions may be a reason for cytoplasmic vacuolate formation. In many cases, a degenerated hepatocyte has a granular cytoplasm an irregular nucleus and a lower glycogen content indicating a decrease in metabolic activity. One of the typical features after exposure of cells to cadmium is hydropic degeneration that shows up with early symptoms of cadmium poisoning and indicates reversible cellular injury. On the contrary if oxidative stress remains unchecked for long then initially reversible degeneration can turn into irreversible death through necrosis or apoptosis of the cells.

Sinusoidal Dilatation and Vascular Congestion

Cadmium exposure dramatically affects hepatic microcirculation. The histological examinations clearly show the dilation of hepatic sinusoids and the congestion of central veins and portal vessels. The vascular permeability increases due to the mediators of inflammation which causes plasma leakage into the neighbouring tissues leading to a swelling of tissues (oedema) and reduced blood flow. When the sinusoids become filled with the blood, oxygen delivery is hampered which leads to the oxidation of the hepatocytes and aggravation of liver damage. And, insufficient blood flow also limits the transportation of nutrients into the liver and getting rid of the waste materials out of the liver, which will in turn, will further damage the liver function.

Inflammatory Cell Infiltration

Kupffer cell activation and the migration of inflammatory leukocytes are hallmarks of CdCl-induced liver injury. Histopathological findings generally include neutrophil macrophage lymphocyte, and monocyte infiltration within the areas of portal triads and central veins. Inflammatory cell infiltrates cause up-regulation of cytokines such as TNF-, IL-1, IL-6, and transforming growth factor-beta (TGF-). Continued inflammation leads to a gradual destruction of the liver parenchyma as well as stimulation of hepatic stellate cell activity leading to fibrosis.

Hepatic Necrosis

Severe and irreversible death of liver cells from too much oxidative damage and ATP shortage is what is meant by cell death termed necrosis. Such cell membrane of death cells becomes permeable and the contents of the death cell leak out. Necrotic change involves this: membrane of the cell is lost; there is a change in the cytoplasm which shows an abnormally increased amount of eosinophilia; there is also a nuclear change where the chromatin is condense and at the end, there is total dissolution of the nucleus. Small necrotic areas are usually detected around the central veins as these regions have relatively lower oxygentension. There is a release of the inside cell parts when necrotyc cells die unlike for apoptotic cells. This would not only bring in the body's immune system but also get the inflammation process going which would be the last straw for the liver[27].

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Apoptotic Changes

Microscopic inspection shows significant number of apoptosis hepatocytes with nuclear condensation, apoptotic bodies, nuclear fragmentation, cell shrinkage. Apoptosis has an advantage over necrosis as apoptosis cell death does not trigger an intensive inflammatory response but excessive mass apoptotic loss has the effect of decreasing tissue regenerative potential and So progresses to compensatory chronic liver failure. Immunohistochemical examinations of the effect of CdCl2 exhibit an increased Bax, caspase-3, caspase-9 and p53 expression in the animals that lead to confirmation of apoptosis.

Fibrosis

Long-term cadmium exposure activates cells in the liver called hepatic stellate cells that can be transformed into myofibroblasts which actually make collagen. Looking at the sections of the liver, progressively larger amount of collagen fibber can be observed to be filling up the portal areas and also going towards the central veins around them. Too much extracellular matrix leads to the distortion of regular liver tissues and finally it results in fibrosis. The production of fibrogenesis and In particular the over-production of collagen is largely under the influence of TGF-, whereas the destruction of matrix is being suppressed. Continuous exposure to cadmium often means chronic fibrosis that in turn would result in cirrhosis.

Ultrastructural Alterations

Results from electron microscopic studies further confirm that cadmium causes cellular damage. The ultrastructural alterations observed have included features like mitochondrion swelling, fragmented cristae, rough endoplasmic reticuli dilation, Golgi apparatus discontinuities, chromatin condensation, lysosome proliferation, and plasma membrane damage. Mitochondrial anomalies are so intimately and precisely tied to failure of ATP synthesis combined with elevated reactive oxygen species generation that this supports the main reason of hepatotoxic effect caused by CdCl as being mitochondria malfunctioning.

Biochemical Markers of Liver Injury

Biochemical testing can offer insights into how well the liver is functioning during exposure to high levels of cadmium. When hepatocytes are injured and their membranes are disrupted or damaged, the liver enzymes which are normally intracellular are released into the bloodstream. This release of enzymes is regarded as one of the most reliable signs that the liver is damaged.

Alanine Aminotransferase (ALT)

Alanine aminotransferase is one of the most sensitive indicators of damage to the liver cells. ALT is mostly found within the cytoplasm of the liver cells where it is involved in amino acid metabolism. The breakage of the liver cell membrane causes ALT to leak out into the blood, which leads to a higher level of ALT in the blood serum. Several studies on animals have been showing a very high level of serum ALT after administration of the CdCl. High ALT level indicates that the membrane was damaged and such high level is also found to be in agreement with the seriousness of histopathological change[28].

Aspartate Aminotransferase (AST)

Aspartate aminotransferase (AST) can be found both the cytosol and mitochondria of Liver cells (Hepatocytes) as well as cardiac and skeletal muscle. Since mitochondrial injury a primary mechanism leading to the toxicity of Cadmium, serum AST levels often go hand in hand with the rising levels of ALT.Very high level increase of AST implies large-scale hepatocellular injury including the destruction of mitochondria. Evaluating together the enzymes AST and ALT give good idea of the amount and direction of liver injury.

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Alkaline Phosphatase (ALP)

Alkaline phosphatase enzyme is mainly responsible for canalicular and bile duct membrane functions and is produced mostly by bile duct epithelial cells. Raised levels of ALP in blood are usually signs of a block or a cholestatic lesion where bile flow is hindered by inflammation and hepatocellular swelling. The production of inflammatory substances after exposure to cadmium might compress bile canaliculi located between liver cells that result in impaired bile flow and higher serum levels of ALP. This way, high blood level of ALP indicates both hepatocellular damage and disturbance of the biliary system.

Total Bilirubin

Bilirubin results from the processing of dead cell contents, mainly haeme molecules that derive from haemoglobin through phagocytosis by reticuloendothelial cells (RE cells) and the subsequent breaking down of haeme. Bilirubin conjugation and excretion are carried out by the hepatocyte cells. Bilirubin handling is hampered when a person suffers from liver damage which is reflected in bilirubin levels higher than normal in the blood. High bilirubin caused by cadmium can be the first sign of liver malfunction that results from the toxic chemical. Elevating bilirubin often goes hand-in-hand with jaundice in cases of liver damage and poisoning. Still, one should keep in mind that other diseases may also exhibit the same symptom, and the patient should undergo a thorough investigation to rule out other possibilities.

Albumin and Total Protein

Albumin is only made by liver cells, and its level is one of the main indicators of the ability of the liver to produce substances, Mainly proteins. Becoming a long-term CdCl sufferer will lead you to have a decrease in producing proteins, and the reason is the damage done by free radicals to the machinery for producing proteins, viz. ribosomes and the endoplasmic reticulum of our cells. Because of Cd-poisoning for so long, not only blood serum albumin levels go down but also, total protein levels come way down as well. Lack of albumin in the blood, medically referred to as hypoalbuminaemia, causes oedema (fluids pooling in certain parts), difficulties in proper drug distribution throughout the body, and diminished bodys ability through antioxidants and enzymatic activities to neutralize free radicals and other harmful substances.

Oxidative Stress Biomarkers

Biomarkers that assess oxidant/antioxidant imbalance be a useful complement to the measurement of regular hepatic parameters. Cadmium causes a marked elevation in MDA LPO NO, and PC whereas a pronounced reduction of GSH SOD CAT, GPx and GR occurs. These major biochemical shifts reveal that oxidative stress plays a role as the primary mechanism leading to liver damage following CdCl administration.

Inflammatory Biomarkers

Cadmium exposure has in turn led to higher levels of TNF-, IL-1, IL-6, NF-B, COX-2 - an enzyme responsible for inflammation, iNOS - another enzyme that makes nitric oxide, a gas messenger used for signaling in cells, and C-reactive protein in experimental studies. The rise in these promediators was closely connected to histological observations of inflammatory cell infiltration and the development of fibrosis in the liver tissue[29].

Correlation Between Histopathology and Biochemistry

Histopathological lesions and biochemical alterations take place at the same time and support each other in the assessment of cadmium-induced liver injury. Animals with severe features like degenerating hepatocytes necrosis inflammatory infiltration, and fibrosis will have A lot elevated levels of ALT AST ALP bilirubin markers of oxidative stress, and inflammation indicators in blood. Because of this, the joint usage of histological and biochemical methods for assessment offers a more detailed characterization of hepatotoxicity and is still the most reliable method in animal experimental toxicology studies.

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DISCUSSION

Cadmium chloride (CdCl) continues to be one of the most toxic environmental factors due to its persistence, bioaccumulation, and induction of toxic effects in multiple organs. The liver is a target to a greater extent, among other organs, since it is a vital organ for the metabolism of xenobiotics, toxin removal, and the overall balance of metabolism. As the review, CdCl-induced liver damage is not attributed to one particular mechanism but is the cumulative result of several interconnected events, like oxidative stress, an inflammatory response, problems related to mitochondria, a cell death process called apoptosis, and changes in intracellular communicating pathways. These events are interrelated in that the impairment of normal liver cell functioning and the development of liver disease as a consequence are brought about gradually and ultimately lead to a form of chronic liver injury. One of the key incidents that trigger the damage caused by cadmium in the liver is an attack by oxidizing species (ROS), i.e. oxidative stress. Even though cadmium is inherently devoid of redox activities, it is able to induce the generation of reactive oxygen species through the breakdown of mitochondrial respiration, lowering of the available amount of glutathione, blocking of antioxidant enzymes, and the mobilization of key micronutrients like zinc and selenium. The consequent state of the imbalance between the generation and removal of radicals can result in the peroxidation of lipids, oxidation of proteins, DNA damage, and destabilization of membranes. It is So a key thing contributing to the death of liver cells. The results of Cd-induced experiments, in which the levels of lipid breakdown byproducts known as a marker for oxidative stress called malondialdehyde (MDA) were found at higher concentrations, together with lower activities of the major antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) were used In the end that the main mechanism leading to toxicity in CdCl is the presence of oxidative stress

As a consequence of oxidative stress, the liver lesion is further enhanced through the activation of different inflammatory response pathways. Reactive oxygen species provoke the nuclear translocation of one of the transcription factors called NF-kB and the signaling pathways mitogen-activated protein kinase (MAPK) and NLRP3 inflammasome, and this ultimately leads to the increased release of several cytokines (e.g. tumour necrosis factor-alpha - TNF-, interleukin-1 (IL-1), and interleukin-6 (IL-6) which are the main players in the inflammatory response. Activation and prolonged stimulation of hepatic macrophages (K cells) and infiltration by inflammatory cells result in a persistent inflammatory hepatic environment leading to deterioration of liver cells and a tendency towards hepatic fibrosis. There is a direct connection between the two events oxidative stress and inflammation that, in a closed loop, reinforce one another by their own mechanisms. The cycle continues, and as each process adds to the other, the liver injury keeps becoming more severe. We also find that the role of disturbed mitochondrial functioning in cadmium-mediated hepatotoxicity is one significant issue this paper has raised. Mitochondria are indispensable for supplying the cell with the chemical energy needed, and the decision to undergo programed cell death apoptosis etc. is also mainly regulated by them. Cadmium interferes with potential energy changes at the mitochondrial membrane, prevents the functioning of the enzyme complexes of the electron transport chain (ETC), and can even trigger the swelling of the mitochondrion by the opening of the mitochondrial permeability transition pore (mPTP).A fall in ATP generation accompanied by an increase in reactive radicals is the result. The leakage of the respiratory protein cytochrome c from a dysfunctional mitochondrion leads to initiating one of the apoptosis pathways involving caspases resulting in a progressive destruction of liver cells. The results of these investigations underscore Really protecting mitochondrial structure and function could be the main focus of the treatment of the liver damage caused by cadmium.The histopathological findings further support the changes in the biochemical profile that have been identified as features of cadmium toxicity. Results from several experiments show that after the cadmium chloride exposure hepatocytes swell, the cytoplasm develops vacuoles, the sinusoids widen, the vessels get blocked by congestion, there is an infiltration of the inflammatory cells to the liver, localized death of cells, and the deposition of the collagen. The structural changes were accompanied by very high levels of the blood components like alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin, showing that the hepatocellular membranes were affected and the liver functions were impaired. Because of this, histopathology and biochemistry combined continue to be one of the most suitable and reliable methods for the evaluation of the toxicity of cadmium on the liver in both experimental and clinical situations[30].Better understanding of the cellular mechanisms of cadmium toxicity has been made possible by new developments in the study of genes and cells. Pathways that lead to the activation of NF-B MAPK PI3K/Akt, JNK, and TGF-

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signaling in the liver result in inflammatory, apoptotic, and fibrotic processes while the suppression of the Nrf2 antioxidant pathway leads to a decrease of antioxidant capacity, a protective cellular mechanism. On one side, such molecular pathways indicate potential therapeutic targets which could be the basis of a new treatment in the future. But, many researchers have found through lab experiments that curcumin quercetin resveratrol silymarin vitamin C, vitamin E, selenium, and N-acetylcysteine as antioxidants remarkably counteract the formation of ROS, reactivate antioxidant enzymes, and mitigate the hepatic tissue damage as revealed by histopathology. Yet, these are mostly lab results which do not directly translate to human use. Unless thorough clinical studies are done, there seems to be a lack of evidence for these substances to be recommended as standard therapeutic agents.With public health, the most effective measures against cadmium toxicity are those that aim to prevent exposure. Environmental laws that restrict air, water and soil pollution are, Because of this, very important. Reduction of emission from factories, workplace protection measures, regular medical checks on industrial workers are just some of examples of how these can be accomplished. Also, periodic inspection of contamination of food as well as drinking water is a must to reduce cadmium exposure. And, identification of sensitive biomarkers that are able to detect early signs of liver injury before major pathological changes occur will help in both disease prevention and management.Further studies should also be devoted to investigating the factors of regulation at the epigenetic level, the role of microRNA and metabolomic variations to name a few, plus understanding how a gene and the environment interact in a situation that cadmium may cause the liver to become toxic. Studies that look into new antioxidants, agents which reduce inflammation, mitochondrial protectants, and targeted therapies at the molecular level could, Because of this, be of huge significance, when it comes to cadmium-related liver disease, to the development of better drugs.

Preventive Care

Preventive strategies should focus on minimizing environmental and occupational exposure through pollution control, workplace safety measures, personal protective equipment, regular biological monitoring, and public awareness.

Promotive Care

Health promotion should encourage nutritional interventions, smoking cessation, environmental surveillance, and routine health screening among populations at high risk of cadmium exposure.

Palliative Care

Individuals with advanced cadmium-induced liver injury require supportive clinical management aimed at reducing oxidative stress, controlling inflammation, and preventing disease progression.

Rehabilitative Care

Rehabilitation should include long-term clinical follow-up, nutritional counseling, occupational rehabilitation, and continuous monitoring of hepatic function to improve quality of life.

Limitations of Current Evidence

The available evidence on cadmium chloride-induced hepatotoxicity is characterized by substantial heterogeneity in experimental design, animal species, exposure duration, dosage, biomarker assessment, and histopathological evaluation. Variability in analytical methods and outcome reporting limits direct comparison across studies and precludes robust quantitative synthesis. Consequently, the current evidence is primarily narrative, and standardized methodologies are needed to facilitate future meta-analyses and strengthen causal inferences.

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Limitations of Human Evidence

Human evidence remains limited because most available studies are cross-sectional with relatively small sample sizes. Differences in exposure assessment, including dietary intake, occupational exposure, smoking status, and biomonitoring methods, increase the risk of exposure misclassification and residual confounding. Furthermore, the lack of longitudinal cohort studies limits the establishment of temporal relationships between cadmium exposure and liver injury. Future prospective studies using standardized biomarkers are required to improve risk assessment.

CONCLUSION

Cadmium chloride-induced liver damage is a complex process that involves many factors like generation of free radicals, liver inflammation, mitochondrial failure, cell death (apoptosis) and finally the liver tissue changes and damage. Even though free radical formation is the first step, different intracellular pathways interacting with each other decides how serious the injury of the liver will be. Cadmium that keeps on going in the body causes degradation and loss of liver cells, infiltration of inflammatory cells, production of fibrosis and failure to carry out the functions of the liver that are vital as the levels of bilirubin ALT AST, and ALP will be higher than usual.

The evidence from experiments has repeatedly shown that the body's own antioxidant system is very badly affected when exposed to cadmium and Because of this, the risk of cell damage increases. Changes observed in microscopic analysis of the liver tissue very well parallel the biochemical and molecular changes. This again indicates that for evaluating liver lesions caused by cadmium, one should consider both a pathological and biochemical approach together.

Even though many mechanisms of cadmium toxicity have been discovered and we understand them at a certain level, there are still some points that remain to be addressed like molecular markers, early diagnostic indicators, and the best treatment strategies. The use of natural antioxidants and components aiming at reducing oxidative stress, inflammation, and dysfunctional mitochondria have provided favorable results in experimental settings; although more clinical trials are needed, to verify their effects and safety for people in general.

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