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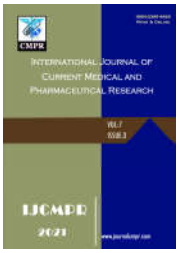

Research Article

POTENTIAL RISKS OF CADMIUM TOXICTY FROM COCOA BASED PRODUCTS: A REVIEW

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ABSTRACT

Cocoa based products like chocolates, candies; cocoa powder may sometimes contain heavy metals like lead, arsenic, cadmium, and nickel from environmental origins. WHO has defined maximum level of heavy metals in chocolates as they are potentially harmful to human health? This review explains about the possible risks involved in overconsumption or chronic consumption of cocoa based products containing cadmium beyond its upper limit. Cadmium has no biological function to play in human or animal body. In fact cadmium is one of the most toxic elements as it tends to stay in liver and kidneys with a very long half-life of 10-30 years and presents serious risks to human health. Epidemiological data suggest that occupational and environmental cadmium exposure may be related to various types of cancer, including breast, lung, prostate, nasopharynx, pancreas, and kidney cancers. It has been also demonstrated that environmental cadmium may be a risk factor for osteoporosis. The liver and kidneys are extremely sensitive to cadmium's toxic effects.

INTRODUCTION

Most of the food is generally and predominantly used for pleasure. Chocolates and cocoa powder are no exceptions to it. *Theobroma cacao* is the biological name for cocoa beans and in Greek Theobroma means food of the Gods. This is exactly what chocolate is known for centuries. Chocolates/ candies, toffees are presented to the children as a token of love.

Cocoa is the essential ingredient for chocolate and cocoa powder. It originates from the seeds (cocoa beans) of the cocoa fruits (cocoa pods), which grow on cocoa trees. The production of cocoa begins in the tropical regions around the Equator, where the hot and humid climate is well suited for growing cocoa trees. 70% of the world's cocoa beans come from four West African countries: Ivory Coast, Ghana, Nigeria and Cameroon. The Ivory Coast and Ghana are by far the two largest producers of cocoa: together they cultivate more than half of the world´s cocoa. These two are followed by other cocoa producing countries like Indonesia, Nigeria, Cameroon, Brazil and Ecuador.

Cocoa plays an important role in immune regulation, inflammation, neuro-protection, oxidative stress, obesity, and diabetes control. Cocoa also can protect nerves from injury and inflammation, protect the skin from oxidative damage from UV radiation in topical preparations, and have beneficial effects on satiety, cognitive function, and mood. Cocoa contains certain flavanoids particularly catechin, epicatechin and procynidines – having the most antioxidant property.(Katz D.L. *et.al*, 2011**).** Despite of having these health benefits of cocoa and its products have some detrimental effects on human health as cocoa is predominantly consumed as energy dense food. These effects are due to the presence of heavy metals coming directly through contaminated soil and eventually overconsumption of most indulgent forms of cocoa beans i.e. chocolates and cocoa powder.

Heavy metals found generally in environment and especially in food are arsenic, lead, cadmium, mercury, chromium, copper, zinc, nickel, selenium, silver, antimony, manganese, and several others.

Cadmium was not known to be a separate element till 1817 when it was discovered as cadmium sulfide; a minor compound of zinc ore. While zinc is very essential element in all almost cells; cadmium has no known biological function. Cadmium is in fact most toxic to life. Cadmium transfers from soil to plants and thus enters the food chain. Cadmium along with arsenic, lead, mercury has no physiological function to play. (Genchi G.*et.al*, 2020).

Although acute toxicity of cadmium caused by certain food consumption is high; chronic exposure to cadmium may accumulate cadmium in some organs. Generally, the intake of cadmium in very small amounts by humans is unavoidable, however effects include abdominal cramps, headaches, vomiting and diarrhoea. With long term exposure, cadmium causes renal damage, severe loss of bone minerals and painful fractures. (Reilly, C., 2002). Accumulation of cadmium in plant and animal bodies may result in certain types of cancers like breast, lung, prostate, nasopharynx, pancreas, and kidney cancers. Cadmium is also adsorbed and distributed in the other organ and tissues such as liver, spleen, pancreas, kidney,

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skeletal, heart and testis. The half life period of cadmium in human body is 10-30 years. Cadmium is not degradable in nature and will thus, once released to the environment, stay in circulation. Cadmium in small amount absorbed in the kidney cause proteinuria when kidney concentration reaches a certain value. Interaction between Cd, Cu and Zn results in cadmium toxicology.

WHO has already shown a concern about the consumption of heavy metals containing foods and set an upper limit to their concentration in food products. This review presents the risks to health particularly in children involved in chronic or over consumption of cocoa beans and their products.

Possible toxic effects on various organs

The present contribution is based on available open literature mainly articles in international journals. This review highlights those aspects of potential health hazards of chronic consumption of cocoa powder containing cadmium. The document does, however, not claim to be an exhaustive presentation covering all relevant issues in full detail.

Effect on Liver

Acute hepatotoxicity involves two pathways, one for the initial injury produced by direct effects of cadmium and the other for the subsequent injury produced by inflammation. Primary injury appears to be caused by the binding of Cd^{2+} to sulfhydryl groups on critical molecules in mitochondria. Thiol group inactivation causes oxidative stress, the mitochondrial permeability transition, and mitochondrial dysfunction. Although cadmium may injure hepatocytes directly, there are compelling reasons to believe that hepatocellular injury is produced in vivo as the result of ischemia caused by damage to endothelial cells. Secondary injury from acute cadmium exposure is thought to occur from the activation of Kupffer cells and a cascade of events involving several types of liver cells and a large number of inflammatory and cytotoxic mediators. In this regard, it is clear that Kupffer cell activation and neutrophil infiltration are important events in the toxic process, and the involvement of pro-inflammatory cytokines and chemokines has also been implicated. However; it is not associated with liver cancer. Acute hepatotoxicity injury, involves a direct toxic effect of the metal, ischemia due to endothelial cell injury, and the latter inflammatory injury, in which Kupffer cell activation and neutrophil infiltration play a major role through a cascade of inflammatory mediators. Some histopathological changes such as loss of normal architecture of the parenchymatous tissue, cytoplasmic vacuolization, cellular degeneration and necrosis, congested blood vessels, destructed mitochondria cristae, fat globules, severe glycogen depletion, lipofuscin pigments, and collagenous fibers formation are observed in liver tissue from rats exposed to Cadmium for 22 days. These cellular changes may result in both apoptosis and necrosis.

Several mechanisms have been postulated for Cadmium-induced hepatotoxicity. Its injury appears to be associated with sulfhydryl groups binding, implicating membrane proteins, cytoplasmic proteins and enzymes. Although the mechanism by which Kupffer cells contribute to Cadmium hepatotoxicity is not fully understood, it is known that activated Kupffer cells, release a variety of cytotoxic mediators that can directly damage hepatocytes. These mediators include reactive oxygen species (ROS), nitric oxide, and cytokines. Studies show that chronic cadmium exposure leads ultimately to hepatic necro-inflammation, NAFLD, and NASH in men and necro-inflammation in women. Particular attention has been paid to the role of tumor necrosis factor α (TNF-α) in Cadmium hepato-toxicity. (Hyder O. *et.al*, 2013).

Effect on Kidney

Chronic exposure to cadmium through diet is relatively low i.e. only 5-10%. But the chronic use of foods with heavy metals by the people with reduced stores of minerals like iron and zinc even the low level of absorption from the gastrointestinal tract may lead to systemic accumulation of cadmium and toxicities. Kidney is the most sensitive organ which gets affected by chronic exposure to cadmium. Cd accumulates in the kidney in the renal proximal tubule. All the three mechanisms – Necrosis, Apoptosis, and Autophagy can lead to cadmium accumulation and finally will result in nephrotoxicity. Cadmium is preferably taken up by the process of endocytosis where cadmium binds with metallothionein in the renal tubule. In the cell Cadmium-MT molecule is degraded in endosomes and lysosomes and release free Cd (2+) into the cytosole. (Johari N. *et al*, 2010)**.** Then it generates reactive oxygen species activating cell apoptosis. This leads to impaired reabsorption of low molecular weight proteins like retinol binding proteins resulting in tubular proteinuria. Continued exposure leads ultimately to renal failure. Importantly renal damage is seen because of accumulation of cadmium mainly in kidney and also in testes is due to the ability of these tissues to synthesize metallothionein, a cadmium-inducible protein that protects the cell by tightly binding the toxic cadmium ion.

Initially the tubular epithelial cells which are attached to each other begin to accumulate cadmium affecting epithelial cell function. This involves mild oxidative stress but responds to autophagy and may be sufficient to repair damage. Beyond this however, if the injury is more severe, apoptosis cell death can occur. If the injury to cells is widespread and severe, repair processes are inadequate, resulting in necrosis of the proximal tubule cells. (Prozialeck *et.al*, 2012) (Please refer Figure No.1).

Effects on bone

Chronic cadmium exposure act on bones either directly on bone cells or indirectly as cadmium first induce renal failure, increasing calcium and phosphorus excretion and thus decreasing vitamin D synthesis and hence also decreasing calcium absorption in the gastrointestinal tract.

Cadmium decreases bone density indirectly through hypercalciuria resulting from renal tubular dysfunction and also direct osteo-toxic effects. There is also decreased serum parathyroid hormone with higher exposure to cadmium thus indicating resorption of calcium from bone. Adverse effects on bone apparently occurred at lower exposures than kidney effects (UCd 0.5~2 vs > 4 µg/g creatinine, respectively**).** (Rodriguez J. *et al*, 2018)

Carcinogenic Effect

The route of entry of cadmium decides cadmium's amount. It has estimated that daily intake of cadmium in uncontaminated areas was 25-60µg/day for a person but the rates might rise up to 61µg/day for a person of about 70 kg body weight. Approximately 3-10 % of ingested cadmium is absorbed from gastrointestinal tract. After absorption cadmium gets transported by proteins with high affinity to cadmium and

albumin into different organs. Approximately 50% of the cadmium is stored in the liver and kidney organs due to their high metallothionein concentration, others including testis, spleen, heart, lungs, thymus, salivary glands, and prostate could store cadmium in slight amounts. (Bishak Y. *et al*, 2015) Cadmium induces cancer by multiple mechanisms. Cadmium acts on mitochondria, awakening the enzymatic and non-enzymatic anti-oxidative defenses. Cadmium induces oxidative stress to resulting in the damage of proteins, lipids, and DNA. Cadmium decreases the activity of DNA repair enzymes, influencing cell cycle proliferation and stimulating carcinogenesis. The most important pathway is oxidative stress by involvement in Cadmium-induced aberrant gene expression, inhibition of DNA damage repair, and apoptosis. Cadmium creates thiol redox imbalance leading to decreased intracellular glutathione content reducing antioxidant activity. Cadmium-induced aberrant gene expression, inhibition of DNA damage repair, apoptosis are caused by oxidative stress done by Cadmium. Cellular thiol redox imbalance causes ROS formation which Cd initiates though Cd is not directly involved in carcinogenesis. This process leads to decreased cellular glutathione content. Accumulated ROS then induce DNA damage and also can interfere with cell signaling. (Chunhabundit, 2016)

Neurotoxic effect

The central Nervous system is especially vulnerable in neonatal development. Cadmium readily passes through placenta to the fetus and also in milk during lactation. The blood brain barrier doesn't let cadmium to enter in adults that easily but as this system is not fully developed in neonates, infants are more prone to cadmium toxicity. *(Korpela H. *et al*, 1986). The protective capacity of the choroid plexus of the brain, proper barrier functioning decide the pathophysiological changes in the brain. Cadmium affects synaptic neurotransmission as well as antioxidant levels in brain; the serotonin sensibility in CNS is increased; by interfering with calcium metabolism, release of acetylcholine is inhibited. Cadmium accumulation in organs prior to birth and at birth might cause irreversible or long lasting changes in the brain in children.

Cadmium can modify hormone levels by affecting hypothalamus, pituitary, testicular glands. Perinatal Cadmium exposure during gestation or lactation period results in learning deficits and altered behaviors in children. The mechanism by which cadmium affects CNS is thought to be associated with oxidative stress. Therefore depletion in antioxidant system and a resultant increase in lipid peroxidation may cause micro-vascular damage. (Wang B. *et al* 2013).

Concluding Remarks

Cadmium toxicity was first given attention after Itai-Itai disease was found to be caused by heavy intake of cadmium in Japan. Children get indulgent in chocolates and cocoa powder and its other products more easily. Cadmium concentration found in different types of chocolates in India is 0.010 to 2.730 µg/g of chocolate. Cadmium accumulates in the body and has the half life period of 10 30 years. The toxic effects occur not only in the kidney leading to proteinuria but the cardiovascular system, digestive, neurological skeletal systems also get detrimental effects. PTWI has been established by WHO as at 7µg/kg body weight. So if a child of 15kg body weight PTWI would be 105µg/ week if chocolate is consumed daily. This is 33.5 % of PTWI but other food sources and water also contain cadmium thus exceeding cadmium intake by much more for children. Though chocolates have some positive health benefits their consumption should be made low for prevention of heavy metals toxicities. Children are the future of the society and wasting our strength in such indulgent food is not acceptable by any nation. (Dahiya S. *et al*, 2005).

Future Scope

The food gets polluted and becomes unsafe for consumption and this is the outcome of modernization. Consumption of food that is rich in certain polyphenols like melatonin, caratenoids, L-carnitine, and coenzyme Q10 is one of the ways to alleviate the harmful effects of heavy metals toxicity. Also there are some ways to reduce soil toxicity on which plants like coca are grown. Removal of cadmium from the soil and lowering the intake of cocoa based products like chocolates and candies are some of the solutions to lower the risks to human health. Although; to protect children from the dangers of food containing heavy metals need further study and investigation.

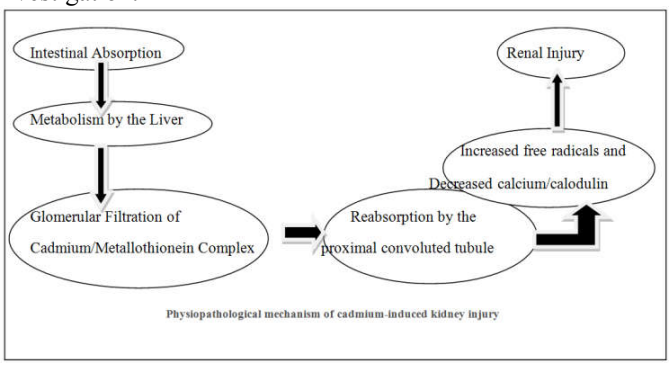

Figure 1

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