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TOBACCO-INDUCED METAL TOXICITY: ROLE OF VITAMINS

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ABSTRACT

Recently, the main theme of world is urbanization as well as industrialization as a result; there has been a growing concern about increase in toxic metals contamination. Nicotine is one of the major constituents of different types of smoking and is the more toxic part also. Thirty metals have been detected in tobacco smoke, including nickel, arsenic, cadmium, chromium and lead. Arsenic and arsenic compounds and chromium and some chromium compounds are causally associated with cancer in humans, while nickel and cadmium and their compounds are probably carcinogenic to humans. So, the present review is to summarize the current knowledge regarding the risks of tobacco consumption which contains several toxic metals. Vitamins consumption through food stuffs, act as an antioxidant. Antioxidants are substances which may play a role in heart disease, cancer and other diseases. Antioxidants, such as vitamins C and E and carotenoids, may help to protect cells from damage caused by free radicals. Several studies reported that metals-induced toxicity can be attributed to oxidative stress started from glutathione mediated metal reductive activation and continued by mitochondrial/lysosomal toxic interaction. Vitamins play a vital role to counteract such alterations in response to heavy metals.

KEYWORDS: Heavy metals, oxidative stress, toxicity, vitamins.

INTRODUCTION

Tobacco (smoking and smokeless) use is the largest single preventable cause of illness and premature deaths. It is a toxic complex and reactive mixture containing an estimated 5000 chemicals. Among them there are several types of heavy metals are found, these are arsenic (As), cadmium (Cd), chromium (Cr), nickel (Ni), lead (Pb), Copper (Cu) etc. There are different types of tobacco smoke, depending upon the components and exposure some are mainstream smoke (MSS, exhaled by the smoker), some are side stream smoke (SSS, yielded by the burning cigarette), and other are environmental tobacco smoke (ETS).[1]

Tobacco is not the only source of heavy metal but the heavy metal are also easily enter in our body through different types of sources like food, water, air, different types. Heavy metals have been used by human from a several decades.[2] All living organisms require varying amounts of heavy metals to do various function of their body.[3] because some heavy metals are act as essential trace elements.[4] But high concentration of heavy metal exposure can cause illness. They accumulate in various vital organs and glands such as the heart, brain, kidneys, bone, liver, etc [5] and disrupt their functions. According to IARC, lead (Pb), cadmium (Cd), and chromium (Cr) are carcinogenic or possibly carcinogenic to humans. [6]

There are a number of possible interactions of micronutrients with secondary mechanisms of toxicity occur by the heavy metal. There are several studies proved that the micronutrients intake has a significant effects on toxicity induced carcinogenesis caused by various toxic metals. Micronutrients can reduce the toxicity of metals by interacting with the metal at its primary site of action. Vitamin E helps to prevent the effects of Cd-induced oxidative damage in blood, liver and kidneys by reducing the oxidative stress. [7] Vitamin E and vitamin C combined lowering the cadmium effects on liver. Vitamin C protects the cell from arsenic toxicity because it acts as an antioxidant. The vitamin C protective thyroid toxicity to which is occur due to excessive exposure of Cr (VI), chromium generates free radicals that are extremely perilous for cell sand bodily tissues; antioxidant vitamins like vitamins C act as free radical scavengers.[8]

The aim of the present review is to summarize the current knowledge regarding the risks of wide spread tobacco consumption which contains several toxic metals. According to IARC four metals are more carcinogenic like cadmium, chromium, arsenic and lead. This review is also examined the protective role of vitamins against heavy metals toxicity.

1. Exposure of heavy metals and their toxicity

1. 1. Toxicological effects of cadmium

The toxicity of cadmium (Cd) depends on the amount of cadmium enter into our body. Since one cigarette packet contains approximately 1000 to 3000 µg/kg of Cd. [9] Cd is hazardous both by inhalation and ingestion. It can cause the acute and chronic intoxications. [10] The most dangerous characteristic of cadmium is that it accumulates throughout a lifetime. Mainly cadmium accumulates in the liver and kidneys and has a long biological half-life of 17 to 30 years in humans [11] and also damage several vital organs, among which the most sensitive are the kidney, the bone and the respiratory tract. [10] Acute Cd poisoning causes pulmonary oedema, haemorrhage, fulminate hepatitis, testicular injury, and lethality; whereas prolonged exposure to Cd products nephrotoxicity, osteotoxicity and immune toxicity etc may occur.[12] Beside this, cadmium also contributes substantially to cancer risk.[13]

1.2. Toxicological effects of chromium

Chromium presents in environment in various oxidation states like Cr (III) and Cr (VI).Chromium in minimal amount or in the form of Cr (III) is considered an essential nutrient needed in human health for insulin, sugar, and lipid metabolism. It is reported that chromium supplementation increases muscle gain and fat loss associated with exercise and improves glucose metabolism and the serum lipid profile. But excessive level of chromium can be manifested in various forms like mental and physical dysfunctions, change in blood composition, and pathological changes in vital organs. Long term effect on exposure may result in slow progressive physical, muscular, and neurological degenerative changes.[14] After absorption, Cr (VI) can be reduced through reactive intermediates such as Cr (V) and Cr (IV) to the more stable Cr (III) by cellular reluctant this reduction takes place at the cost of inflicted cellular damage. In the metabolic processes of chromium, it can induce oxidative stress with glutathione (GS) radical to oxidize the surrounding environment, with the potential to attack adenine and guanine in DNA and to produce DNA adducts. With DNA damage and/or incomplete DNA repair, this can lead to carcinogenesis.[15]

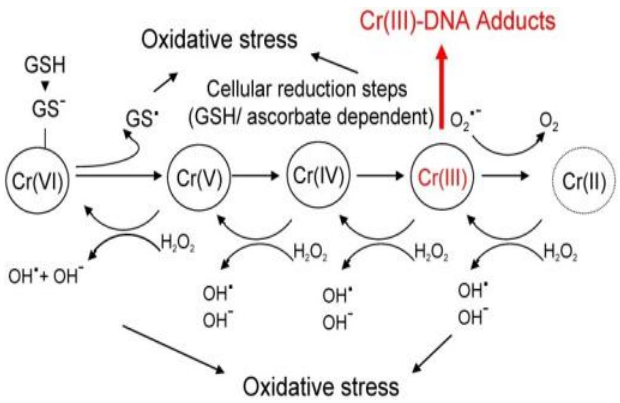

Figure 1: Mechanism of chromium toxicity.

1.3. Toxicological effects of lead

Lead (Pb) had modest early uses in ancient medicines and cosmetics. Today, it has industrial uses in, for example, building materials, paints, and gasoline but it has no beneficial role in our body. It enters in our body through multiple routes and also from different types of source like air, soil, pesticides, bathing, waste from the battery industry, leaded gasoline and also from the tobacco either smoking tobacco or smoke less. Then gets distributed and stored in almost every organs of the body resulting in the defective functions of the organ. [16] Lead is a highly poisonous metal affecting almost every organ in the body. Generally nervous system is the mostly affected or target organ, both for children and adults. Infants and young children are especially sensitive to even low levels of lead, which may contribute to behavioural problems, learning deficits and lowered IQ.[17] Different studies are also shown that the biochemical and toxicological effects of lead have indicated deleterious effects to hematopoietic, renal, neurological, reproductive, and skeletal system.[18]

1.4. Toxicological effects of arsenic

Tobacco, mainly cigarette smoking is the most important exposure of arsenic to the human body which influence the toxicity. Because As-containing pesticides used in tobacco farming remain in tobacco through processing into cigarettes and is present in small quantities in cigarette smoke. But the smoking is not only one source of arsenic but it can be also enter in our body through the second way like air, water, soils, foodstuffs and anthropogenic sources etc. [19] The third type of sources are sedimentary and meta-sedimentary bed rocks, paints, dyes, soaps, metals, certain drugs are contains arsenic, pesticides, fertilizers and animal feeding operations also release arsenic to the environment in higher amounts. Arsenic toxicity can be either acute or chronic. Lower levels of arsenic or acute exposure of arsenic toxicity can causes nausea and vomiting, reduced production of erythrocytes and leukocytes, pricking sensation in hands and legs, damage to blood vessels and abnormal heart beat is seen. And chronic arsenic toxicity is termed as arsenicosis most of the reports of chronic arsenic toxicity focus on skin manifestations, internal cancers, neurological problems, pulmonary disease, peripheral vascular disease, hypertension and cardiovascular disease and diabetes mellitus. [20] Pigmentation and keratosis are the specific skin lesions that indicate chronic arsenic toxicity.[21] Sometime the arsenic are highly carcinogenic and can cause cancer of lungs, liver, bladder and skin.[19]

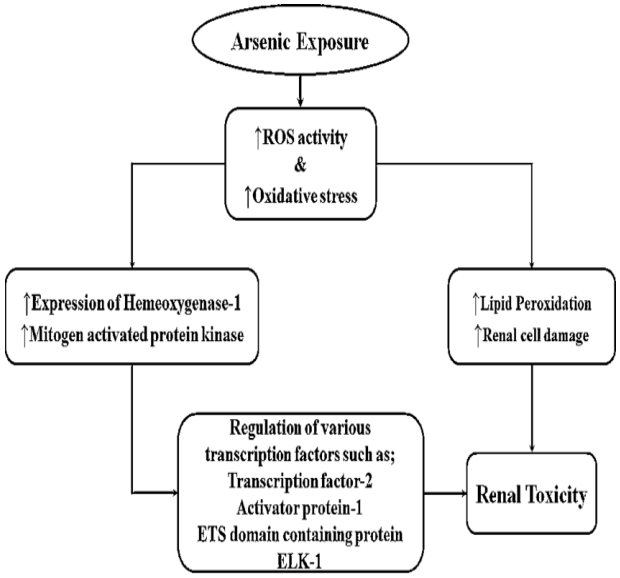

Figure 2: Mechanism of arsenic toxicity.

2. Role of vitamins against toxicological effects of heavy metals

There are a number of possible interactions of micronutrients with secondary mechanisms of toxicity occur by the heavy metal. There are several studies proved that the micronutrients intake has a significant effects on toxicity induced carcinogenesis caused by various toxic metals. Vitamins, the important part of micronutrient act as an organic molecule (or related set of molecules) needs in small quantities for the proper functioning of its metabolism. Essential nutrients cannot be synthesized in the organism, either at all or not in sufficient quantities, and therefore must be obtained through the diet from different types of food sources. There are several classes vitamins like water soluble and fat soluble but all vitamins are not help to reduce the metal-induced toxicity level, some of them are play vital role in metal toxicity, these are vitamin-C, vitamin E, vitamin A etc.

2.1. Vitamin E supplementation on metal toxicity

2.1.1. Protective role of vitamin E on cadmium toxicity

Vitamin E is a very vital micronutrients it contains eight natural fat-soluble compounds, including 4 tocopherols like d-alpha-, d-beta, d-gamma and d-delta-tocopherol and 4 tocotrienols likes d-alpha-, d-beta-, d-gamma- and d-delta-tocotrienol.[22] Vitamin E has various important roles like increased immune function, DNA repair; help in metabolic process, beside this it also act as an antioxidant; so it can help scavenging free radicals. A major contributor to non-enzymatic protection against lipid peroxidation.[23] and prevents the cell by scavenging free radicals in biological membranes.[24] There by it also protect the cell from metal toxicity because metal generate free radicals in our body and effects many organs. Cadmium enters in our body through different way and accumulation in various organs. If the Cd retained in our body for a long period, it may promotes oxidative stress in tissues by increasing lipid peroxidation.[25] It also contributes to developed different pathological problem in different organ of our body. The activity of Glutathione-S-Transferees (GSH) in liver is frequently decreased depending upon the accumulation of Cd. The effects of Cd on GST is generally occur its high affinity. Generally the reactions of glutathion with Cd may result complex formation or the oxidation of glutathion. [26] The rate of lipid peroxidation may decrease by several dietary antioxidants.[27] Vitamin E is one of the most important antioxidant, which can protect the cellular structures by reducing oxidation reduction reaction. Vitamin E scavenging peroxyl radicals and then vitamin E converted into tocopheroxyl radicals and after that it return to its original structure by reacting with any soluble antioxidants.[28] There by the cadmium induced oxidative stress which effects mainly kidney and liver, may be control by the help of vitamin E.[29]

2.1.2. Protective role of vitamin E on chromium toxicity

Chromium in minimal requirement is need to perform normal function of our body .But In large amount of chromium may accumulate in our various organ which may be toxic and sometime it also act as a carcinogenic agent. Chromium (VI) can easily pass through cell membrane because of its low molecular weight then convert into its more stable form chromium (III). This is a metabolism process of chromium (VI) which generate the ROS (Reactive Oxygen Species), it interfere with the normal function of protein, lipid, DNA and produce cellular oxidative stress. Chromium induced oxidative stress may increased MDA (melondialdehyde) levels as well as decrease the glutathione level and also glycogen level in liver.[30] Vitamin E plays a vital role to reduce the chromium toxicity level by re-establishing the GSH, SOD,CAT, and also reducing the levels of MDA levels their by recovery of impairment of cells.[31] So alpha-tocopherol or vitamin-E is able to reduce the chromium toxicity level.

2.1.3. Protective role of vitamin E on lead toxicity

Vitamins are organic compounds which are not synthesized in our body but necessary in the diet very little amount for normal growth and healthy body. Lead is probably the most broadly studied heavy metal because of its various cellular, intracellular and molecular mechanisms behind the toxicological manifestations caused by lead in the body. A free radical can be defined as any molecular species capable of independent existence that contains an unpaired electron in an atomic orbital. Many radicals are unstable and highly reactive. They can either donate an electron to or accept an electron from other molecules, therefore behaving as oxidants or reluctant. In case of lead, free radicals are generating by two way. Firstly lead generates the ROS (Reactive Oxygen Spices) by producing singlet oxygen, hydroperoxides and hydrogen per oxide etc. Secondly the amount of antioxidant is slowdown.[32] Vitamin E help is both conditions, it is an antioxidant

molecule is stable enough to donate an electron to a rampaging free radical and neutralize it, thus reducing its capacity to damage. These antioxidants delay or inhibit cellular damage mainly through their free radical scavenging property. These low-molecular-weight antioxidants can safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. [33]

2.1.4. Protective role of vitamin E on arsenic toxicity

Arsenic can cause acute and chronic poisoning. Gastrointestinal, cardiac, renal, bone marrow, central nervous system and hepatic damage may be noted at different stages of arsenic poisoning. Chronic arsenic exposure has also been associated with a greatly elevated risk of cancer; possibly cancers of lung, liver, and kidney.[34] But some dietary antioxidant likes vitamin E increase the metabolism of arsenic and creates a burden to stop arsenic toxicity. Vitamin E is a fat soluble vitamin, scavenging free radicals and protects the cell from lipid peroxidation. It also acts as a enzyme which help to stimulate antibody production. Heavy exposure of As in detected in our different organs like kidney, liver, lungs blood etc increase serum biochemical parameters. Some workers have suggested that such effect may be the results of cellular damage or increased plasma membrane permeability. Several studies from several countries about arsenicosis are done but the exposure of arsenic in our body through different route is not controlled the only way to administration as vitamin.[35]

2.2. Vitamin C supplementation on metal toxicity

2.2.1. Protective role of vitamin C on cadmium toxicity

Soluble cadmium salts can accumulate in any organs liver, kidneys, testes, lungs, heart, and brain, through different types of sources industrial or smoking. But among them kidney is the most target organ, kidney can be affected by very minimum amount of cadmium. Cadmium is also help to production of ROS (Reactive Oxidative Species) , sometimes our body natural defence system are failed then oxidative stress may seen. At a low concentration of ROS generation may hamper several physiological processes such as apoptosis, fermentation and proliferation. At a high concentration, ROS are extremely toxic to our body it may cause DNA damage, lipid peroxidation, and protein degradation and ultimately damage the cell as well as organ. When our body's normal defence system like antioxidant enzymes are failed, in this situation some small molecular antioxidant like vitamin C is help to protect our body from free radicals. Vitamin C or ascorbic acid interferes with oxidizing radicals. Vitamin C scavenging aqueous ROS generation by rapid electron transfer, it may stop or inhibits lipid peroxidation and protect our cell. [36]

2.2.2. Protective role of vitamin C on chromium toxicity

Chromium exist in our environment in various oxidative states like Cr^{3+}, Cr^{4+} , Cr^{5+},Cr^{6+} but the more predominant oxidative state is Cr^{3+} and Cr^{6+}. By this chromium metabolism process free radicals or ROS production is occur and damaged the living tissue of various organs. To protect the oxidative damage our body has some defence system, beside this some non enzymatic antioxidant like vitamin C is also help to lower the oxidative stress. It is well known that vitamin C is an important biological reducing agent in humans and animals, which has the capability of reducing Cr (VI) induced structural and functional damaged. [37] Chromium-VI also increase the risk of hypothyroidism by decreasing the free tri-iodothyronine (FT3), free thyroxin (FT4). This may include hyperplasia, colloid retraction and resorption, which were readily discernible.[38] Some laboratories results shown that this Cr (VI) induced hypothyroidism may be treated by vitamin C. The mechanism of vitamin C help to decease the FT3 and FT4 hormones is still unknown. But the some studies prove that vitamin C is help to back thyroid hormone to its normal value.[39]

2.2.3. Protective role of vitamin C on lead toxicity

Vitamin C is a water-soluble vitamin which is necessary for normal growth and development. It is required for collagen synthesis which is necessary for skin, tendons, ligaments, and blood vessels formation. Vitamin C helps in the wound healing and formation of scar tissue. It repairs and maintains cartilage, bones and teeth and acts as one of the major antioxidant. Several studies results show that RBC membrane structure and function may be impaired due to the accumulation of lead. Lead interferes with oxy-haemoglobin and generates free radicals, therefore osmotic pressure is increased. [40] Lead toxicity may alter the membrane enzymes activity and composition of membrane proteins. The toxicity of lead is treated by the antioxidant vitamin C, this vitamin help to absorption dietary iron and iron help to increase the activity catalase enzyme. Catalase has a predominant role in the disposal of hydrogen peroxide in human erythrocytes. Catalase enzyme help to scavenging free radicals produced from the lead toxicity and protect the cell.[41]

2.2.4. Protective role of vitamin C on arsenic toxicity

Arsenic is recognized globally as the most serious inorganic contaminants in drinking water, as there is no safe and effective treatment for the cases of arsenic poisoning. It is very toxic metal for our body; acute exposure of it can hamper several normal function of our body, it is suspected that the arsenic impair testicular function via an oxidative stress. As also decreases the GSH level in kidney and liver, if the GSH level is decrease then it failed to donate electron at the conversion time of pentavalent arsenicals into trivalent arsenical. Thus, it is possible that the depletion of testicular GSH levels by arsenic may ultimately make the testicular cells even

more sensitive to oxidative stress. So male reproductive system may be affected by arsenic toxicity and decreases in epididymidal sperm count, testicular 17β-HSD and 3β-HSD activities. Vitamin C play a vital role by trapping the free radicals and also increase the level of GSH their by the effects of arsenic on our body is decreases. [42]

3.3. Beta-carotene supplementation on heavy metal toxicity

3.3.1. Protective role of Beta-carotene on cadmium toxicity.

Several study shown that beta-carotene along with $CdCl_2$ is did not cause any significant changes in our body because beta carotene act as an antioxidant which trapped free radicals and protect the organ. The nature of beta carotenoids is lipophilic, so it has a tendency to react with hydrophobic substance. Thus, it is reacting with the lipid core hydrobhobic membrane; thereby it helps to protect the cell membrane from cadmium induced oxidative stress and cell damage. [43] Cadmium is widely distributed in the environment because of its many industrial applications. The health risk to humans from acute and chronic cadmium exposure has been well documented. Previously, It was reported that single-dose cadmium administration increased lipid peroxidation and decreased GSH in the liver. [44] It was proved by some studies that the lipid peroxidation level is decreased by beta carotene but the mechanism is still unknown.[45]

3.3.2. Protective role of Beta-carotene on chromium toxicity

There are several antioxidant vitamins are present, beta-carotene is one of the most effective naturally occurring antioxidant which prevent lipid peroxidation and protect the cell. Beta -carotene inhibit the apoptosis process done by chromium their by prevent the apoptosis process. Beta-carotene trapping the free radicals, which produced mainly when the chromium loss their electro and transfer one from to another form. Beta-carotene help to scavenger singlet oxygen molecules and inhibit the chain reaction occur within the cell their by prevent the lipophilic radicals, lipid peroxidation and prevent to occur any diseases done by chromium toxicity.[46]

3.3.3. Protective role of Beta-carotene on lead toxicity

The mechanisms of lead-induced oxidative stress include the effect of lead on cell membrane, DNA, and antioxidant defence systems of our body. There are generally two way by which lead damage the cell membrane. On cell membrane, the presence of double bonds in the fatty acid weakens the C/H bonds on the carbon atom adjacent to the double bonds and makes H removal easier. Therefore, fatty acids containing zero to two double bonds are more resistant to oxidative stress than are the polyunsaturated fatty acids with more than two double bonds. [47] After incubation of linolenic, and arachidonic acid with lead, the concentration of a final product of oxidative stress, malondialdehyde (MDA) was increased with the number of double bonds of fatty acid.[48] Another mechanism for lead induced membrane oxidative damage is the effect on changes in the fatty acid composition of membrane because fatty acid chain length and instauration are associated with membrane susceptibility to peroxidation in later increasing lipid peroxidation rates.[49] Several studies are proved that beta-carotene is helpful for the prevention of lipid peroxidation; thereby prevent some diseases including multiple sclerosis, atherosclerosis, age-related macular degeneration, and cancer. The antioxidant effects against lead toxicity by different algae or food containing beta-carotene is seriously helpful for those are working lead exposure factories or heavy smoker. Some experimental reported that the beta-carotene help to increase the SOD level and GPx level, these both enzymes play a defence role against oxidative stress. Carotenoids also scavenging free radicals and prevent the lipid peroxidation to protect the cell.[50]

3.3.4. Protective role of Beta-carotene on arsenic toxicity

Beta-carotene, like all carotenoids, is an antioxidant. An antioxidant is a substance that inhibits the oxidation of other molecules; it protects the body from free radicals. Several studies reported that antioxidants through diet help people's immune systems, protect against free radicals, and lower the risk of developing cancer and heart disease. B-Carotene is an antioxidant that has greater efficacy against the reactive oxygen species singlet oxygen ($^{\cdot}O_2$) compared with vitamin E and vitamin C. [51] Chronic ingestion of arsenic causes the development of skin lesions. Taiwanese study that determined that low serum beta-carotene levels were associated with increased risk of arsenic-induced skin cancer. [52] β-carotene also possessed remarkable ameliorative effect against arsenic-induced toxicity in albino mice mediated by its antioxidant and antigenotoxic properties. Some researchers have postulated that deficiencies in specific nutrients, such as beta-carotene may increase susceptibility to arsenic. [51]

DISCUSSION

Metals, are present in tobacco either smoking or smokeless tobacco induce a wide range of physiological, biochemical, and behavioural dysfunctions via induction of oxidative stress in humans. Tobacco compounds are toxic complex and reactive mixture containing an estimated 5000 chemicals. Among them here we study four heavy metals like arsenic (As), cadmium (Cd), chromium (Cr), and lead (Pb). These four metals are very common in our environments, their source is not only the tobacco but also different types of factories are good source of this metal. Minimal amount of metals is need our body to do various functions like increase metabolism, dental applications, reduce the atherosclerosis risk etc, but if the amount of heavy metals enter in our body is high then it can be accumulate in various organs like kidney, liver, lungs . Different types of metal enter in our body through the ingestion or inhalation, their mode of action is also different. The notable effects are generally seen in lung,

liver, and kidney because the metals present in the tobacco can easily enter into our body through the lungs and most of the metals are accumulate in lungs and liver and affected them by creating different diseases. Despite that kidney helps in filtration and reabsorption of all the metals that's why kidney is also get affected by tobacco inhalation.

Cadmium accumulates in the liver and kidneys and has a long biological half-life of 17 to 30 years in humans and also damage several vital organs, among which the most sensitive are the kidney, the bone and the respiratory tract. Cd absorbed in the intestines is delivered first to the liver via portal circulation, bound mainly to albumin, where it is taken up from the sinusoidal capillaries to the hepatocytes. Oxidative and nitrative stress developed in response to toxicants damaging bio molecules as well as disrupting signalling pathways, which in turn leads to pathogenesis of multiple human diseases. Cd-induced hepato toxicity is closely related to inflammation, since after acute exposure, the damaged liver is often infiltrated by polymorpho-nuclear neutrophils (PMN), which, in addition to Kupffer cells, contribute to the hepatotoxicity by enhancing inflammatory mediators and promoting necrosis. Cadmium is also producing free radicals through lipid per oxidation and effects several organs. Some vitamins like beta-carotene, vitamin E and vitamin C play a potent role to reduce the toxic effects of cadmium and protect the cell apoptosis. Vitamin E scavenging peroxyl radicals and then vitamin E converted into tocopheroxyl radicals and after that it returns to its original structure by reacting with any soluble antioxidants.[28] There by the cadmium induced oxidative stress may be control by vitamin E supplementation.

Chromium such a types of metal which enter in our body as a form of chromium (VI) but then it may convert more stable form of chromium Cr (III). This process produces ROS; in this review we can see that there is a possible correlation between diseases and the exposure of ROS generation. Buffering and muffling reactions between ROS generation and elimination to redress the deleterious effects caused by oxidative stress are maintained by complex antioxidant (enzymatic and non-enzymatic) systems. In terms of a reactivity standpoint, the enzymatic antioxidant system constitutes the first line of defence, followed by reduced thiols and low molecular weight antioxidants and then by a broad range of products from dietary sources (vitamins and minerals). Our body's normal defence systems for overcoming the deleterious effects of oxidative stress generated by production of reactive oxygen species (ROS) are essential to maintenance of cellular homeostasis by depletion of the cellular antioxidant pool characterized by enzymes such as (GPx) glutathione peroxidase, GSH-reductase, GSH-transferees, catalase (CAT) and superoxide dismutase (SOD) that contribute significantly to the metabolism and detoxification of reactive oxygen species (ROS). But sometimes heavy metals are inhibition of the activities of such enzymes and increase the production of ROS, lipid per oxidation may occur and various diseases is born from it .There is a another way to depletion of free-radical scavengers by dietary supplements like beta-carotene, Vitamins E and vitamin C. These vitamins have antioxidant property. So they can engulf free radicals and protect cell from toxicity.

Lead is a very dangerous metal, from a several decades it use as production of medicine but if it enter in our body high amount then it may contribute to several diseases behavioural problems, hypertension, kidney problem learning deficits and lowered IQ etc. The mechanism of lead induced toxicity is not fully understood. It was reported that low level of lead toxicity may lead to renal disorders.[53] The association between PbB and cystatin C/serum creatinine in the general population is present also within a normal range of estimated GFR and almost at the detection limit of PbB. This may be indicative of the fact that factors other than glomerular filtration are involved in the cross-sectional relationship. Some vitamins are help to decrease the lead effects on renal like vitamin E accept free radicals and make them H_2O and O_2. Ascorbic acid help to excrete lead through urine without hampering any organ.

Arsenic is recognized globally as the most serious inorganic contaminants in drinking water, as there is no safe and effective treatment for the cases of arsenic poisoning. One case control study characterized by low-to-moderate arsenic exposure levels, found a statistically significant positive dose-response relationship between urine arsenic and CKD status assessed based on eGFR arsenic exposure levels, found a statistically significant positive dose-response relationship between urine arsenic and renal disease. Among the studies that did not adjust for confounders, arsenic levels were higher in urine and blood. In a study from Austria, median serum arsenic levels were similar in participants on dialysis compared to healthy non-dialysis participants. Overall, based on direction and strength of the associations, temporality and evidence for a dose response, the evidence is mixed for an association between arsenic and CKD outcomes at both high and low levels of arsenic exposure. CKD status assessed based on GFR. Some dietary antioxidant likes vitamin E increase the metabolism of arsenic and creates a burden to stop arsenic toxicity. Arsenic also produces lipid peroxidation through free radicals generation. Vitamin C can help to screening them and stops lipid peroxidation. Effects of beta-carotene on arsenic toxicity are still not clear.

CONCLUSION

However, some heavy metals are produce in our environment through different types of industry or smoking and they enter in our body through different route. These heavy metals are very harmful of our body at a high dose, sometime at a low amount are also less toxic. Our body has normal defence system (enzymatic or non enzymatic) but when the toxicity level is too high

and body's normal defence system not working properly then dietary supplementation are needed. Some vitamins like vitamin E, vitamin C and beta-carotene, act as an antioxidant and they are most potent against heavy metal toxicity. Different foods are the major sources of vitamins. Mechanism of the supplementation of these vitamins against metal toxicity is not still clear but several studies proved that vitamins play a vital role to counteract the heavy metals-induced toxicity.

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