

Chromium and selenium concentration in cancer



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The ratio between chromium and selenium concentration among various age groups of cancer group has also been studied and it shown in table 5. 48, and it has been observed that all groups of cancer patients present somewhat similar ratio of chromium and selenium concentration in their blood. Moreover, the concentration balance of chromium and selenium has conspicuously been disturbed as it illustrated in table 5. 49. For instance, the breast cancer mortalities in various countries were studied and ascertained a direct correlation with the estimated dietary intake of zinc, chromium and cadmium and inversely proportional to the concentration of selenium (238).

The summary of stage wise distribution for chromium and selenium has been illustrated in Table 5. 50 and it observed that all four stages of cancer patients present a sort of consistency in chromium and selenium proportion in the blood of cancer patients as shown in Table 5. 51. In view of this fact, it may be elucidated that the demarcation among various stages of cancer is arbitrary division and this periphery does not present any association of stages with the distribution-ratio of chromium and selenium in the blood of cancer patients.

However, the reduction of $0.064 \mu\text{g ml}^{-1}$ of selenium concentration in the blood of cancer patients corresponds to more than 52 % decrease as compared to the selenium level in the blood of control group. These variations in concentration may be the result of the disease of cancer however the type of cancer does not influence the levels of selenium in the blood of cancer patients.

However, the significant decrease in selenium concentration in whole blood and plasma has been observed in another study where the tannery workers were exposed to chromium compounds and have shown a considerably lower selenium concentration in their blood and they excreted lower amount of selenium in their urine as compared to the worker those were not exposed to the chromium. It may confirm the point of view that chromium and selenium have some kind of interaction and biological selenides are formed with chromium and in due course of time they accumulate in some organs. It was also demonstrated that the tannery workers who were exposed to air with high concentrations of chromium compounds at their workplace exhibited significantly higher erythrocyte and plasma GSH-Px activity than workers of other departments (239).

Therefore, higher level of selenium stipulates the main function of selenium is to induce and maintain the enzyme glutathione peroxidase, which prevents cellular damage by catabolizing organic peroxides (240)

The enzyme, SeGSH-Px, catalyzes the oxidation-reduction reaction between reduced glutathione and peroxide. Therefore, the pathological lesions lured with selenium deficiency are considered to be caused by peroxidative damage that is the product of depressed SeGSH-Px activity (241-242).

However, once chromium absorbed and retained in biological tissue chromium compounds occur as chromium (III). Glutathione and cysteine seem to be the most important cofactors for the intracellular reduction of chromium (VI) (243).

The absorption of metal in the human body is a complex process and depends on various factors including dietary components. About 40% of ingested metal is absorbed in the small intestine (244). Furthermore, a variety of neurodegenerative diseases such as Alzheimer's, Parkinson's, Creutzfeldt-Jakob, and neuronal damage caused by stroke and ischemia may be associated with pathological disruption of metal trafficking (245-247).

Chromium is potentially toxic and carcinogenic at higher doses. All chromates that exhibit oxidation state (VI) can aggressively enter the cell through channels that are specified for the transfer of isoelectric and isostructural anions, such as SO_4^{2-} and PO_4^{2-} . However, the insoluble chromates are engrossed by cells through phagocytosis. As soon as the chromates get inside the cell they are competent enough to generate free radicals immediately. Yet, in the presence of cellular reductants the chromium inside the cell can cause a broad series of DNA lesions such as DNA-protein crosslink, Cr-DNA adducts, DNA-DNA cross links, and oxidative damages. The glutathione quickly reacts with chromium (VI) and forms a complex and generate chromium (V) and chromium (III) through slow reduction of chromium (VI) inside the cell. The chromium (V) and chromium (III) species exhibit the tendency to alter the DNA conformation. The reduction of chromium (VI) can be commenced through GSH, or in the presence of other reducing agents. The chromium (V) and chromium (III) can react with H_2O_2 through Fenton reaction and produce hydroxyl radical ($\cdot\text{OH}$) that has the potential to damage DNA. There are evidents that interacellular reduction of chromium (VI) results in extensive formation of Cr-DNA adducts, among which chromium (III) - mediated DNA cross-link of

glutathione, cysteine, histidine and ascorbate represent an important group of DNA modifications. Therefore, Cr- DNA adducts are responsible for both the mutagenicity and genotoxicity of chromium. The chromium (VI) is considered as carcinogen for lungs cancer for human (248). Numerous epidemiological studies have been performed for more than 100 years on workers exposed to chromium in order to determine its level of carcinogenicity. Altogether, these studies indicate that exposed individuals have approximately 2- 80 fold increased relative risk of developing lungs cancer (226).

On the other hand, an inverse association between serum selenium level and cancer risk is biologically possible. The results of the study indicated that the treatment with selenium improved GPx levels. GPx detoxifies H_2O_2 by reducing it to water. It also protects cytosolic organelles from oxidative damage by preventing lipid peroxidation. Selenium could reduce oxidative stress through antioxidant selenoproteins such as glutathione peroxidase, selenoprotein P, and thioredoxin reductase. (249-250).

There are numerous promising possibilities that may be presented as an account for the observed variations for selenium in whole blood levels associated with malignant disease, as compared to healthy and control group (251). It includes chemotherapeutic-induced necrosis, which could release selenium from tissues into the circulation, preferential sequestration by tumor cells (252-253) and alteration of properties of proteins, especially enzymes, at elevated concentration of selenium in tissues (254-255).

Furthermore, the possibility of depression in activities of specific enzymes

with loss of vital enzyme activity, and impaired tissue function resulting from a selenium-deficient state (256).

The depletion of selenium in the blood of cancer patients may suggest its reciprocal accumulation in the malignant tissues in view of the studies (257-261) who have reported higher concentration of selenium in the cancerous and neighboring tissues cells. Availability of excessive selenium in the cancerous cells may be expected to facilitate the synthesis of selenoproteins e. g. Trx, TrxR etc. which are known to provide protection to the tissue cells against the oxidative stress, carcinogens, and help to reduce cancerous cell growth. The results of recent studies (262-264) regarding the diversified multiple functions of selenoproteins has generated tremendous interest in the understanding and elucidation of mechanisms that triggers the role of these proteins from anti-apoptosis in the normal cells to pro-apoptosis in malignant cells. There are numerous studies (265-267), who have proposed different mechanisms to explain the inhibiting effect of selenium on malignant neoplasm; for example modulation of cellular division rate, decrease in formation of carcinogenic metabolites or cellular protection by an antioxidant system. It is generally believed that due to the anti oxidative characteristics of selenoproteins, these proteins can protect the cells and DNA from oxidative damage; in addition, these proteins can react with carcinogens directly to save cells and DNA from their lethal actions. It has been suggested (263), that nitrative inactivation of Trx plays a proapoptotic role if the reactive nitrogen species are increased; and antinitrating treatment may have therapeutic value in those diseases, such as myocardial ischemia/ reperfusion, in which pathological apoptosis is increased. The

situation is reversed in malignant tissue cells where apoptosis is beneficial for the inhibition of the cell growth. Therefore, in view of the aforementioned studies, it is possible that the pathological conditions in which production of nitrogen species is increased that may favor the inactivation of Trx and therefore enhance the apoptotic role of this selenoprotein. A kinetic study of the reaction of NO and O₂ in aqueous solutions, based on pH indicator, has been performed by using stopped-flow spectrometry. The results of these studies have shown that at physiological concentrations of O₂ and NO, the auto-oxidation of NO does not limit its diffusion from the site of production in endothelial cells to a spatially removed target molecule such as guanylate cyclase in myocytes and platelets. A Trx interacting protein Txnip has been reported (31), which inhibit the antiapoptotic activity of Trx where as NO suppresses the expression of Txnip and enhances the Trx activity, therefore perhaps the oxidative character of Trx in malignant cells as reported in the above mentioned studies may well be interpreted as the inhibition of its antioxidant activity. In different studies (267-268) it has been suggested on the basis of their results that selenite induces apoptosis by producing superoxide ions which activate p53, a well known protein involved in carcinogenesis, which in turn support apoptosis. A key role has been assigned (269), to Trx-2, located in mitochondria, in interaction with electron transport chain, determining tumor necrosis ROS generation, NF- κ B activation and apoptosis.

Intestines are the main sites where selenium absorption is measured at maximum. In liver selenium joins many other amino acids and generate selenocysteine and selenoproteins. Selenoproteins consist of active form of

selenium and are transferred to all over the body. Kidney and liver, however, have higher concentration of selenoproteins. It is reported that a small quantity of selenoproteins are also exist in blood and serum. Furthermore, being a part of selenoproteins the selenium is an essential part of glutathione peroxidase as well that is the reason selenium is believed to be an antioxidant (36).

Glutathione plays a role of a protector in the body of an organism and ensnare the balance of free radicals, peroxides and preserves the redox status of the cell (270). In addition, glutathione peroxidase provides defense mechanism against free radicals that may cause destruction of cell membrane. The free radicals are generated when hydrogen peroxide produced in the mitochondria of the cell during the regular metabolism. The stress is a foremost cause of excessive production of hydrogen peroxide that sequentially create a disproportion in free radicals inside the cells. Chemical structure of cell membrane comes under the attack of free radicals and gives away their loosely bounded electrons to the free radicals. Consequently, a chemical structure of cell membrane turns into a reactive entity and begins to instigate an electron from adjacent structure and this chain reaction serves to damage the cell membrane causing the cell to die.

Proactive role as a safeguard of glutathione peroxidase quickly transform hydrogen peroxide into water a way before it could generate harmful reactive species called free radicals. Another study highlights defense mechanism of vitamin E in which glutathione peroxidase and vitamin E follow a similar pathway in order to discontinue the chain reaction by engaging the free radicals within the cell membrane. Therefore, it is an effective

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combination of selenium and vitamin E that can control the production of free radicals and prevent the damage of cell membranes as well as DNA and other cellular structures (270).