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Biochemical Significance of EDTA in Human Physiology

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Abstract: *Ethylene Diamine Tetra-acetic Acid (EDTA) has great significance in human physiology to cure myocardial, atherosclerosis, occlusive peripheral arterial disease and cholesterol metabolism. Many medical researcher's/ scientist's and also clinical practitioners around the world have great interest to cure such problems at low dose without bypass surgery. Many medical researchers/ scientist says that the bypass surgery does not cure the patients and does not remove the actual causes of the problems and does not prevent the heart attacks. EDTA can greatly reduce the release of free radicals which develops as a Bi-products of oxidation-reduction in metabolical reactions. EDTA bind up these ionic metals and make them chemically inert and rapidly removing them from body. To control the cholesterol/ lipid metabolism, the metallic ions must easily change their electrical valence by one unit in lipid per-oxidation process. EDTA also remove or dissolve the calcium deposition in arterial surface where cholesterol ions deposit and in the plaques and atheromas on the arterial surface. It also cure the carcinogenetic process which occur by mutagenic factor of free radicals in human body. It may be probably act by blocking the slow calcium current and biochemical binding of calcium ions in to the arterial surface. In heart patients, EDTA increase the efficiency of myocardial oxidative phosphorylation and improve the myocardial function.*

Keywords: *myocardial problem, EDTA, cholesterol metabolism and free radicals.*

I. Introduction

EDTA generally known as a chelating agent and have a great value in human physiology. It is not present in human body but have great significance in related to the human activity. Medical researchers/ Scientist are using it as disodium salt in different way of life, i.e., in-vitro (for hematological studies) and in-vivo as a chelating agent to cure and treat the different the physiological as well as metabological problems. As EDTA formed a more complex by their chelated effect through a bi-dentate or a multi-dentate ligand i.e., it has greater numbers of points of attachment of ligand to the metal ion and develop more stability of complex. The clinical research related to EDTA chelating therapy came to virtual standstill in 1960 as bypass surgery, first came into vogue. In early work, a data published by Kitchell [1] which reports ended with negative conclusion. In past decade, many medical literature demonstrate that EDTA is not effective to treat the cardiovascular problems in human beings. Further, a lowest dose of EDTA provides a better result as it is used for systolic blood pressure in ischemic extrimities [2].

The use of chelating agent EDTA (disodium salt) as a clinical treatment for atherosclerosis is increasing rapidly worldwide. In this regard, many reports published and confirm safety and effectiveness and intravenous treatment of EDTA for occlusive atherosclerosis arterial problems [3-7]. More than 1 millions patients of such problems have received more than 20 millions infusions without any adverse reactions at low doses. Researchers have also report the laboratory data which provide further support for the effectiveness of the EDTA therapy. The di-sodium salt of EDTA is more effective to cure the cancer and reduce the mortality [8]. EDTA is generally used to remove the toxic elements from the body. These toxic elements are lead, mercury, arsenic also increase in ischemic myocardium and remove by chelating therapy.

The coronary artery problems/ disease developed in human by miss-metabolism of lipids mostly cholesterol. Cholesterol is a precursor to vitamin-D, without cholesterol vitamin-D deficiency may occur. Vitamin-D produced in skin by ultra violet radiations of sunlight. Un-oxidized cholesterol is one of the most important anti oxidant. Sum of the cholesterol derives hormones including dehydro epi -andosterone (DHEA), glucocorticosteriods, testosterone, progesterone, estrogen, etc. are functioned as a free radical scavengers [9]. Total body cholesterol is derived primarily from cholesterol synthesis within liver cells. The serum cholesterol level increase in body due to free radical stress and an indicator of exposer to excessive free radicals which increase the risk of atherosclerosis and apoptosis. When blood cholesterol oxidized in the form of low density lipoprotein (LDL) cholesterol, a risk factor also increase and it contributes to atherosclerosis. Similarly, vitamin-E is statistically hundred times more significant as a predictor of coronary heart disease as compare to high

cholesterol level. Clinically, the laboratory research demonstrated that both EDTA and an antioxidant glutathione prevent the LDL cholesterol production [10].

II. Biochemical Significance

The dietary restriction of cholesterol and drug prescription reduce the blood cholesterol in some way but have a significant toxicity and cost effective much more than anti-oxidant nutritional supplements. In this way, a report has been published as a co-relation between low blood cholesterol and increase the cancer risk [11]. Cancer is caused in body parts, free radicals which damage to nuclear materials and chromosome. The genetic materials mutate suddenly by the adverse effect of such free radicals and cause some syndromic problems in human body. They may be directly affect the DNA synthesis as well as RNA molecule during the protein synthesis. Free radicals act as a primary initiators and subsequent promoters of malignant changes. The cellular respiration requires transfer of electron across mitochondrial membrane within the cell. For every electron a super oxide radicals is produced. An anti-oxidant prevents the damage to vital intracellular structure during this process. In human physiology, the intake food cannot metabolise without free radicals as a bi-product during this process breathe oxygen through lungs and transport into the circulatory system and carbon dioxide release. The super oxide radicals are released during oxidative phosphorylation of ATP molecules and cellular protection provide these radical through mitochondrial super oxide dismutase (SOD), a manganese containing enzymes.

The metabolism of many chemicals including prescription drugs, artificial colors, flavors, inheld fumes takes place in endoplasmic reticulum(ER) of liver cells and other organs, produces many toxic free radicals which influences the body activity and cause the atherosclerosis, cardio vascular problems, carcinogenic characters in human body. The detoxification process releases hydroxyl free radicals and peroxides [12-14].
The leukocytes and macrophages cells also develop free radicals. The disease causing organism are ingested and destroyed by free radicals during phagocytosis. If anti-oxidant is inadequate and some physiological symptoms like heat, pain, redness, swelling develop on human body i.e. without anti-oxidant enzymes life does not exists. When free radical in living tissue exceed the safe level , the cell destruction, malignant mutation, tumor growth , enzymes damages etc. occurred and human body degenerate and finally die. During this process of metabolism, beta carotene is inactivated by free radicals and must be reactivated by other antioxidants e.g., vitamin-C & Vitamin – E.

The lipid peroxidation process begins when it exposed to air and accelerated by heat. Iron and copper are two potent catalyst of lipid per-oxidation which increase the rate of rancidity i.e. oxidation reaction rate (it is a form of oxidized lipid- rancid). The free radical damage contributes to degenerate salinity, Alzheimer's and Parkinson's syndrome, dementia and other nervous system problems. The brain and spinal cord contain the highest concentration of fat of any organs. Nervous system fats are very rich in highly unsaturated arachadonic and docosa-hexanoic acid, because of that the rate lipid per-oxidation increases exponentially with the number of unsaturated Carbon- Carbon double bonds, docosa-hexanoic and arachidonic acid per-oxidize many times more readily than most other lipids.

The brain and spinal cord therefore require anti-oxidant protection. The high concentration of free radicals can damage the nuclear materials in arterial cells and causing mutation and uncontrolled cell replication. It is presumably that the higher concentration of free radical effects and damage the central nervous system (CNS) and causes harmful disease. The neurological characteristics are particularly depend on voltage sensitive and ion sensitive conductance channels which regulate the function of post synaptic neurons. They come into functional importance only when the neuronal membrane potential is moved away from resting values. These sensitive ions are atleast potassium (K^+), calcium (Ca^{++}) & chloride (Cl^-). K^+ or Ca^{++} is mediated has been reported to be linked to transmitter receptors complexes [15-17].

Lipid peroxidase increase the activity of guanylate-cyclase which spread mitosis. Cell damage of this type may occur in any part of the body and die as cell membranes become leaky. DNA damage result in mutation, atheromata and cancer. Lymphoid tissues and other cells of the immune systems also become damage rapidly and related tissue become stiffer and lose their flexibility as cross linkage in connective tissue elastin and protein molecules which results the organ function Detroit [12,13, 18]. The patient joints become inflamed, hypertrophic and deformed with arthritis. Antibody production and cellular immunity are impaired by free radicals. The oxidized cholesterol and lipid peroxides are potent immunosuppressant's [12, 13].

The use of EDTA can help to support the normal healing and inactivate such catalyst as EDTA combine with dietary fat restriction to eleviate the progression of multiple sclerosis (MS) [19, 20]. EDTA increase the efficiency of mitochondrial oxidative phosphorylation and improves myocardial function, quite independently of any effect of arterial blood flow. In human body the every cell is with fat in the form of bi-polar phospholipid membranes. Towards outer and inner surface, a water soluble polar end whereas toward the center of the membrane a fat soluble non-polar end present. Normally the phospholipid allows them to twist around each other in cis configuration. The un-oxidized cholesterol required to prevent the damage widely

disbursed within the cell membrane and act as an anti-oxidant including with vitamin-C, vitamin-E, co-enzyme Q-10, etc. Similarly free radical also damage the calcium-magnesium metabolism which results to deposition in blood artery and cause a factor of atherosclerosis and coronary disease. Free radical damage causes calcium to leak into smooth muscles in arterial valve which wind up to calmodulin, activating myosin kinase. In this way EDTA remove the free radicals and dissolve the problems of coronary disease in human beings [10, 13]. EDTA binds those ionic metals which is necessary to catalyze the lipid per-oxidation and tiny traces remaining in distilled water can initiate and accelerate the reaction [21]. For lipid per oxidation catalyze, a metallic ion must easily change their electron valency by one unit and to essential element (nutritional), iron and copper are most potent catalyst.

III. EDTA Affinity

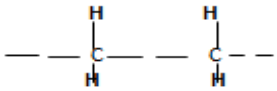
The affinity of EDTA to blood with calcium, magnesium, iron, copper, lead, zinc at physiological pH are inorder to decreasing stability are Fe^{3+}, Cu^{2+}, Pb^{2+}, Ca^{2+} and Mg^{2+}.Fe^{3+} is in top whereas Fe accumulate slowly in women because of monthly iron loss in menstrual period [22]. Due to these cause, younger women have more protection against atherosclerosis in comparison to aged women. The risk of atherosclerosis in men are four times more of same age group. After, hysterectomy, the risk of atherosclerosis, cardiovascular disease is equal to the male persons with or without hormones replacement (when ovaries are not removed) [23].

It is clearly indicated that slower iron accumulation reduces the atherosclerosis. Similarly, periodic donation of blood to the blood bank, prolong to life expectancy. During EDTA therapy, it has high affinity to un-bound iron and effective rapidly to remove it from body.

By reducing the damage of free radicals, EDTA therapy play an active role for healing damage tissues for the time lapse of several month following chelation before full benefit are achieved. The other benefit of EDTA chelation occur from uncoupling of di-sulphide and metallic cross linkage between molecules through normal calcium metabolism, by reactivation of toxic metal ions and restoration of normal protocyclin production along arterial walls. Now, this well documented effective and without any adverse effect, this therapy may be accepted worldwide.

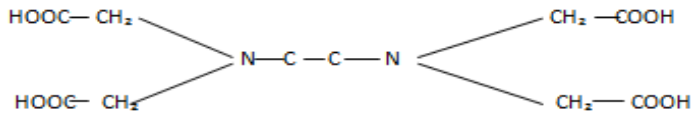
Ethylene Diamine Tetraacetic Acid (EDTA) is a stable disodium salt at room temperature.

Ethylene

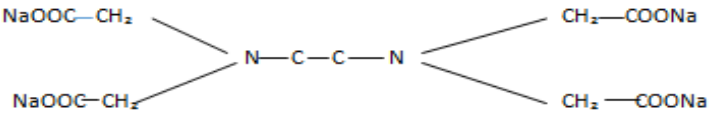


Diamine (containing two amino group attach with carbon atoms of ethylene).

and acetic acid group attach with each nitrogen atoms i.e.,

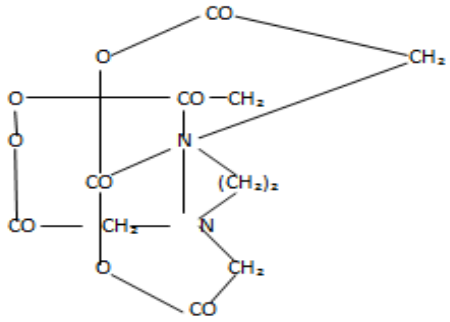


And this stage of compound react with two sodium molecules and develop di-sodium stable compounds.



And it has six pairs of unshared electrons which can donate a cation. These six atoms are also known as dentate i.e. teeth of the EDTA molecule which bind up with calcium ions.

Chemical Structure: Calcium ion bounded EDTA



As EDTA active to reduce the release of free radicals because of that it bind up the ionic metals e.g. calcium etc. and make them chemically inert and rapidly remove them from human body. It occurs may be due to the presence of 1,2-diamine ethane tetra acid (an excellent complexing agent) and 1,2- diamine ethane tetra acetic acid (ethanoate ions are able to form ethanoate complex with nearly all poly valent cations) [24].

The dissociation constant of that two hydrogen atoms are probably held in the form of Zwitterious. The pK value of that ions are $pk_1 = 2.0$, $pk_2 = 2.7$, $pk_3 = 6.2$ and $pk_4 = 10.3$ at 20°C. These values are suggesting that it behave as a di carboxylic acid with two strongly acidic group and two ammonium protons. The first group ionizes is about at 6.3 pH region and second in about 11.5 pH.

Similarly, the effect of EDTA on cholesterol metabolism and other free radicals to remove or reduce some metallic ions may occur at different pH level during physiological and metabolical reactions and develop a stable complex. All these stable complex are soluble in aqueous medium and easily tolerate and excrete by human body. Chemically, cholesterol ($C_{27}H_{45}OH$) is a white or faintly yellow odourless. Crystal form and affected by light. Melting point of cholesterol is 148.5°C, boiling point is 360°C, specific gravity of 1.067 at 20/4°C and specific rotation 34-38° at 25°C. it has great affinity with calcium layer in the arterial wall of human body.

The stability constant (log K) of different metal with EDTA are:

Ca^{2+}- 10.7, Fe^{2+}- 14.3, Cu^{2+}- 18.8, Na^{+}- 1.7, Fe^{3+}- 25.1

The minimum pH at which complex exist are: 1-3 for Fe^{3+}, 4-6 for Fe^{2+} & Cu^{2+} and 8-10 for Ca^{2+} & Mg^{2+}.

During the biochemical reaction to remove calcium ions from arterial atherosclerosis (a stage of cholesterol layer on calcium ion) it bind up with calcium ion as tetrahedrals and hexahedral stage and develop a calcium complex with two protons liberation.

IV. Conclusion

Thus EDTA is most active disodium salt to remove the free radicals and toxic element from human body as it uses in small dose in vivo (intravenously). It has great potential to cure & treat the atherosclerosis, cardiovascular problem including different malignant, non-malignant, cellular damage; disease in human body without any adverse effect. It also has a property to treat the mutagenic syndromic, carcinogenic problems that occurs due to the free radical production during metabolic reaction (oxidation-reduction) at different physiological pH in human body. There is no de-calcification occurs in bone and other part due to the strong stable calcium-phosphate compound available in human body.

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