



International Board of Clinical Metal Toxicology

CHELATION AND DETOXIFICATION

CHELATION.

Clinical Metal Toxicology is the medical concept of “chelating” harmful metals. We use chelating agents in the treatment of pathological conditions. Examples are atherosclerosis and lead intoxication.

The Greek origin of the word chelate signifies the plier-like claws of a crab.

The most widely accepted use of chelation therapy in medicine is for the removal of toxic metals, such as lead, arsenic, cadmium, mercury, iron, copper or aluminum from the body. A more controversial, but clinically useful indication for chelation therapy, and more specifically disodium EDTA chelation therapy, is the treatment of all forms of atherosclerotic diseases, including, coronary, cerebral, and peripheral arterial disease as well as other degenerative conditions.

A chelate is a water-soluble complex between a metal ion and a complexing agent. It may further be defined as: an equilibrium reaction between a metal cation and a complexing agent characterized by the formation of more than one bond between the cation and the complexing agent resulting in a heterocyclic ring structure, incorporating the metal ion. The complex usually does not dissociate easily in solution, but forms an inert complex. In labile complexes, however, the metal ion can be readily exchanged. Metal complexes of transition elements are well known here, chelation occurs within a much wider range of elements. Chelating agents yielding soluble metal complexes are also called sequestering agents. Chelating agents control metal ions by blocking the reactive sites of the ions and preventing them from normal activity. This phenomenon is in effect as long as the chelator is present in the body

A chelating agent has at least two functional groups which donate a pair of electrons to the metal, such as = O, -NH₂ or -COO⁻. Furthermore, these groups must be located so as to allow ring formation with the metal.

Chelating agents are widely found in living systems and are of importance in cellular metabolism. For example, chlorophyll is a chelate of magnesium and hemoglobin is a chelate of iron.

Successful in vivo chelation treatment of metal intoxication requires that a significant fraction of the administered chelator in fact chelate the toxic metal. This depends on metal, chelator, and organism-related factors (e.g., ionic diameter, ring size and deformability, hardness/softness of electron donors and acceptors,

route of administration, bioavailability, metabolism, organ and intra/extracellular compartmentalization, and excretion). In vivo chelation is not necessarily an equilibrium reaction, determined by the standard stability constant, because rate effects and ligand exchange reactions considerably influence complex formation. Hydrophilic chelators most effectively promote renal metal excretion, but they complex intracellular metal deposits inefficiently.

Lipophilic chelators can decrease intracellular stores but may redistribute toxic metals to, for example, the brain. In chronic metal-induced disease, where life-long chelation may be necessary, possible toxicity or side effects of the administered chelator may be limiting. The metal selectivity of chelators is important because of the risk of depletion of the patient's stores of essential metals.

DMPS, DMSA, DTPA, Deferoxamine have gained more general acceptance among clinicians, undoubtedly improving the management of many human metal intoxications, including lead, arsenic, and mercury compounds.

Deprivation of iron by chelating agents has been proposed as a method of cancer treatment, alongside the well-known mechanism of iron-promoted oxidative damage (e.g., Bleomycin).

Natural Chelators

Water, Carbohydrates, including polysaccharides, Organic acids with more than one, coordination group, Lipids, Steroids, Amino acids and related compounds, Peptides, Phosphates, Nucleotides, Tetrapyrroles, Ferrioxamines, Ionophores, such as gramicidin, monensin, valinomycin, phenolics etc.

Synthetic Chelators

BAL, Deferoxamine, Deferiprone, DMPS, DMSA, D-Penicillamine, EDTA, Tetrathiomolybdate, Prussian Blue, DTPA, etc

DETOXIFICATION

The aim of Chelation is to relieve the body of toxic metals. Chelated toxic metals need to be eliminated, usually via the urine, occasionally also by the bile and stool. This process of detoxification should be well-understood in order to deliver the proper treatment to a patient. Usually, metal intoxication is not the only intoxication and if the detoxification process is compromised elimination of metal complexes may be compromised as well

The process of detoxification involves two phases.

The body's primary defense against metabolic poisoning is carried out by the liver. The liver has two mechanisms designed to convert fat-soluble chemicals into water soluble chemicals so that they may then be easily excreted from the body via watery fluids such as bile and urine. The two pathways are known as phase I and phase II

Phase I

This pathway converts a toxic chemical into a less harmful chemical. This is achieved by various chemical reactions (such as oxidation, reduction and hydrolysis), and during this process free radicals are produced which, if excessive, can damage the liver cells. Antioxidants (such as vitamin C and E and natural carotenoids) reduce the damage caused by these free radicals. If antioxidants are lacking and toxin exposure is high, toxic chemicals become far more dangerous. Some may be converted from relatively harmless substances into potentially carcinogenic substances. Human liver cells possess the genetic code for many isoenzymes of P-450 whose synthesis can be induced upon exposure to specific chemicals. This provides a mechanism of protection from a wide variety of toxic chemicals. Excessive amounts of toxic chemicals such as pesticides can disrupt the P-450 enzyme system by causing over activity or what is called 'induction' of this pathway. This will result in high levels of damaging free radicals being produced.

Toxins and xenobiotics are converted into a water soluble metabolite or a primary metabolite in the process of biotransformation. Primary metabolites are then cleared later in Phase II of the liver detoxification cycle. Toxins (drugs, pesticides, gut toxins, hormones, metabolic by-products, histamine, etc.) enter into the liver detoxification Phase I and are converted into substances that are water soluble and then excreted via the kidneys, sweat, and bile. This conversion results in the formation of free radicals. There is one molecule of Glutathione used for each molecule of toxin removed. A toxin initially enters phase 1, the p-450 cytochrome system, and is reduced to smaller fragments. These fragments then progress to phase 2, where they are bound to molecules such as glutathione, glycine and sulfate. This process creates a new non-toxic molecule that can be excreted in the bile, urine or stool.

Some substances need further detoxification and must enter Phase II for elimination. These primary metabolites are now more toxic than they were originally before Phase I. These Phase I products can cause tissue damage and can react with a cell protein thus forming a new antigen which may lead to immunological reactions. The more active compounds could bind with the DNA causing mutation which could lead to cancer; many carcinogens are first activated by the liver (e.g. benzopyrene). What should occur is that the primary metabolite reacts with the Phase II enzymes and is rendered harmless. An example of the phase one pathway is the Cytochrome P-450 mixed function oxidase enzyme pathway. These enzymes reside on the membrane system of the hepatocytes. The family of P-450 enzyme systems is quite diverse, with specific enzyme systems being inducible by particular drugs, toxins or metabolites. It is this characteristic that has allowed the development of special tests to check the function of the various pathways the substrate is the substance that is acted upon by the enzyme. Substances that may cause over activity (or induction) of the P- 450 enzymes are: Caffeine, Alcohol, Dioxin, Saturated fats, Organophosphorus pesticides, Paint fumes, Sulfonamides, Exhaust fumes, Barbiturates.

Phase II.

This is called the conjugation pathway, whereby the liver cells add another substance (e.g. cysteine, glycine or a sulphur molecule) to a toxic chemical or drug, to render it less harmful. This makes the toxin or drug water-soluble, so through conjugation, the liver is able to turn drugs, hormones and various toxins into excretable substances. For efficient phase two detoxification, the liver cells require sulphur-containing amino acids such as

taurine and cysteine. The nutrients glycine, glutamine, choline and inositol are also required for efficient phase two detoxification. Thus, these foods can be considered to have a cleansing action. The phase two enzyme systems include both UDP-glucuronyl transferase (GT) and glutathione-S-transferase (GSH-T). Glutathione is composed of three amino acids (cysteine, glutamic acid, and glycine). Adequate glutathione levels are also dependent on adequate levels of methionine since it is the precursor to cysteine. Glutathione is a powerful antioxidant and is very important because of its dual role as an anticancer agent and antioxidant. Glutathione conjugation is the primary process by which the body removes fat soluble toxins (heavy metals, solvents, pesticides, fertilizers, etc). It can be depleted by large amounts of toxins and/or drugs passing through the liver, as well as starvation or fasting. Phase II reactions may follow Phase I for some molecules or act directly on the toxin or metabolite. During Phase II detoxification the substances are conjugated with a water soluble substance creating a product that is less toxic and water soluble.

Eggs and cruciferous vegetables (e.g. broccoli, cabbage, Brussels sprouts, cauliflower), and raw garlic, onions, leeks and shallots are all good sources of natural sulphur compounds to enhance phase two detoxification.

Provided activation of Phase I and Phase II is simultaneous, this water soluble end product is excreted safely in the bile or in the urine. Phase I and Phase II pathways of detoxification need to be in balance. This will determine if the exposure to a xenobiotic will cause toxicity or immune problems. If Phase I reactions are producing primary metabolites faster than Phase II can neutralize them, then toxic consequences will result. Substances that activate Phase I reactions can be undesirable if Phase II can not handle them. The best scenario is simultaneous activation of Phase I and Phase II.

One or both detoxification phases can be inefficient or overloaded. A particularly damaging combination in an ill person is an excessive overload of toxins coming into Phase 1, with an inefficient Phase 2. In some cases this combination is believed to be the cause of marked environmental sensitivities, drug intolerances and interactions that characterize many chronic fatigue and fibromyalgia patients. As patients improve clinically, serial testing of their liver detoxification capacity shows corresponding improvement.

If a patient is very ill with severe toxic symptoms, hepatic detoxification must be performed very slowly and gradually. It is always preferable first to reduce toxin exposure and any liver inflammation. In addition, leaky gut syndrome should be addressed and repaired prior to any liver detoxification.

Lipid Peroxidation

Lipids may also be damaged by free radicals, and often metals, especially copper and iron, are involved. These free radicals products are a major cause in the development of atherosclerosis.

Oxygen-dependent deterioration of lipids, known as rancidity, is a major problem in the storage of oils. The same oxidation process is also considered important today for natural products used in human consumption such as fats, oils, dressings or margarine.

Lipid peroxidation can be defined as the oxidative deterioration of lipids containing any number of carbon-carbon double bonds. Lipid peroxidation is a free radical-related process that in biologic systems may occur

under enzymatic control, for instance the generation of lipid-derived inflammatory mediators, or non-enzymatically. This latter form is associated mostly with cellular damage as a result of oxidative stress

During classic rancidification of fats iron and copper complexes can catalyze further radical reactions. Oxygen is seven to eight times more soluble in non-polar media than in polar media. In the plasma membrane there are hydrophobic and hydrophilic substances interdigitated into and interacting with the plasma membrane hydrophobic and ionic forces. This hydrophobic middle zone in the plasma bi-layer is the non-polar medium where oxygen is so soluble. Also, it is the location where for the polyunsaturated fatty acids with their allylic carbon-hydrogen bonds which is susceptible to free radical attack. Thus, the hydrophobic middle zone has the highest concentration of oxygen, with its di-radical potential for doing damage to the plasma membrane's polyunsaturated fatty acids. In this way the resulting saturate chains become more compacted with the membrane, becoming less fluid and poised for membrane disruption. Cholesterol has a protective antioxidant function in the normal cell membranes. The unsaturated fatty acids tails on the phospholipids are free to wave fluidly around the non-polar end of the cholesterol molecule. Cholesterol's presence in the hydrophobic middle zone perpendicular to the membrane's surface is thus poised to accept the di-radical by its allylic bonds. Also the steroid cholesterol thus serves as a physical barrier between the free radical and the allylic bonds of the fatty acids. The steroid rings allow more allylic bonds to suspend the di-radical simultaneously between them and thus become the favorable environment for the di-radical oxygen. Following an incident that causes more free radicals the amount of cholesterol in the membrane is decreased. Thus it appears that that one of cholesterol's roles to protect normal plasma membranes from free radical attacks. This may be accomplished by maintaining fluidity in the membrane by preserving the polyunsaturated nature of the fatty acid tails on the phospholipids.

HISTORY OF CHELATION

The following is certainly not an exhaustive study on the History of Chelation and deals predominantly with the EDTA chelator. It tries to be an incentive to read more about this intriguing story of medicine that was initiated and developed outside universities and medical schools and nevertheless became a remarkable success.

Chelation may be defined as an equilibrium reaction between a metal ion and a complexing agent, characterized by the formation of more than one bond between the metal and a molecule of the complexing agent, resulting in the formation of a ring structure incorporating the metal ion.

The Swiss Alfred Werner proposed the concept of this metal-ligand bonding, with the metal atom as the center of an octahedral ring structure, as early as 1893. At that time it was quite a revolutionary concept, as quantum mechanics was not yet fully understood. At that time it was not yet called "Chelation".

The word Chelation was first proposed by Morgan and Drew in 1920, because they compared the way a heterocyclic ring structure grabbed the metal with the pincer-like action of a crab.

One chelator, which later became of clinical importance, was EDTA. It was synthesized by a German scientist F. Munz of the Hoechst Farbwerke in Germany. It was developed from nitrile-triacetic acid, which was used to soften water for more uniform dyeing in the textile industry. A patent for Europe was obtained in 1935.

First synthesis and patent of EDTA in the USA in 1945

In 1933

Frederick Bersworth and William Warren manufactured EDTA from formaldehyde and cyanide, at the Clark University, Worcester Massachusetts. Bersworth applied for a patent in the USA, which was finally granted in 1945 under the name of Versene.

First clinical application of EDTA Chelation.

In 1941 S.Kety employed sodium citrate for the experimental treatment of lead poisoning, because of the complexing action of citrate on the lead ion.

Other Chelating Agents.

Also, because of the memories of using warfare gas in the First World War, scientists were lead to develop chelators, which could bind arsenic, used in lewisite or mustard gas. This preparation, dimercaprol, was called British Anti Lewisite, or BAL. It is still being used for acute arsenic and some other heavy metal poisoning.

D-Penicillamine was developed, as a chelator for copper, iron, mercury, lead and arsenic in 1956. Walshe reported about its application for Wilson's disease.

In the present several refinements in structure and action have been developed and have been given rise to a broad range of more powerful and less toxic chelating agents for multiple applications, such as **DMPS, DMSA, DTPA** etc. The importance of these chelators is increasingly significant. Our environment is so polluted that almost every person has a certain degree of metal intoxication and this intoxication attributes to the majority of present day illnesses and pathological conditions.

Detoxifying people is almost always the first condition to make further treatment successful.

DMPS

DMPS was developed in the 1950s in the former Soviet Union and has been used to effectively treat metal intoxication since the 1960s. Because it had potential use as an antidote for the chemical warfare, it was not available outside the Soviet Union until 1978, at which time Heyl, a small pharmaceutical company in Berlin Germany started to produce it. It has an excellent safety record in removing mercury from the body and has been used safely as Dimaval in Europe for many years. The best and only brand of DMPS that should be used is from Heyl in Germany.

EDTA

Initially we will discuss more in detail the development of one of the chelating agents: EDTA First clinical application of EDTA Chelation in lead intoxication.

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The first report of EDTA for lead detoxification in veterinary practice appeared in 1954 ([Holin](#)).

EDTA and Calcium

The initial application of EDTA to bind calcium was still not forgotten. Also in the fifties several researchers and clinicians used it to remove calcium in hypercalcemic states or they tried to remove calcium from undesired depots in the body, with varying success. Eventually, the American FDA approved EDTA for the emergency lowering of serum calcium in hypercalcemic states, such as Calcinosi Universalis, a rarely occurring disease

It was noticed that patients receiving EDTA Chelation for lead intoxication also experienced improvement of atherosclerotic disease. The initial concept was that by removing calcium from the calcified arterial plaques the vascular wall would become less stiff, thus causing widening of the vascular lumen. This proved to be incorrect and has caused much of the controversy between chelation therapists and mainstream medicine. One still standing hypothesis is that EDTA removes calcium from metastatic calcium depots in tissues. Although this may be true in some instances, it is certainly not the most important effect of EDTA on calcium. The chelation of calcium in the clotting cascade and in platelet membrane receptors is probably the main reason that EDTA has such a striking effect in atherosclerotic arterial disease.

Another FDA-approved application of EDTA is for the control of ventricular arrhythmias caused by **Digitalis Toxicity**. The chelation of calcium on the myocardial cell membrane reduces the irritability of these cells.

Clinical acceptance of EDTA

However, although the initial concept of EDTA's action was incorrect, many benefits were reported in the years after 1950, such as lowering of serum cholesterol levels, improvement of angina pectoris and claudication and improvement of rheumatoid arthritis etc. Clinical acceptance was not unanimous, though, but a major breakthrough seemed to occur, when in 1960 Norman E. Clarke, then chairman of the department of Medical Research, Providence Hospital, Detroit wrote in The American Journal of Cardiology on "Atherosclerosis, Occlusive Vascular Disease and EDTA". In his summary, he stated: "The treatment of atherosclerotic vascular complications with the chelating agent EDTA is supported by a large volume of information".

And more support came from cardiologists J. Roderick Kitchell and Lawrence Meltzer, who in 1960 and 1961 reported on "the Treatment of Coronary Artery Disease with Disodium EDTA" and "the Potential Uses of Chelation Methods in the Treatment of Cardiovascular Diseases" and "the Long Term Use, Side Effects and Toxicity of Disodium EDTA". All articles were in favor of EDTA Chelation therapy. In 1963 Kitchell had not yet changed his mind and in an interview with Medical World News he stated: "peripheral vascular occlusive disease of the blood vessels shows remarkable changes following treatment with EDTA". Also, his associate Meltzer was quoted as saying "considering the absence of any valuable method for treating diabetic vascular

disease until this time, chelation assumes great importance” These statements were not just impressions, they were made after a 3 year study, supported by the John A. Hartford Foundation.

Halstead began to write his textbook ”The Scientific Basis of EDTA Chelation Therapy” in 1974. This outstanding book, (in 1997 revised by Rozema), must still be considered as standard textbook for the student in EDTA chelation therapy.

In the eighties and early nineties Rudolph and McDonagh must be mentioned as the major contributors to the literature of clinical evaluation of EDTA chelation therapy. They have published about almost all clinical aspects of the treatment.

Several other authors, amongst them Cranton and Frackelton, have published several major articles on EDTA, which may also be considered recommended literature for the chelation student.

Many articles may be found on the Internet. The IBCMT secretariat has also older important articles available, which are mentioned in this chapter. The remainder may be found in Chapter XIV

The Structured Denial of EDTA

Then, we can only guess what occurred, but it is significant for what is still happening today, the structured denial of all arguments, which are substantiated by hard numbers, or evidence-based data, which prove that EDTA chelation, is the most important contribution to the long-term treatment of atherosclerotic disease. Only one month after the publication of their last article Kitchell and Meltzer published “Treatment of Coronary Artery Disease with EDTA- Reappraisal”, that was published in the American Journal of Cardiology, and this article was a denial of the facts they had reported earlier. One can only guess at the motives, but it has set the trend of all opposition against EDTA Chelation therapy, which is still going on amongst cardiologists mainly, all over the world. The reason for this witch-hunt is still puzzling Chelation doctors. Is it because cardiologists are so narrow-minded or is it because pharmaceutical companies want cardiologists to use their expensive products, in which they have invested gigantic amounts of research money? Well, if that last fact is the case, it means that EDTA is indeed a threat for the pharmacy because it is so effective, so inexpensive and free from side effects. This makes sense, because it is unlikely that all cardiologists are narrow-minded. At any rate, after the last publication of Kitchell and Meltzer EDTA chelation therapy got only laboriously off the ground.

The first symposia on EDTA Chelation Therapy.

In 1959 and 1960 Marvin J. Seven, who had six years experience with chelation therapy helped to arrange the first two major symposia on chelation therapy. The proceedings of these conventions were published as a textbook “Metal Binding in Medicine” and as “Proceedings of a conference on Biological Aspects of Metal Binding”. These books, if still available can be recommended to everyone who is studying chelation. This is the base for our present knowledge of the phenomenon of chelation. Unfortunately Seven died in 1961 and progress of chelation therapy in the USA was severely retarded in the next decade.

Other developments in EDTA chelation therapy

Outside the USA, in the Soviet Union and Czechoslovakia important scientific and clinical work was conducted independent from the development in the USA. The group of Zechmeister, Brucknerova, Malinovska, Hadasova and others at the University of Brno published their first results of the therapeutic application of chelation in patients with atherosclerotic disease in 1966. Still more impressive is their experimental work with limited budgets on the effect of calcification of the arterial wall. It was this research that came to the attention of the Chelation society in the USA who hurried to bring Anton Zechmeister to the USA in 1986 to testify for the FDA. It also led to the internationally organized symposia in Plzen, Czechoslovakia, on the Interaction of Chelating agents and Metals.

In the USA emeritus professor Martin Rubin, former associate of Frederick Bersworth may be considered as one of the earliest experts on the scientific clinical application of EDTA chelation therapy. He was the president of the International Chelation Research Foundation and wrote several basic scientific papers on the subject.

Organizations

In 1973 the American Academy of Medical Preventics (AAMP) was founded “ to perform and encourage investigational research into the nature of the aging process in man and to establish standards for the diagnosis and for the medical treatment of atherosclerotic disease and all associated phenomena” In the 1977 members of AAMP realized that chelation therapy needed to become a well defined sub-specialty of medicine, if it ever would get recognition. In 1981 they made a proposal to the board of AAMP to establish a separate organization called the American Board of Chelation Therapy (ABCT). The specific purpose of this organization was and remains the testing of the proficiency of physicians to perform EDTA Chelation therapy. In 1995 the International Board for Chelation Therapy (IBCT) emerged from ABCT, intended to serve the interests of the non-American doctors. The newest development is that both sister organizations expanded their objectives and IBCT changed already its name into The International Board of Clinical Metal Toxicology (IBCMT). This was followed in 2003 by ABCT which name currently is ABCMT. Both organizations run a website since 2001.

In 1988 ABCT conducted a workshop for the first time outside the USA, in the Netherlands. Presently, IBCMT conducts every year at least two international workshops in addition to the two combined workshops with ABCT in the USA. The workshops are usually followed by the written or oral exams, which are needed to become certified in Clinical Metal Toxicology.

Attacks

In spite of, or maybe because of growing popularity and acceptance of EDTA chelation therapy attacks from mainstream medicine, surgeons and cardiologists continue. Most of them are individual without providing well-founded arguments: “it is quackery”; “it is not scientifically proven”; “it is dangerous, and many deaths have been reported” etc. But some of them are well organized and even well founded, such as the “PATCH Study” of 2001. The desire to hurt the chelation community however is usually greater than the patience for accurate scientific work. So far all these studies have been flawed for not following the protocol and manipulating

statistics. This is especially painful for the Patch Study, which was well subsidized and appeared in 2001 in an authoritative magazine such as the Journal of the American Medical Association (JAMA). This study claimed that EDTA did not work. It was heavily criticized for the poor setup and manipulation of the statistics, by several authorities, amongst them a cardiologist with outstanding reputation.

Another study, conducted by Guldager and Jorgensen in Denmark, early in the nineties, also tried to prove that EDTA chelation therapy was not effective. However, when taken into court by the Danish Chelationists, it turned out that they had not followed the protocol, and even that a patient who got benefit from the treatment was told that this would not be recorded, because “then they could not prove that EDTA doesn’t work”.

The Netherlands

In 1983 the Dutch Government ruled that there was insufficient evidence for the efficacy of EDTA in the treatment of Atherosclerosis, and the administration of EDTA and other chelating agents for the treatment of heavy metal intoxication should be restricted to well-equipped hospitals. The Chief Health inspector reacted with a letter to all physicians, stating: “physicians who continue to describe chelation therapy on ill-founded indications (other than heavy metal intoxication) should seriously consider the possibility that their activity will compel the Health Inspection to disciplinary action. Three Dutch doctors committed a unique fact in Dutch Medical History and brought the State of the Netherlands in 1985 to court, in order to have the Inspector’s letter revoked. In first instance they lost the case. But after much deliberation, and hiring another attorney (for considerable personal investment) they appealed. In March 1986 the High Court of Justice pronounced that the verdict of 1985 should be quashed, The Chief Health Inspector was ordered to publish within three weeks a new letter stating that his first letter was unlawful. Since that time, EDTA Chelation therapy is tolerated in the Netherlands, and no doctor has been challenged for conducting this treatment.

Present situation with regard to EDTA

At this time we rather refer to **Clinical Metal Toxicology** when we discuss chelation therapy, because “chelation” is still too much associated with the misconception that EDTA could chelate calcium out of the calcified plaques in the arteries. We use chelating agent for many more pathological conditions than atherosclerosis.

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