Journal of Nutrition and Food Security
Shahid Sadoughi University of Medical Sciences
School of Public Health
Department of Nutrition
Nutrition & Food Security Research Center

eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2019; 4(3): 206-217 Website: jnfs.ssu.ac.ir

Molybdenum Cofactor Biology and Disorders Related to Its Deficiency; A Review Study

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ARTICLE INFO

REVIEW ARTICLE

Article history:
Received: 12 Sep 2018
Revised: 3 Nov 2018
Accepted: 26 Feb 2019

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ABSTRACT

Background: Molybden, as a vital and essential micronutrient is directly involved in the metabolism of other elements including carbon, sulfur, and nitrogen. Molybdenum alone is not biologically active unless it binds to specific cofactors. Except for the bacterial nitrogenase, which contains molybdenum-Iron complex, molybdenum cofactor (Moco) is considered as the bioactive component placed in active site regions of molybdenum-containing enzymes. This review aimed to discuss the biological mechanisms involved in molybdenum metabolism highlighting Molybdenum cofactor deficiencies. ***Methods:*** Articles indexed in Pubmed, Google Scholar, and Scopus databases were used to extract the required information. ***Results:*** Moco, as the cofactor of sulfite oxidase, xanthine dehydrogenase, aldehyde oxidase, and nitrite reductase plays a substantial role in maintaining normal body homeostasis and reactive oxygen species (ROS) production. Lack of Moco is found to be associated with many inborn genetic disorders, such as mental retardation, brain immaturity, nervous shocks, and neurodegenerative diseases. ***Conclusion:*** Moco insufficiency compromises normal human body metabolism since it is reported to regulate the metabolic pathways of other elements. Although in recent years, substitution- and gene-therapies have been introduced to restore the metabolic pathways of patients with MoCD type A and B, the definitive treatment for this type of inborn disease has still remained ill-defined. More investigations are needed to completely understand the underlying pathophysiology of molybdenum-related diseases.

Keywords: *Molybdenum cofactor; Xanthine dehydrogenase; Sulphite oxidase; Biosynthesis*

Introduction

During the past decade, advances in the methods for identification and analysis of materials have increased the awareness regarding the role of trace elements in the human body. In the past,

This paper should be cited as: Ghasemzadeh N, Karimi-Nazari E, Yaghoobi F, Zarei S, Azadmanesh F, Zavar Reza J, et al. ***Molybdenum Cofactor Biology and Disorders Related to its Deficiency; A review study.*** *Journal of Nutrition and Food Security (JNFS)*, 2019; 4 (3): 206-217

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[DOR: 20.1001.1.24767417.2019.4.3.8.0]
[DOI: 10.18502/jnfs.v4i3.1313]

minerals were specifically classified into high-consumption and low-consumption nutrients and ingredients. However, trace elements such as copper (Cu), zinc (Zn), iron (Fe), and molybdenum (Mo) can have obvious unique functions in the human body. Furthermore, the elements such as chromium (Cr), nickel (Ni), cadmium (Cd), arsenic (As), and selenium (Se) are required as essential compounds for biological enzymes or structural proteins. Some of the essential elements of body metabolism, such as zinc, have many structural and regulatory functions, including the role of blood coagulation and aging. So, the body immune system's optimal function has a double dependence on them (Zarei *et al.*, 2017). The lack of trace elements leads to undesirable pathological conditions. Moreover, the beneficial curative effects of these elements in the structural form of nanoparticles reduced the carcinogenicity and the harmful effects of free reactive oxygen species (ROS) (Abbasalipourkabir *et al.*, 2015).

Molybdenum, as a trace element and micronutrient, is the only element in the second column of the periodic table that displays biological activity. In nature, two categories of molybdenum cofactors have evolved. One is the Iron-molybdenum cofactor in bacterial nitrogenase and the other is molybdenum cofactor (Moco) formed by joining of molybdenum with pterin from the large family of enzymes. Molybdenum acts as an enzyme activating portion in a wide range of metalloenzymes in bacteria, fungi, and animals. In this paper, we aimed to review the absorption process of molybdenum in the cell through the formation of Moco, its storage, its final changes while entering into the apoenzyme (inactive metalloenzyme), and diseases related to its deficiency.

Since long time ago, Molybdenum was known as the essential nutrition for plants, animals, and microorganisms (Bortels, 1930). Molybdenum in the form of anion MoO_4^{2-} is abundant in the ocean water and soil, but the only available form in plants and bacteria is anion molybdate. Very small quantities of Molybdenum are preserved in the organisms that depend on it. However, signs of poisoning have been reported in organisms that used excessive amounts of molybdenum (Turnlund, 2002). On the other hand, the unavailability of molybdenum can cause death in the organism. In the case that molybdenum is available for the cell, it should be in the form of Moco complex to serve its biological functions.

Absorption or uptake of molybdenum into the cell

The creatures absorb molybdenum in the form of molybdate anion, which requires a special absorption system to sweep the molybdate in the presence of competitive anions in bacteria. Bacteria perform this with the help of high-tendency ABC-type carriers in the presence of ATP hydrolysis (Hagen, 2011). Molybdate-bound specific proteins exist in some bacteria with the capacity to store 8-molybdate anions for further use of the cell (Pau and Lawson, 2002). In addition, the study of Molybdate in isolated vacuoles, showed that this organelle acts as a storage compartment of molybdenum in plant cells, which require Mot2 to evacuate vacuolar molasses to the cytosol (Tejada-Jiménez *et al.*, 2011). In contrast, the mechanism of homeostasis, the transport of molybdate in bacteria, and the transport of molybdate in eukaryotes (algae and plants) are still ill-defined. Mot1 and Mot2 proteins transfer molybdenum (sulfate carriers) from the cell membrane width to an extra-affinity. Obviously, none of them is found in the plasma membrane. Common reports showed that Mot1 is located in the internal membrane system besides the mitochondrial membrane (Baxter *et al.*, 2008, Tomatsu *et al.*, 2007). Thus, the second most controversial issue is that Mo enters into the molybdenum cofactor in the cytosol. In Chlamydomonas algae, genetic shreds of evidences recommend the existence of a unique system for transporting molybdenum. Recently, molybdate carriers have been productively cloned using these protozoa (Terao *et al.*, 2000).

Molybdenum cofactor

In a type of molybdenum-containing co-factor, the molybdenum is bound to a tricyclic pterin

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called Moco. Another type of molybdenum-containing cofactor, found only in a bacterial nitrogenase, is the Fe-Mo cofactor including Fe_3S_3 and Fe_4S_3, which are linked by three sulfur bridges. Nitrogenases are the enzymes that convert nitrogen into ammonia under atmospheric pressure and temperature using ATP. Nitrogenase is required for the stabilization of biological nitrogen, which plays a fundamental role in the nitrogen cycle in the biosphere. The main supply of nitrogen is also available in many herbaceous species such as beans. In contrast to nitrogenase, all the identified enzymes containing molybdenum include the pterin-type cofactor (Hille, 2002).

Primary studies on mutant fungus Aspergillus and Nicotiana tabacum plant revealed a new phenotype, which was characterized by a mutation in two molybdenum-containing enzymes of citrate reductase and xanthine dehydrogenase. Since molybdenum is the only common bond between the two enzymes despite their difference, it is proposed that both enzymes should share a cofactor with molybdenum that is Moco. Due to the specific nature of pterin in Moco, the non-cofactor metal of molybdopterin is called metal-containing pterin (MPT). The structure of pterin in Moco has a specific nature, which has evolved to control and maintain the special properties of molybdenum revitalization. The task of the cofactor is to determine the correct position of molybdenum in the active center to control the regenerative behavior and to participate in the transfer of electron from molybdenum to the pterin ring. The pterin has various regenerative states and involves well in the transfer of electrons to other prostatic groups. Crystallographic analyses of molybdenum enzymes have shown that the cofactor, unlike the previous assumptions, is not located at the protein level, but is trapped in the inner part of the enzyme and provides a tunnel structure for various substrates (Kisker *et al.*, 1997). If Moco suddenly separates from the holo-enzyme loses molybdenum. So, the enzyme will be lost due to rapid and inaccurate oxidation. Therefore, the molybdenum-containing enzymes in non-cofactor form seems to be inactive.

Biosynthesis, storage, and entry of molybdenum cofactor

The mutation in the pathway of Moco biosynthesis and disruptions in this biochemical pathway results in the loss of essential metabolic functions since all the molybdenum-dependent enzymes lose their function, which ultimately leads to the death of the organism (Trigiano and Gray, 2004). Moco biosynthesis is divided into four phases by a protected biosynthetic pathway (Kisker *et al.*, 1997), including the synthesis of cyclic pyranopterin monophosphate (cPMP), metal carrier metal (MPT), and the lowest carrier of adenylated metal (MPT-AMP) (**Figure 1**). Moco biosynthesis starts in a coordinated reaction set catalyzed by two proteins called MOCS1 and MOCS2 throughout the conversion of guanosine triphosphate (GTP) to pyranopterin cyclic monophosphate (cPMP). Chemical synthesis of cPMP is considered as the first step in the Moco biosynthesis pathway (Santamaria-Araujo *et al.*, 2012). In the second step, during a dewatering reaction, two sulfur atoms are transferred to the cPMP-diolate for the formation of MPT. This step is catalyzed by the enzyme MPT synthase (Fräsdorf *et al.*, 2014, Mendel and Leimkühler, 2015). The third and the fourth stages of this pathway are two successive reactions leading to the MPT adenylating followed by the introduction of molybdenum into MPT (Schwarz *et al.*, 2009). In humans, this reaction is catalyzed by a multifunctional protein called Gephyrin, which consists of two domains: the N-terminal with the adenylation function (GEPH-G) and the C-terminal with the task of entering molybdenum into the protein structures (Belaidi and Schwarz, 2013). In addition, Gephyrin plays a role in the vertebral nerve system and is associated with glycine and gamma-aminobutyric acid (GABA) receptors (Tyagarajan and Fritschy, 2014). Figure1 illustrates the biosynthetic pathway of the molybdenum cofactor (Mendel, 2007).

After passing throughout the synthetic route, Moco joins an appropriate apo-enzyme. Due to the fact that Moco is unstable and susceptible to the presence of oxygen, it seems that this co-factor is not found in free form within the cell (Rajagopalan

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and Johnson, 1992). So, after the synthesis, it immediately joins the apo-enzyme or to a carrier protein to protect and store the protein. The availability of sufficient amounts of Moco is necessary for the synthesis of molybdenum-containing enzymes (Aguilar *et al.*, 1992). The main mechanism involved in the entry of Moco into the molybdenum enzymes is not properly understood. A study conducted in in-vitro systems showed that human episulfide oxide oxide could be combined to Moco directly (Leimkühler *et al.*, 2001). However, Chaperon proteins or Moco carrier proteins are required to combine Moco into the target apo-enzymes that occur in the cells. Special printing systems for protein folding and molybdenum entry to the apo-enzyme structure were found for some enzymes containing molybdenum in bacteria (Blasco *et al.*, 1998).

Clinical importance of co-factor deficiency and therapeutic strategies

For advanced organisms such as humans or plants, the deficiency of molybdenum in nutrition or malnutrition conditions affects the ability of the cell to use molybdenum. Since some enzymes need molybdenum, the metabolic function of the cell is disturbed (Duran *et al.*, 1978). The infants born with this disorder have several problems, including nutritional problems, severe and progressive neurodegenerative disorders, and deformities in their head and brain. Up to now, three or four mutations in molybdenum synthesis pathway genes have been correlated with Moco deficiency (Reiss and Johnson, 2003), which can be responsible for pathogenesis of this disease. The most important of such mutations are located in the coding regions of *MOCS1*, *MOCS2,* and *Gephyrin*. No cure has ever been found for the human Moco deficiency (MoCD). Moco deficiency cannot be cured with large quantities of this cofactor, because this coenzyme is very unstable in the outer protective zone of apo-enzyme. Moreover, its half-life in aqueous solutions and neutral pH was just a few minutes (Kramer *et al.*, 1984). Genetic analysis of the patients showed that most of these cases had deficiency in the first phase of the Moco biosynthesis, which is the conversion of GTP to Z or cPMP precursors (Reiss, 2000). The precursor Z is more stable than Moco and has a well-known structure in all organisms. Studies showed that mice with mutated *MOCS1* were similar to humans with this kind of genetic defect (Lee *et al.*, 2002). Similar to humans, heterozygous mice showed no symptoms in this regard. However, homozygous animals with Moco deficiency exhibited similar symptoms of the human deficiency and died 10 days after birth. As a result of the mutation, no active MPT or Moco was found in them and molybdenum enzymes did not show any activity. Repeated injections of precursor Z into mice lacking *MOCS1* prolonged their life spans and restored the MPT and molybdenum enzyme activities partially. Cessation in the treatment with precursor Z resulted in a progressive decrease in MPT and activity of the enzyme-containing molybdenum, which ultimately led to the animal death up to 15 days after the minimum injection (Schwarz *et al.*, 2004).

Enzymes containing molybdenum

Four molybden-dependent enzymes have been identified in humans; all of them contain a Moco-based pterin in their active states, catalyze the regenerative reactions, and use water as an oxygen receptor or oxygenator. These enzymes are essential for the key reactions involved in the metabolism of carbon, nitrogen, and sulfur. To the best of our knowledge, more than 50 molybdenum-containing enzymes have been identified; most of which have a bacterial origin. Among the aerobic bacteria, nitrate reductase, dimethylsulfoxide (DMSO) reductase, formate dehydrogenase, and trimethylamine N-oxide (TMAO) reductase are the most well-studied enzymes containing molybdenum. In contrast, only a limited number of enzymes exist that contain molybdenum in eukaryotes classified into the xanthine oxidase (XO) family containing xanthine dehydrogenase (XDH), aldehyde oxidase(AO), nicotinate hydroxylase, and pyridoxal oxidase, as well as the SO group including sulfoxide (SO) and nitrate-β-kdktaz (NR). Pyridoxal β oxidase and nicotinate hydroxylase are found exclusively in Dorosophilamlonogastrium (Warner and Finnerty,

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1981) and Aspergillus (Lewis *et al.*, 1978), but xanthine dehydrogenase, aldehyde oxidase, sulfite oxidase, and nitrate reductase are found in all eukaryotes. Nitrate reductase that exists in autotrophic organisms such as plants, algae, and fungi is required for nitrogen uptake. In general, the reactions catalyzed by enzymes containing molybdenum are characterized by the transfer of oxygen atoms (Hille, 2002). The molybdenum-containing enzymes in eukaryotes have specific functions and distribution within the cell, which are explained briefly in the following:

Xanthine dehydrogenase: The members of this family catalyzes a wide range of aldehydes and aromatic heterocycles. Xanthine dehydrogenase is a key enzyme in degradation of purine, which is a hypoxanthine oxidation to xanthine and xanthine to uric acid by the simultaneous release of electrons from the substrate. This enzyme plays a major physiological role in the metabolism of reactive oxygen species. In humans, the activity of xanthine-dehydrogenase is high in the liver and lungs, although the highest rate of xanthine-dehydrogenase activity is in the primary areas of the digestive tract in rats and mice. In addition, mouse xanthine dehydrogenase plays a role in the mammary glands secretions. Therefore, along with the enzyme function, xanthine dehydrogenase acts as a structural protein associated with the cell membrane. The position of xanthine dehydrogenase in plant and animal cells is not fully characterized. However, some studies have established its location in the cytosol or peroxisome of the rat liver cells (Sanders *et al.*, 1997, Yesbergenova *et al.*, 2005).

Aldehyde oxidase: is a cytoplasmic enzyme that catalyzes the oxidation of various types of aldehydes as well as aromatic and non-aromatic tri-rings converting them into carboxylic acid. The aldehyde oxidase enzyme has a great structural similarity to xanthine dehydrogenase enzymes, because both enzymes possess characteristics such as high degree of sequence homology, almost identical molecular mass, ability to bind to the same cofactors, and hydroxylase property. The aldehyde oxidase enzyme is considered to be an X-linked enzyme and phylogenetic analyzes have shown that aldehyde oxidase proteins are derived from xanthine-hydrogenase synthase after the primary copy (Rodríguez-Trelles *et al.*, 2003). A remarkable characteristic that distinguishes aldehyde oxidase from xanthine hydrogenation is the ability to bind to the substrate in the molybdenum center and to bind with the electron receptors. The aldehyde oxidase enzymes are non-flexible oxidizers that cannot be connected to NAD^+ and exclusively use molecular oxygen as an electron receptor. However, aldehyde oxidase can produce superoxide by transferring the electron to the oxygen molecule (Badwey *et al.*, 1981). In many animals, aldehyde oxidase can be coded only by a gene, which results in the production of a homodimeric enzyme that has the highest level in the liver and lungs (Huang *et al.*, 1999).

Aldehyde oxidase: In contrast to xanthine dehydrogenase, little information exists about the physiological role of the aldehyde oxidase. Aldehyde oxidase has the ability to convert retinal to retinoic acid, an active metabolite of vitamin A and a major regulator for the growth and differentiation of tissues in various organisms (Terao *et al.*, 2000). Therefore, aldehyde oxidase may be associated with the progression and control of the homeostasis in various tissues. This enzyme may contribute to ethanol toxicity by oxidizing the acetaldehyde into acetic acid (Shaw and Jayatilleke, 1990).

Sulfite oxidase: This enzyme performs sulfite oxidation to sulfate, which is the final step in decomposition of the sulfur-containing amino acids. This enzyme basically contains the second end of iron amine that includes both cytochrome b 5 and the second carboxylic terminal. It is also effective in binding and demonizing the cofactor of molybdenum to the enzyme. The plant sulfate oxidase does not seems to contain the second cytochrome b 5 (Kaiser and Huber, 2001). Therefore, the plant sulfate oxidase is the most structurally simple type of enzyme containing molybdenum found in eukaryotes, which only contains Moco as a cofactor. The reaction of the sulfide oxidation is a two-electron transfer reaction, by which the electron is transferred from the sulfite

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to the molybdenum center; therefore, the Mo^{VI} is converted to the Mo^{IV}. However, in the case of a plant enzyme, the electron is transmitted to the oxygen molecule and at the same time the hydrogen peroxide is formed (Hänsch *et al.*, 2006). However, in animal species, it is transmitted to Fe III in the second cytochrome b 5 and ultimately to Fe II to cytochrome c. The animal type of sulfite oxidase is located in the mitochondria between inner and outer membranes, but the plant type is a peroxisomal protein and its physiological roles have not been determined yet. Sulfite is a strong nucleophilic ion and can react with a wide range of intracellular compounds. So, sulfite oxidase is required to remove the excess amounts of sulfite. Recent studies indicated that this enzyme is capable of producing hydrogen peroxide. Consequently, sulfite oxidase activity may be related to the metabolism of free oxygen species and oxidative stress (Nowak *et al.*, 2004).

Nitrate reductase: This enzyme is another member of the sulfite oxidase family, which does not exist in animals, is the key enzyme in nitrate absorption, and leads to the conversion of nitrates to nitrite in plant cytosols. This enzyme, similar to aldehyde oxidase and xanthine-hydrogenase has three distinct molecular domains. The N-terminal of the enzyme specifically binds to the molybdenum cofactor, which is followed by a Hem-binding cytochrome b 5; whereas, the second N-terminal binds to the flavin-adenine nucleotide (FAD). These two N-terminal domains are mainly separated by hinge I and hinge II regions (Kaiser and Huber, 2001).

Defects of molybdenum enzymes and molybdenum sulfurase cofactor

The severe phenotype seen in humans is a rare disease associated with death in childhood. The symptoms of sulfite oxidase deficiency include mental retardation, intractable seizures, severe developmental delay, microcephaly with weakness of brain growth, feeding difficulties, and improper lens placement in the eyes that can be attributed to the high or low amounts of sulfite or a combination of both (Atwal and Scaglia, 2016, Reiss and Johnson, 2003). High levels of sulfite are highly toxic to the organism, especially the nervous system and brain tissue. **Figure 2** simply illustrates the possible defects in Moco synthesis and correlated disorders (Reiss, 2016).

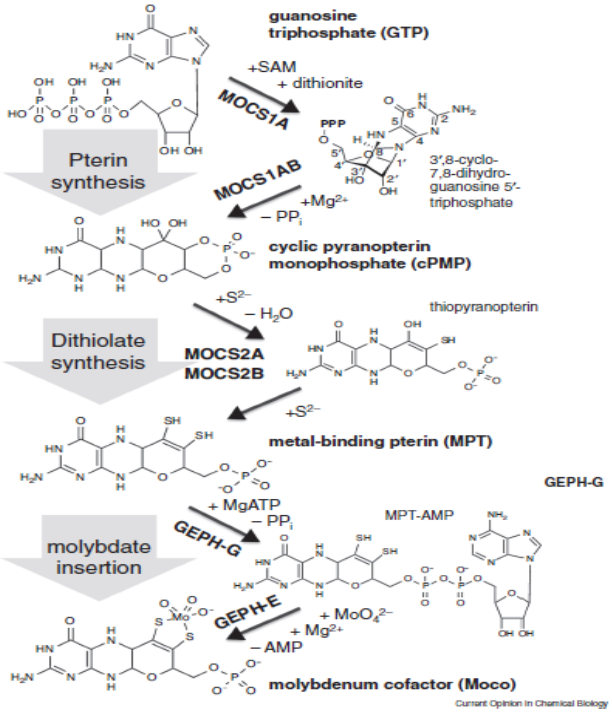

Figure 1. The biosynthetic pathway of the molybdenum cofactor (Schwarz, 2016)

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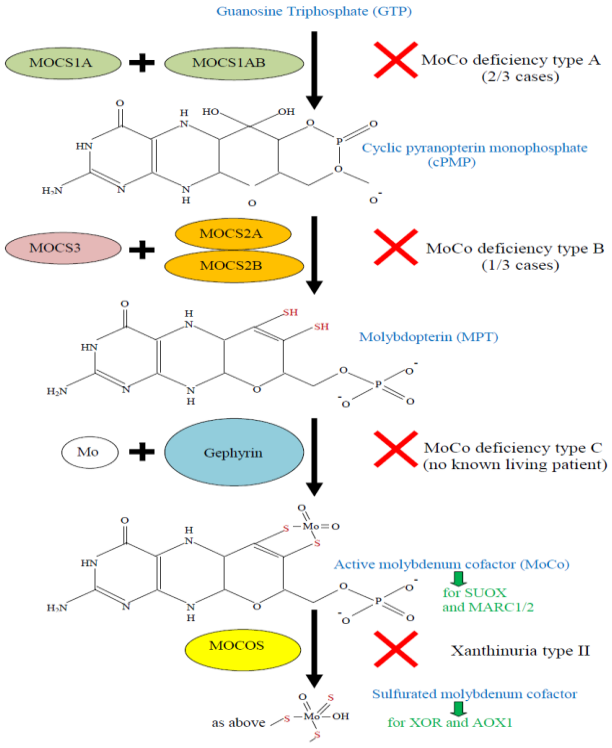

Figure 2. Biosynthesis of the molybdenum cofactor and its association with corresponding inherited diseases. (Reiss, 2016)

The accumulation of sulfite is associated with changes in other sulfur-containing metabolites, including cysteine, thiosulfate, homocysteine, and threonine. Furthermore, sulfate plays a role in the synthesis of sphingolipid, which is a major component of the myelin sheath. The deficiency of sulfite oxidase is not clinically different from molybdenum-related defects. Many of the symptoms of Moco deficiency are reflected in sulfite oxidase deficiency, which leads to the accumulation of sulfite. Therefore, sulfite oxidase is considered as the most important molybdenum-containing enzyme and accumulation of sulfite is the primary cause of the severe neurodegenerative disorders. Contrary to the deficiency of sulfite oxidase in humans, its absence in plants is not related to certain phenotypes. The resistance of sulfide oxidase mutants is reduced when they are exposed to high levels of SO_2 gas.

In comparison to the deficiency of sulfite oxidase in humans, many patients exist with hereditary deficiency of xanthine dehydrogenase known as xanthinuria type I. This autosomal recessive disorder may lead to kidney stones, urinary tract disorders, acute kidney problems, and muscle ailments. Studies on mice with quenched gene encoding xanthine dehydrogenase showed that these animals were unable to maintain specific functions due to the destruction of the milk gland epithelium. On the other hand, mice with homozygous mutations in the gene encoding Xanthine dehydrogenase died six days after birth (Dent and Philpot, 1954). The researchers concluded that women suffering from xanthine dehydrogenase deficiency may have problems with breastfeeding. Increased activity of xanthine dehydrogenase is associated with hyperuricemia, which is determined by the increased concentrations of uric acid in the serum. This, in turn, can lead to the formation of urate crystals in the joints. Allopurinol is a well-known inhibitor of xanthine dehydrogenase enzyme used to treat hyperuricemia and gout. Defects in Moco-containing sulfurase in vertebrates and plants are characterized by the lack of xanthine

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dehydrogenase and aldehyde oxidase; although the activity of sulfite oxidase and nitrate reductase in plants is preserved to some extent. In mammals, this disease is known as xanthinuria type II, which is differentiated from xanthinuria type I by allopurinol load test (Ichida *et al.*, 1998).

On the other hand, in the absence of sulfite oxidase activity, accumulation of sulfite in the cell leads to the increased ROS production. Sulfite inhibits the glutamate-dehydrogenase enzyme and this in turn reduces the ATP synthesis in mitochondria (Zhang *et al.*, 2004). The accumulated sulfite passes through the plasma membrane and circulates throughout the body. Outside the cell and under the influence of sulfite, the disulfide bridges revive and affect the stability and folding of the proteins. The first mechanism is the reaction of sulfite with cysteine leading to the formation of sulfocysteine, which is abundant in patients with deficiency of the sulfite oxidase and molybdenum. S-sulfocysteine that is structurally similar to glutamate and can be linked to N-methyl-aspartate, is suggested to cause shock and brain damage in patients. Early studies in mice have shown that S-sulfocysteine produced a similar type of brain injury as glutamate. The formation of S-sulfocysteine leads to the evacuation of sulfite deposits, which directly affects the glutathione biosynthesis (Parmeggiani *et al.*, 2015). Recently, H2S has been shown to play a pivotal role in cell signaling. Its reduced forms can also contribute to the pathogenesis of age-related disorders, such as Huntington's disease (Paul *et al.*, 2014). Initial efforts to treat this disease, which aimed at reducing the sulfite via dietary restrictions, were clinically successful, although in some cases with delayed symptoms of sulfite oxidase deficiency, the food constraints were very effective (Del Rizzo *et al.*, 2013).

Treatment is based on the symptoms of the disease and in many cases, medications such as phenobarbital and midazolam are used to control the shock since both medications target at GABA- mediated (GABAergic) neurotransmission. Moreover, a relative improvement was observed in the course of the neurological shocks by application of N-methyl-D-aspartate (NMDA) receptor antagonists because NMDA receptor antagonists inhibit the neuronal degradation in people with mild defects (Kurlemann *et al.*, 1996). Besides the mentioned treatment strategy, a study reported restoration of molybdenum cofactor-dependent enzyme activities in a patient diagnosed with MoCD by substitution therapy with intravenous cyclic pyranopterin monophosphate (cPMP). After one- to two weeks of therapy, all urinary markers of MoCD returned to their normal levels in the patient. This regimen yields to significant improved neurodevelopmental outcomes as started sufficiently early to maximize the treatment efficacy (Schwahn *et al.*, 2015, Veldman *et al.*, 2010).

Conclusion

Individuals need 50µg to 18mg of micronutrients per day. The biologically active forms of these elements serve as the catalyst for chemical reactions or as constituents of the large molecules in human body. Variety of the reduction and oxidation mechanisms (Redox), in which molybdenum is involved, reflect the number of enzymes that have a strong dependence on this element as a cofactor. Up to now, two major electron-transfer systems have been found in nature, which control the redox state and the molybdenum catalytic efficiency. Although the importance of each molybdenum cofactors is not well-defined in the catalytic activity of the enzyme, it seems that all molybdenum cofactors play active roles in the mentioned enzyme's active site by forming sulfur-containing chelates for trapping and activating the substrate. In humans, four molybdenum-dependent enzymes are known and all of them contain a pterin-based molybdenum cofactor (Moco) in their active site region. By use of water as oxygen donator or acceptor, these enzymes are mostly responsible for catalyzing redox reactions. However, Mo-enzymes have been reported to serve other recently known functions because they are able to catalyze the reduction of nitrite to nitric oxide (Schwarz, 2016).

The most important human defect associated with the deficiency of molybdenum cofactor is MoCD, which is the result of an almost complete loss of

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activity in sulfite oxidase, xanthine oxidase, and aldehyde oxidase enzymes. The MoCD is classified into three kinds based on the type of the defective enzyme in molybdenum metabolism. Patients with MoCD mainly suffer from progressive neurological lesions, which may lead to death in the middle of childhood if not handled properly (Scriver *et al.*, 2001). The accumulation of sulfite in the brain due to the deficiency of sulfite oxidase is one of the most important causes for the incidence of clinical symptoms associated with MoCD. The catalytic activity of other animal and plant enzymes, such as sulfurase and nitrate reductase, also depends on the molybdenum and its coenzyme, but Moco deficiency in these cases produces milder defects. Furthermore, receptor agonists of some mediators such as GABA are used as a potential therapeutic strategy to reduce the process of nerve cell destruction in patients with sulfite oxidase deficiency. In recent years, a novel therapeutic strategy has been established for patients with pathogenic variants of *MOCD1*. Patients harboring this genetic background can benefit cyclic PMP treatment as it can transform the neonatal lethal condition of MoCD type A to normal neurological outcomes in patients struggling with this type of MoCD. However, more recently, a murine model was introduced for MoCo deficiency type B with a slightly accelerated morbidity compared to type A. Since these patients would not appropriately respond to cPMP substitution and other replacement regimens, gene therapy might be the only option to pursue the treatment of this type of MoCo deficiency (Reiss, 2016).

However, no definitive treatment is known for this genetic disorder. Molybdenum and its cofactors seem to have substantive functions by regulating the metabolism of the other essential elements to maintain the body hemostasis (including iron). However, further studies are required to answer the basic questions regarding the pathophysiology of diseases related to molybdenum deficiency.

Acknowledgement

We present our gratitude for the Vice-Chancellor of Research and Technology in Yazd Shahid Sadoughi University of Medical Sciences for providing us the access to scientific databases.

Authors' contribution

Sargazi S and Zavar Reza J designed search sterategy. Ghasemzadeh N, Yaghoobi F, and Azadmanesh F searched and collected the data. Karimi-Nazari E and Zarei S wrote the draft of the paper. Sargazi S made critical revisions. All the authors approved the final version of the present work.

Conflict of interest

The authors declare no conflict of interests regarding this study.

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