Major and trace elements in lithogenesis

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KEY WORDS

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ABSTRACT

The process of crystallization in the urinary tract occurs when the equilibrium between promoting and inhibiting factors is broken. Many theories have been published to explain the mechanism of urinary stones formation; however, none of these theories has paid attention to trace elements. Their role in lithogenesis is still unclear and under debate. The findings of some studies may support the thesis that some major and trace elements may take part in the initiation of stone crystallization for instance as a nucleus or nidus for the formation of the stone, or simply contaminate the stone structure. This review presents a comprehensive account of the basic principles of the basic data and the role of major and trace elements in lithogenesis.

Urinary stones affect 5-15% of the population in industrialized countries, and their prevalence is rising [1]. The lifetime risk of developing symptoms of urolithiasis in the western world ranges from 10% to 15%, and in the Middle East, the risk can reach as high as 25% [2]. High recurrence rates mean that stones are considered a serious socio-medical problem. Although important advances have been made in understanding the multifactorial pathophysiology of stone formation, there is not yet a complete and satisfactory explanation of this process. Urinary stones are composed of various organic and inorganic compounds. The inhibitory activity of some urinary components like citrate, phytate, pyrophosphate, and glycosaminoglycan is well known but little attention has been paid to trace elements [3, 4, 5]. Stone disease is known to be a multifactorial disorder in which inhibitory crystallization deficit plays a major role together with supersaturated levels of different salts, promoters, and inhibitors of crystallization. The process of crystallization of supersaturated urine components and the formation of solid concretions can be modified by the activity of promoters and inhibitors and by some morphoanatomic, dietary, and environmental factors [6, 7]. The role of trace elements in pathogenesis of urinary calculi formation is still unclear and under debate. In recent years the role of trace elements in lithogenesis has received steadily increasing attention [8-22]. Their clinical use in the prophylaxis of stone disease is not evidence based. However, it is well documented that some trace elements have an effect on the crystallization of stone components; they act at the surface of the crystals, as their concentration in urine is too small to affect the lattice ions in solution [17, 22]. It has also been documented that some trace elements influence the external morphology of growing crystals and may increase or decrease the speed of the crystallization process [23, 24]. According to Goldschmidt's rule, some heavy metal ions (e.g., zinc and strontium) can substitute calcium in crystals because of their similarity in charge and size [10]. It has been demonstrated by some authors that metals such as magnesium, zinc, aluminum, iron, and copper may act as inhibitors of calcium oxalate growth at very low concentrations [10, 17, 22]. Some studies focus on determining the total levels of elements in studied materials; others focus on the interactions of elements with promoters or inhibitors such as citrate, glycosaminoglycans, pyrophosphate, and Tamm–Horsfall protein [14, 15, 17, 20-24, 25, 26-28]. Some authors reported data about higher metal content in the core than in peripheral layers of the stones. It may suggest a possible lithogenic effect of heavy metals [10, 12, 14]. Some authors compare the role of trace elements to that of vitamins and essential amino acids [20]. However, the data concerning their role in various disease states, including urinary stones, is still insufficient.

Some of elements described in this paper are considered as „trace". This term has been applied to those which are found in a sample in an average concentration of less than 100 parts per million measured in atomic count, or less than 100 micrograms per gram. The essential trace elements like fluoride (F), iron (Fe), iodine (I), manganese (Mn), molybdenum (Mo), nickel (Ni), selenium (Se), silicone (Si), germanium (Ge), vanadium (V), copper (Cu), zinc (Zn), chromium (Cr), and lithium (Li) must be present in the body in minimal concentrations to guarantee specific functions, such as electron transfer, redox, and enzymatic reactions among others. They play an important role in biological systems and are necessary for vital functions in the human body. On the other hand, some of them, especially arsenic (As), mercury (Hg), cadmium (Cd), lead (Pb), and antimony (Sb), act as toxins when accumulated in human tissues, displacing essential elements from their physiological active sites and act directly as cellular toxins [23].

Characteristic of chosen elements

Copper is an antioxidant; its concentration is highest in the liver, kidney, heart, and brain [29]. It is involved in the processes of skeletal development, phospholipid synthesis, electron transport, connective tissue, and blood cells formation among others. The cases of copper excess are rare, but liver disorders, including cirrhosis, may occur. Bird and Thomas were the first to point out the inhibitory effect of copper on the mineralization process of rachitic rats' cartilage [21]. Komleh et al. reported that, contrary to zinc excretion, the copper and manganese urinary levels were lower in stone formers than in normal subjects [20]. Meyer and Angino noticed the inhibitory activity of copper against growth of calcium phosphate crystals but not on oxalate [22].

Magnesium is the one of the most important minerals; it is needed by every cell of the human body and is involved in more than 300 biochemical reactions. Only 1% of total magnesium is found in blood, the rest is present in combination with calcium and phosphorus [29]. Magnesium is considered as a one of the most important inhibitors of lithogenesis in urinary tract, but its real role in this process has never been fully explained. Studies showed decreased calcium oxalate in vitro crystallization and growth in the presence of supraphysiologic concentration of Mg [30]. Several studies demonstrate that a low level of magnesium in urine is a risk factor for lithogenesis [22, 25, 28]. Some early studies showed that

dietary Mg deficiency causes experimental urolithiasis, and high levels of this element in urine reduce the concentration of oxalate available for calcium oxalate precipitation [31]. On the other hand, some data show that urinary Mg excretion is not significantly different in stone patients and healthy controls [32, 33]. Schmiedl and Schwille found no difference in urinary magnesium level in recurrent stone disease when compared to control group; whereas Atakan et al. found urinary Mg level to be higher in healthy controls and no differences in serum levels [8, 34]. This may support the thesis about its role as a potential inhibitor of lithogenesis.

Iron is the most frequent trace element in human body [11]. It is known as an element deficiency, of which is the most common in the world, causing anemia [29]. Its functional role in human body is well documented [35]. This element is responsible for muscle and cognitive functioning, carrying oxygen via hemoglobin and myoglobin. It is also highly involved in the enzymatic and immune reactions. In serum, iron is in 60-70% bound to transferin. Its excess may cause many disorders like liver damage, diabetes mellitus and skin pigmentation. The role of iron in lithogenesis is not clear. The Fe^{3+} ions have the ability to establish stable chemical interactions with oxalate ions on the surface of calcium oxalate crystals, thus disturbing their development [17, 27]. This interaction can be modulated by the action of common urinary components eg. phytate and pyrophosphate, which create the stable complexes with ferric ions. It is interesting that ferric ions are probably unable to act as a powerful inhibitor in the presence of physiological concentrations of citrate, due to the formation of highly stable complexes in solution without inhibitory activity [17]. Some authors reported that Fe does not affect the formation and growth of calcium oxalate crystals [22].

Zinc is the second frequent trace element in the human body [11]. Its deficiency may cause a reduction in an immunological response, steroidogenesis, CO_2 transportation, reproduction, and many other crucial processes. It has been shown that zinc supplementation is effective in reducing morbidity and mortality from diarrhea, malaria, HIV-infections, and gastrointestinal disorders by protecting the immune system response [36]. The data concerning the role of Zn in lithogenesis are divergent (see below) [18, 20].

Cadmium is a widely disseminated metal that can be imported and accumulated in living cells thereby drastically interfering with their biological mechanisms. Molecular aspects of Cd-dependent regulation of gene expression and signal transduction pathways in different model system are well documented [37]. The long-term exposure to cadmium leads to renal damage due to massive low-weight tubular proteinuria [38, 39]. On the other hand, a study of almost 2,700 renal cadaver samples showed that subjects who had died of renal disease had lower Cd concentrations. [40]. Only few studies can be found in medical literature with respect to Cd in lithogenesis. Hofbauer suggested that it might have some inhibitory effect on calcium oxalate crystallization [37]. The prevalence of urinary stone disease in coppersmiths was found to be 18,5% [41].

Boron is an ultra-trace element, and is poorly studied with respect to its biological role in human. It can be found in the bone and in the brain taking part in cell membrane functioning, calcium, phosphorus and fluoride metabolism [29]. Hunt et al. reported low calcium oxalate urine excretion in postmenopausal women as a metabolic response to dietary boron supplementation during low magnesium intake [42]. Low concentration of boron has been observed in patients with cystine stones [43].

The toxicity of **lead** is well documented and some authors reported its higher amount in calcium-containing stones than in organic phases [10]. It is also suggested that the reduction of Pb concentration observed when compared to historical data is a result of changes in pollution e.g., replacement of lead water pipes by those made of polyvinyl [44]. Its role in lithogenesis is unknown, but some authors have found a correlation between lead in stones and urine, which may lead to the conclusion that it may play some role in the process of crystallization in the urinary tract [26].

Vanadium is probably the essential trace element. In vitro and animal studies indicate that vanadate and other vanadium compounds increase glucose transport activity and improve glucose metabolism. In general, the toxicity of vanadium compounds is low and most of its toxic effects result from local irritation of the eyes and upper respiratory tract rather than systemic toxicity [45]. The author found in own study a positive correlation between V level and the content of magnesium phosphates and phosphate salts [26]. This suggests that this element may promote or support the crystallization of phosphate-containing crystals in the human urinary tract. The results of the same study demonstrated the group of three elements that showed positive two-element correlations in pattern "stone – urine – hair" (V–V, Pb–V, Pb–Pb, and Al–Pb). In the study of stones done by Abboud [46], vanadium was not detected, but the stones were collected from a poorly industrialized area of Jordan.

Selenium acts similarly to vitamin E as an antioxidant (glutathione peroxidase) and anti-inflammatory agent in the form of selenoproteins. It plays important role in protein biosynthesis, supports liver, testicular, heart function, and growth [29, 47]. Supplementation with Se in many diseases appears worthwhile, but interestingly there are only a few studies available. It is believed that Se may protect against some cancers, including urological ones. The SELECT (Selenium and Vitamin E Cancer Prevention Trial) study showed that selenium and vitamin E, alone or in combination at the doses and formulations used, did not prevent prostate cancer in this population of relatively healthy men [48]. There are also studies suggesting that higher levels of selenium taken from supplements or received naturally were associated with an increased risk of diabetes [49]. The role of Se in lithogenesis is poorly documented. There are only single papers that suggest that it, similarly to other metal elements, may have some interactions with stone constituents or be captured in the structure of crystals incidentally [10, 50].

Manganese is a component of antioxidative enzymes and plays an important role in the metabolic pathway of carbohydrates, proteins, and lipids. One of the metaloenzymes, which includes manganese, is carboxylase. Mn affects reproductive capacity and pancreatic function [29]. Male rats receiving varying doses of manganese were noted to have viscous, gritty urine in the urinary bladder and the high-dose groups had urinary bladder stones [51]. Mn concentration in the serum and urine of active stone patients is shown to be lower than healthy people [6, 20]. Turgut et al. reported that low level of manganese might interfere with the fragility of urinary stones in ESWL (extracorporeal shockwave lithotripsy) therapy [52]. Hofbauer suggested that nickel, manganese, lithium, and cadmium could be of significance in the pathological mechanism of stone formation, not from mineralogical or crystallographic viewpoints but for the smooth flow of enzymatic reactions in biological systems [18].

The first paper on trace elements in urinary stones was published in 1963 [53]. Nagy et al. reported the examination of Ag, Al, Ba, Bi, Cd, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Si, Sr and Zn in 85 kidney stones by spectro-analytical method. Eusebio and Elliot and Sutor as a first studied the influence of some trace elements on the crystallization process of calcium oxalate [24, 54]. They reported about inhibitory activity of Co, Ni, Pb, Sn, V and Zn on this process. So far only one epidemiologic study on trace elements in urinary stones was done by Levinson et al. in the USA [55]. After evaluating 20 elements in 186 stones they found no statistical difference in the trace element assemblages of mineralogically

identical stones from the three geographical areas. Joost et al. found significantly higher concentration of Fe, Sb, Sr, and Zn in stones made of calcium oxalate; Fe, As, and Zn in stones made of phosphates; and Sb (antimony) and As in stones made of uric acid [11]. This observation can be explained by the effect of heterogenic isomorphism, which is the insertion of a foreign element into a crystal lattice of a salt. The same phenomenon is observed in crystals of apatite, in which phosphorus can be replaced by arsenic ion. Bazin et al., after an analysis of the distribution of seven metals in 78 stones, showed a high proportion of Zn and Sr in phosphate stone and, contrary to results of Joost et al., a lower proportion of these elements in calcium oxalate stones [10, 11]. In the author's study, a positive correlation of Zn and Sr concentrations in stones with calcium phosphate content, but not with calcium oxalate content, was found [26]. Durak et al. studying the distribution of five metals (Fe, Cu, Cd, Zn, and Mg) in 47 stones and hair, found significant differences among the element levels in stones, patient hair, and control hair [28]. The role of Zn in lithogenesis remains unclear. Early studies by Bird and Thomas and recent publications by Atakan et al. showed that low Zn level in the urine of stone formers suggests its potential inhibiting action [8, 21]. Other data, however, show increased excretion of Zn and Cu in stone formers or even no difference between stone formers and healthy populations [11, 16, 56]. Turgut et al. reported that low concentrations of Zn, Mn, and Mg in calcium oxalate monohydrate stones appear to make them resistant to ESWL [52]. There are similar data concerning Cu, Fe, Mg, and Zn [57]. Słojewski et al. observed the negative correlation between Mg level and the content of calcium oxalate and uric acid [26]. This finding supports the conclusions of some authors who treat Mg as an inhibitor of calcium oxalate stones [8]. Scott et al. found a high concentration of Mg and K in phosphate stones and a relatively low concentration of Na in calcium oxalate stones [25].

Increased scientific interest in trace elements has led to a search for reliable methods of quantifying and monitoring their levels in human body tissues. It is believed that not single elements, but rather their relationships may play a role in the crystallization process. We do not know whether elemental imbalances may be responsible for the process of lithogenesis. The concentration of some heavy metals (including Pb, Cd, Ni, and Al) is found to be higher in the nuclei as compared with the crust [12]. This finding may support the thesis that these heavy metals may take part in the initiation of stone crystallization for instance as a nucleus or nidus for the formation of the stone, or simply contaminate the stone structure. The process of crystallization in the urinary tract occurs when the equilibrium between promoting and inhibiting factors is broken. According to results of many studies trace elements may play some role in the mechanism of stone creation; however, further investigations are needed.

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