ZINC IMBALANCE AND THE OPPORTUNITY OF ZINC SUPPLEMENTATION IN ALCOHOLICS AND DRUG USERS

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ZINC IMBALANCE AND THE OPPORTUNITY OF ZINC SUPPLEMENTATION IN ALCOHOLICS AND DRUG USERS (Abstract): Zinc deficiency is well-documented to be associated with alcoholism, being considered a consequence of unbalanced eating habits in such patients. The present review focuses on zinc imbalance in drug addicts and on the possible beneficial role of zinc administration as dietary supplement. All relevant literature published up to May 2015 was searched. The search was performed using the keywords “zinc” plus “alcoholism”, “addiction”, “dependence”, and the name of different drugs of abuse (classes or representatives). Human and animal studies were included. In alcoholism, zinc deficiency is not only due to malnutrition and malabsorption which are characteristic to this condition, as there is evidence of increased elimination and altered distribution of zinc. In opioid addicts, zinc deficiency is also commonly encountered and opioid administration in animals determines changes in zinc distribution. Studies regarding the zinc status in other drug abusers are inconsistent. Zinc deficiency in drug addicts also seems to affect some neural mechanisms involved in the downward spiral of addiction, as decreased zinc is associated with depression-like symptoms, known to induce drug-taking behavior. Moreover, zinc deficient animals are resistant to dynorphin-induced feeding. Conclusion: Based on evidence in the medical literature, the present review pleads for a beneficial role of zinc supplementation in alcoholics and opioid-users, not only in order to correct or prevent a metabolic imbalance, but also to influence some cerebral mechanisms involved in drug-taking behavioral patterns.

Keywords: ZINC, DEPENDENCE, ADDICTION, ALCOHOLISM.

Zinc, the second most important trace element in humans (after iron) (1), plays mainly structural and catalytic roles (2). It is important for the antioxidant defence, as a co-factor of Cu-Zn superoxide dismutase (3). Zinc finger proteins acting as transcription factors regulate gene expression (4). The brain is one of the organs with highest Zn²⁺ levels, containing approximately 1.5% of the estimated 2-3 g of zinc in the human body. Within brain zinc is nonuniformly distributed: the olfactory bulb has the highest level, followed by the frontal and parietal cortices (5). Within the central nervous system, zinc influences synaptic plasticity, hormone release, and nerve impulse transmission (6).

Zinc deficiency affects over 15% of world population and the prevalence of inadequate intake varies from 7.5% in high-income regions to 30% in South Asia (7). More than 80% of pregnant women
have a zinc intake lower than recommended (8). Severe deficiency is rare, but mild and moderate zinc deficiency is widespread. Deficiency symptoms are rather nonspecific, including growth retardation, male hypogonadism, delayed wound healing and cell-mediated immune dysfunction (9), but response to repletion occurs very fast (10). Disorders mainly related with brain dysfunction (behavioral changes, depression, emotional instability, anxiety, socializing deficits, impaired memory and learning, anorexia, autism spectrum disorders, attention deficit hyperactivity etc.) are frequently associated with zinc deficiency (11, 12). In some of these conditions, it is debatable if decreased zinc is a consequence or a cause. Under moderate zinc deficient diet, brain zinc is maintained within normal limits, due to increased uptake (13).

Addiction is a chronic, relapsing disorder, characterized by loss of control over drug-taking. The association between zinc deficiency and alcoholism is well-known, being considered a consequence of unbalanced eating habits in such patients. There is also evidence of decreased zinc levels in opioid-users. On the other hand, zinc deficiency reduces food intake and causes depressive-like symptoms, known to induce drug-taking behavior. In this context, the present review focuses on zinc imbalance in drug-addicts and alcoholics and aims at discussing the possible beneficial role of zinc administration as dietary supplement in such persons.

All relevant literature up to May 2015 was searched. The search was performed using the keywords “zinc” plus “alcoholism”, “addiction”, “dependence”, “smoking” and the name of different drugs of abuse (classes or representatives). Human studies on the status of zinc and other metallic trace elements possibly interacting with zinc in addicts (alcoholics including) were included. Animal studies on the interaction between addictive substances and zinc metabolism were also considered.

In order to discuss the opportunity of zinc supplementation, searching strategies were consequently adapted.

**RELEVANT FINDINGS**

There are many studies reporting low zinc levels in drug addicts and drug users, most of them referring to alcoholics and opiate users. To our knowledge, studies on zinc levels in nicotine addiction or cigarette smoking are scarce, whereas those referring to zinc status in users of psycho stimulants or cannabis are absent. Low zinc status in case of different types of drug addiction is documented to represent rather a consequence of the toxic capacity to influence zinc distribution and elimination than a factor predisposing to drug-seeking behavior; however, malnutrition is common among drug addicts (14), especially in women (15), and this might represent an explanation for the low zinc levels in these subjects.

**A. Alcohol**

a. **Human studies.** Decreased serum zinc in alcoholics has been widely reported and known for a long-time. About 90% of alcoholics, with or without liver disease, were reported to have inadequate dietary zinc intake (16). It is believed that long-term ethanol consumption is responsible for zinc malabsorption, since it was shown that decreased zinc absorption only occurs in patients with alcohol-induced cirrhosis, where ZnCl₂ labeled with 65Zn was absorbed in a reduced proportion compared to controls (37±17% vs. 55±16%, p<0.01),
whereas in non-alcoholic cirrhotic patients zinc absorption was similar to that of healthy controls (47±11%) (17). Similar results on reduced zinc absorption were also reported by Dinsmore et al. (18). In delirium tremens patients, zinc is decreased in both serum and erythrocytes (19). Alcohol users’ exhibit increased urinary zinc elimination (20); the reduced zinc-binding capacity of albumin in patients with decompensated alcoholic cirrhosis is probably responsible for this (21). Controversial data regarding zinc metabolism in alcoholic cirrhosis have also been published: Mills et al. (22), reported increased intestinal absorption, whole-body content and total daily elimination of zinc in alcoholic cirrhosis, but with no changes in the biological half-life of zinc.

b. Animal studies. Interestingly, one study investigating the effect of 20% ethanol solution administration (intragastric, 2 g/kg daily) for five days, revealed that, on the day 5 animals presented higher zinc levels in serum and heart, but decreased zinc concentration in brain, lungs, kidney, liver, spleen and muscles (23).

B. Opioids

a. Human studies. Low serum zinc levels are reported in heroin users, with a slight tendency to increase during detoxification, yet not reaching control level (0.815±0.144 mg/L on admission for treatment and 0.859±0.205 mg/L at the end of hospitalization in opiate users vs. 1.118±0.114 mg/L in controls) (24). Moreover, zinc deficiency is correlated with the period of abuse in heroin addicts (25). Low serum zinc level is accompanied by increased serum copper level (26), the same being reported for the intraerythrocytic levels of zinc and copper. The antagonism between copper and zinc in both intestinal absorption levels and biological actions is well documented (27); the competition between zinc and copper at the level of DMTα transporter seems to be responsible for this. Copper facilitates zinc elimination through urine, but copper excess facilitates zinc storage (28). The antagonism between zinc and cupric bivalent ions occurs in the conditions of certain chemical similarities between them. So, as decreased zinc is accompanied by increased copper, it is reasonable to consider that zinc deficiency has better conditions to more clearly manifest in opioid users. Zinc level in the cerebrospinal fluid of former heroin addicts is lower than in controls, but generally within normal ranges (29). During methadone detoxification in opioid addicts, zinc elimination is strongly increased (600±50μg/g creatinine in patients vs. 300±50μg/g creatinine in controls, p<0.001), while copper elimination is slightly, but significantly decreased (23±3μg/g creatinine in patients, p<0.05 vs. controls) (30). On the other hand, heroin samples on the illegal market were shown to contain variable amounts of trace elements, including zinc, but these have little contribution to zinc intake and product toxicity (31) and they are believed to appear from the metallic container used in the processing/cutting stage (32).

b. Animal studies. Morphine administration in rats decreases the serum zinc level, but it increases liver cytosolic zinc and metallothionein (a family of cysteine-rich proteins involved in both zinc and copper metabolism) levels. If the effect of morphine on liver metallothionein levels is mediated mainly by the morphine effect on specific receptors (being antagonized by naloxone), zinc accumulation in the does not recognize this type of mediation, as
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Naloxone does not alter it; however, glucocorticosteroid and β-adrenergic mediation seem to be at least in part responsible for the increase in zinc and metallothionein liver levels, as their antagonists (RU 486 and labetalol, respectively) diminish that increase (33). Increased liver metallothionein levels (3-folds vs. control) were also reported by other authors (34), these being accompanied by increased brain and kidneys metallothionein levels (5 and 2-fold, respectively vs. controls). Interestingly, one study on the effect of morphine escalating doses in mice (intraperitoneal; 15 mg/kg on day 1; 30 mg/kg on day 2; 45 mg/kg on day 3; 60 mg/kg day 4; 50 mg/kg on day 5) showed on day 5 animals presented increased serum zinc concentration and increased zinc levels in the heart, spleen and muscle, but decreased in the brain, lungs, kidney, and liver (23). Intracerebroventricular administration of the δ-opioid agonist (D-Pen2, D-Pen5) enkephalin results in decreased Zn$^{2+}$ content in parietal cortex, hippocampus and striatum; the effect is time- and dose-dependent and it is antagonized by naloxone pre-treatment (5).

C. Nicotine addiction and smoking

a. Human studies. A positive association between smoking and serum zinc concentration (p=0.0003) was evidenced, but only in women (35), whereas other studies report no influence of smoking habit on zinc levels in urine (36), placenta, cord blood and maternal blood of women at delivery (37). However, the hair of tobacco smokers contains less zinc, calcium, magnesium, iron, and copper compared to controls (38).

b. Animal studies. Infusion of 50 mg nicotine for 21 days in rats did not modify serum zinc levels, but increased Cu-Zn superoxide dismutase activity (39).

**DISCUSSION**

In alcohol addiction the associated malnutrition and malabsorption are considered the cause of lower magnesium and zinc levels. However, increased urinary zinc elimination, probably related to decreased albumin capacity to bind zinc and zinc altered distribution, is also involved. Eating-related characteristics, as well as kinetic particularities, may also explain the tendency to zinc deficiency in opioid addicts. On the other hand, when discussing the eating habits, it should not be disregarded that zinc deficiency is associated with anorexia and zinc ions are important regulators of eating and liquid-intake patterns. For instance, acute third ventricle injection of minute zinc amounts (3 to 300 pmol) induces a dose-dependent antidipsogenic action in dehydrated rats, almost complete at the highest dose. The effect is reversed by naloxone, indicating that it may be, at least in part, due to stimulation of central opioid peptides (40). Zinc-deficient animals have low levels of hypothalamic dynorphin (a leucine-enkephalin opiate peptide and a potent inducer of spontaneous feeding) compared to ad libidum-fed controls and are also relatively resistant to dynorphin-induced feeding (41). Zinc ions inhibit anorexigenic proopiomelanocortin neurons in the hypothalamic arcuate nucleus (42). All these suggest that in zinc deficiency-induced anorexia appetite dysregulation is mediated via the endogenous opioid system, including alterations in receptor affinity, a post-receptor defect and alterations in the dynorphin synthesis and/or release.

Decreased zinc influences certain mechanisms responsible for the downward
spiral of addiction, as it is associated with depression-like symptoms (11, 12), which are known to induce drug-taking behaviour (43). Normalizing zinc level in zinc-deficient opioid-users and alcoholics may reduce the use of drug by attenuating depressive symptoms.

As to opioid dependence, there are studies revealing increased naloxone-precipitated withdrawal by zinc chelators (in mice) (44) and decreased withdrawal due to zinc administration during the induction phase of morphine-dependence (in rats) (45). This is an argument for a possible beneficial role of zinc supplementation in opioid users or addicts and it can be explained by zinc ions capacity to decrease opioid binding to μ-opioid receptors, as there is evidence that Zn$^{2+}$ lowers the affinity of different ligands to receptors (46). The idea is reinforced by the low levels of zinc in opioid users.

Assessment of trace element status is often disregarded in drug users. Zinc deficiency is considered a consequence of reduced intake or impaired absorption in alcoholics, but it seems to be also related to increased elimination. In drugs addicts zinc deficiency is not just a dietary imbalance with metabolic consequences, but it also may contribute to the persistence of drug-taking behavior by inducing depressive symptoms. Also, zinc deficiency favors anorexia, which may contribute to further imbalances.

CONCLUSIONS

Our present review pleads for a beneficial role of zinc supplementation in opioid users and alcoholics. This is based not only on the low zinc levels documented in ethanol and opioid users, but also on the fact that correcting zinc status may improve the eating habits and lower the craving by attenuating depressive-like symptoms. The low toxicity of orally-administered zinc salts is an additional argument. The status of trace elements in drug users should be more carefully assessed.

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