New aspects on trace element metabolism disturbances in man and pet animals

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SUMMARY
Considering the biological and clinical consequences of trace element disturbances, more attention should be devoted to trace element metabolism and status in humans and animals. In humans, trace element intakes and status are frequently marginal in large segment of the population, resulting in an higher risk of nutrition-related diseases. Regarding the essential protective roles of zinc and selenium against oxidative damage and decline of immune functions, or the beneficial effects of chromium on glucose tolerance, there is now increasing evidence that appropriate supplementations, restoring marginal trace element status, could reduce in human the risk of degenerative diseases, and, in animals could participate to the improvement of functions like reproduction, immunity, or vision and taste. Surprisingly, little information is available concerning the real mineral requirements of pets and additional research also needs to be done to evaluate the efficiency of supplementations. Numerous questions need to be answered about the nature and forms of supplementation, the doses administrated and the duration. Interpretation of the studies is also often limited by, mainly, use of inappropriate indicators of status. Most of the reported parameters reflect biological modifications and few studies focused on clinical or functional signs, such as number of infections, overall health or incidence of diseases. The objective of this paper is to review what is currently known about trace element biological functions, assessment of the status and biological and clinical consequences of trace element metabolism disturbances in man and animals. Recent supplementation trials and their possible beneficial effects will also be evaluated.

KEY WORDS : trace elements - requirements - supplementation - human - pet.

Introduction
Trace elements have been found to play a role in a number of essential metabolic functions and their importance in biochemical research has grown accordingly. Recent investigations have renewed interest in trace elements such as zinc, copper, selenium and chromium, in man and in animal. Trace element dietary low intakes and/or modified absorption, storage and utilization, increased requirements in some groups of subjects result in an enhanced risk of deficient status in
large segments of population in developing countries. The incidence of deficiencies appears to be especially important for Fe, Se, Zn, and Cr. Trace element status influences growth and reproduction (Zn, Se), immune functions (Zn, Se, Fe), lean body mass (Cr), bone density (Cu, Zn, Cr), cognitive functions (Zn, Se), insulin sensitivity (Cr) and oxidative stress (Zn, Se, Cu, Fe). Antioxidant trace elements (Zn, Se, and Cu) are involved in cellular antioxidant defenses and protection against accelerated aging processes. In relation with these biological functions, trace element deficiencies lead to impaired growth, altered immune functions, increased oxidative stress, decreased cognitive functions, enhanced glucose intolerance and loss of bone density. Several supplementation trials, in humans, have shown beneficial effects, particularly in improving immunity, restoring growth, decreasing lipoperoxidation, preventing loss of bone density and improving glucose tolerance. These results are important to alleviate the incidence of infections, cardiovascular diseases, osteoporosis and diabetes. In animals, reports focusing on trace element metabolism and functions are not abundant, especially in pet animals. Most of the trials aim to investigate and to improve trace element status and related functions (reproduction, growth, immunity) in dairy cattle, pigs and sheep.

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Risk factors of trace element deficiencies in man and animals

In man, numerous factors tend to limit the trace element nutriture [23]. Physiological modifications and environmental influences are significant factors contributing to the impairment of trace element status frequently observed. Decreased food intakes may be related to impaired appetite, modified dietary habits currently described in Western countries, or be associated with reduction of taste and smell. Modified dietary habits which may affect food selection are well documented in groups of population such as teen-agers, pregnant women or elderly. In parallel, economic, social, environmental or mental problems also may contribute to nutritional disorders. Chronic diseases also can significantly affect absorption, and availability of trace elements, mainly as a consequence of drug treatment. Lastly, modifications in food habits may also impair trace element intakes and/or absorption. High sucrose consumption increases chromium and copper urinary losses. Meals, rich in fibers or phytates, decrease iron and zinc absorption, and the frequently advised decrease in the consumption of fat- and cholesterol-rich products modifies iron, zinc, and copper intakes. The calcium enrichment of daily food intakes, common in postmenopausal women, decreases absorption of zinc and iron. In a calcium rich diet, zinc availability was reported to decrease of 50 %. In addition, caloric intake below 1500 kcal/day cannot fulfill the biological needs for micronutrients. Thus, low caloric intakes, associated with environmental and metabolic factors may result in increased risks of trace element deficiencies.

Deficiencies in pets are uncommon as a result of the widespread feeding of complete and balanced pet foods that meet the nutrient profiles specified by expert panels. However, deficiencies may arise when the animal's intake is reduced, when the diet is poorly formulated or stored or when the animal is unable to digest, absorb or utilize the nutrient as a result of disease or genetic factors. Dietary interactions that reduce nutrients availability can result from errors in formulation, prolonged storage or injudicious oversupplementation of an otherwise balanced diet [53]. Thus, in companion animals, acute deficiencies are scarce and related to pathologies and pet food commercially available is supposed to bring adequate requirements and to prevent deficiencies. However, sub deficits, leading to decreased immune functions, impaired growth and reproduction, or globally sub optimal health state, cannot totally be ruled out. Essential trace minerals are necessary nutrients for normal function of the tissues and processes intimately related to reproduction. A dietary deficiency in essential trace elements will be manifested either as the inability to establish or maintain pregnancy or the reduction in the size of the litter.

Trace element biological importance, requirements and disturbances

ZINC

Zinc is required for the structural integrity and catalysis of numerous enzymes essential for nucleic acid and protein synthesis. Its influence in growth and reproduction is crucial. The role played by zinc for cellular protection is related to the maintenance of membrane integrity and function, partly due to scavenging of free radicals [11]. It is a component of antioxidant Cu-Zn SOD and metallothioneins and more than 200 proteins. Zinc, by competition with other transition metals such as Fe or Cu, protects SH groups from oxidation, and may influence transcription factors such as p53. As described recently, Zn depletion results in increased cellular death by apoptosis [49]. Zinc is involved in bone structure, in taste and smell olfactory acuity and in several hormonal functions [7]. Finally, it is essential for host-defense mechanisms, particularly T lymphocyte maturation and responses involved in cell-mediated immunity and the functional capacity of phagocytes [16]. Among numerous physiological functions influenced by zinc are maintenance of membrane stability, neurologic health, immune functions, vision, reproductive function, wound healing and protein metabolism, [46, 52, 24]. Zinc, as recently shown, is also an essential nutrient for brain and in maintaining cognitive functions [50].

The RDA for adults varies from 12 to 15 mg/d in the USA and 8 to 12 mg/d in Europe, depending upon sex. In humans and in animals not fed commercially formulated diets, zinc
ingestion correlates with protein intake, absorption occurring mainly in the small intestines and excretion occurring mainly in the feces. Based largely on research conducted with production animals, the NRC recommends a minimum of 39 mg zinc/kg of dry matter for companion animals. However, clinical signs of zinc deficiency have been observed even when dietary zinc is added. The apparent deficiency can be explained in part by reduced bioavailability resulting from dietary antagonism and interaction with other minerals. Dogs and cats may also experience a higher demand for zinc under circumstances of stress, during growth periods, levels of high activity, gestation, lactation or illness [42]. The zinc demands of pet animals vary by breed, genetics, life stage, nutritional status and environmental stress. The organic zinc form is also more likely to satisfy these varying demands, especially when the need is greatest. Absolute dietary deficiencies of zinc are considered rare in dogs and have not been reported in cats. However, a relative deficiency can occur in some dogs related to a decreased bioavailability of dietary zinc (soy-based dry food). As recently reported by WATSON [53], skin diseases can be related to zinc deficiency in cats and dogs. Indeed, zinc plays a critical role in regulating many aspects of cellular metabolism which are with the maintenance of a healthy coat and skin. Zinc, as a cofactor for RNA and DNA polymerase is of particular importance in rapidly dividing cells, including these of the epiderm. Zinc is also essential for the biosynthesis of fatty acids and is involved in the metabolism of vitamin A. In adult pets, signs of zinc deficiency are confined mainly to the skin, but these may be accompanied by impaired growth and other abnormalities in young animals. Appetite may be depressed as a result of a diminished taste and smell. Prolonged deficiency can result in weight loss, impaired wound healing, conjunctivitis and keratitis. Lymphadenopathy is also a common feature, particularly in young animals. Most commercially formulated pet diets contain additional zinc concentrations. It has been demonstrated that calcium and phytate levels are factors that significantly affect zinc utilization and thus determine the use of organic zinc sources as beneficial. In puppies, the bioavailability of Zn propionate was 60 to 80% greater than that of the organic zinc sources as beneficial. In puppies, the bioavailability of Zn propionate was 60 to 80% greater than that of the organic zinc sources as beneficial. In puppies, the bioavailability of Zn propionate was 60 to 80% greater than that of the organic zinc sources as beneficial. In puppies, the bioavailability of Zn propionate was 60 to 80% greater than that of the organic zinc sources as beneficial. 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found in other antioxidant compounds such as selenoprotein P and thiorodoxin reductase. It can also modulate the immune system, maintaining in lymphocytes a pool of reduced glutathione and stimulating immunocompetent cells [39]. Selenium deficiency has been associated with an increased risk of cancer and cardiovascular disease, an increased incidence of infections [44] and, as recently reported in the EVA study [10] with the decline of cognitive functions. Dysfunction in thyroid metabolism could also be associated with selenium deficiency since selenocysteine is part of 5'deiodase type I and plays a key role in the metabolism of thyroid hormones. Finally, selenium acts in detoxifying heavy metals (Hg, Cd, Pb) and xenobiotics. This function offers an interesting field of action in patients consuming multiple drugs.

Selenium intakes in Europe are globally lower than in North America. They are below the RDA (55 to 70 µg/d) and are far from the optimal estimated intake for full activity of glutathione peroxidase (80 to 100 µg/d). Several supplementation trials were reported. Both plasma selenium and glutathione peroxidase activity were improved in all the published studies using different selenium forms, doses (60 µg/d to 125 µg/d) or association with antioxidant vitamins. Decreased lipoxygenation, assessed by plasma TBARS, was reported in some trials. A stimulation of parameters reflecting an improvement of immune response as lymphocyte proliferative response to mitogens was reported in a Belgium study in elderly people supplemented with 100 µg/d as selenite for 6 months [45]. Other studies with selenium alone or in combination with other micronutrients showed also beneficial effects. A significant effect of high doses of Se (200 µg/d) on cancer incidence has been reported by CLARK and COMBS [15]. The incidence of prostate cancer decreased of 69 % in this double blind study. It is a matter of debate to define the level of requirements and optimal selenium supplementation. The WHO in 1996 [54] concluded that selenium intakes required for two thirds of the maximal activity of GSH peroxidase were recommended in healthy adults but all the studies conducted using doses higher than RDA showed beneficial effects on biological and clinical parameters.

In animals, most of the studies focused on selenium status in cattle and pigs. In Se deficient cattle, an increase of oxidative stress, assessed by erythrocyte resistance to oxidative damage capacity, was reported [27]. In weaning pigs, supplemental selenium at 0.2 mg/kg of diet was required to support the full expression of SeGPx [35]. In calves, the beneficial effect on Se status, as a result of prepartum maternal Se supplementation with 13 mg/d for 15 days was recently reported [19]. Se deficiencies have been also associated with increased incidence and severity of intramammary infections (IMI). Giving selenium supplements to dairy cows strengthens the inflammatory response to IMI and induces a growth-suppressing effect on mastitis [47].

CHROMIUM

Over thirty years ago, chromium was certified to be an essential trace element and has been defined to be required by humans [41]. Its main function is to maintain normal glucose tolerance by regulating the insulin [3, 1]. This element attracted first a great deal of attention in consideration of its relationship with the aging process and diabetes [6]. Chromium requirements range from 50 to 200 µg/d while western diets contain around 15 µg/1000 kcal. Due to the large consumption of refined food products, people in most of developing countries have been estimated to consume Cr deficient diet that contains only 40-60 % of the recommended daily requirements (50-200 µg). The reported chromium intake has ranged from between 25 to 37 µg/d. Deficiencies in Cr result from metabolic and physical stresses, such as pregnancy, carbohydrate loading, extreme physical exertion, trauma and disease, accelerating Cr mobilization and urinary losses, and depleting body stores of chromium.

DAVIS et al. [17] demonstrated a continuous decline in tissue chromium concentrations with age confirming previous reports. Poor nutrition might explain this decline and is consistent with several studies of chromium metabolism [4]. However, it is still unanswered whether the decline is a normal physiological development or due to poor nutrition. The consequences of chromium deficient intakes and status lead to increased glucose intolerance and risks of diabetes. Chromium deficiency results in fasting hyperglycemia, glycosuria, hypoglycemia, elevated circulating insulin, decreased insulin receptor number and binding, modifications of lipid metabolism and neurological disorders [3]. Most of these manifestations are alleviated by supplemented chromium. Variable responses to supplemental chromium, depending upon age and degree of glucose intolerance, have been reviewed ANDERSON [6]. Subjects with marginally impaired glucose tolerance respond within 3 weeks to 200 µg of inorganic chromium, but older subjects with more severe glucose intolerance may require higher amounts of chromium. Chromium supplementation has been also shown to increase bone density while increasing the excretion of urinary DHEA in post menopausal women [20]. This effect of chromium, related to an impact on the glucose/insulin disturbances is important in osteoporosis.

In animals, the importance of dietary chromium has been demonstrated in numerous species such as the mouse, rat, guinea pig, turkey, fish and pigs, as well as in human and a review of NRC on chromium animal studies has been recently published [43]. Chromium supplementation of cattle diets [31] showed beneficial effects on glucose and/or lipid metabolism in a number of studies. Several forms of supplemented chromium have been investigated in ruminants. These include chloride, tripicolinate, nicotinic acid complex, aminoacid chelate and high chromium yeast. Calves supplemented with Cr chloride (0.40 mg/kg) had a lower peak of insulin response than controls [32]. In dairy cattle, beneficial effects of supplemental chromium may also relate to its immunomodulatory potential or alternatively to the ability of Cr to alter bacterial growth [40]. In swine [37], the positive effects of chromium supplementation on insulin sensitivity of growing pigs have been also recently demonstrated [26]. From recent publications, and considering also the effect of chromium supplementation in growing swine and in reproducing swine, it seems that there is considerable potential for
the swine-producing industry to profit from the use of supplemental chromium.

**Assessment of trace element status** [14]

**STATIC INDICES**

Trace elements can be measured directly in body fluids that reflect their levels in the organism. Serum and plasma are very popular because sampling is easy and data can be controlled using reference materials and interlaboratory comparison studies. However, it is known that non specific variations may be encountered when using serum measurements. For example, zinc decreases during infection, copper decreases during pregnancy or inflammation. For this reason, leukocytes or platelets have been proposed as reflecting tissue level. However, numerous methodological problems still exist, regarding, for example the quantity of blood to be drawn, the good separation of cells, contaminations during sampling and standardization of interlaboratory results. Except for manganese, selenium and antioxidant enzymes such as Cu-Zn SOD, Se GPx, red blood cell measurements are not useful.

Urine trace element levels are not commonly used in the assessment of human mineral studies, except for assessing urinary losses in some pathologies (Zn in diabetes) or effect of supplemental intakes (Cr).

Saliva and sweat have been used because they are very rich in hormones, growth factors, enzymes and proteins. However, variations in levels are very large and these indices may not be sufficiently sensitive to detect marginal mineral status.

Hair analysis, despite exogenous possible contamination remains very popular. Hair content is supposed to reflect element status but the usefulness of this material is not firmly established and its extensive commercial exploitation is not justified.

Tissues from biopsies (muscle, liver, bone) could be promising for the assessment of severe trace element depletion.

Serum copper and serum ceruloplasmin are not sensitive enough to reflect copper status. They remain very low even when hepatic copper is elevated. Moreover, the well-known influence of estrogen and inflammation on serum copper and ceruloplasmin levels has to be considered. In pets, as in other species, plasma copper concentrations did not reflect the copper intake and status.

Serum zinc is a rather good index of status, if hemolysis or platelet contamination are avoided. Results must be interpreted according to species, age, and global nutritional status (albuminemia, since zinc and albumin are strongly correlated). Erythrocyte zinc is a doubtful parameter. Leukocyte and platelet zinc levels are still matter of debate since there are discrepancies among published data. Urinary zinc is sometimes used to follow the mechanisms of deficiency. Hair analysis has yielded more interesting results with zinc than with other trace elements.

Serum or plasma selenium is one of the most valid direct indices of selenium status. This variable correlates well with tissue and erythrocyte selenium concentrations and with glutathione peroxidase activity in erythrocytes.

Direct assessment of chromium status has been investigated using serum chromium determination. In most of the Cr supplementation studies, the efficacy of the supplemental intake is monitored by Cr urinary level.

Serum manganese is a sensitive method to assess manganese status and effect of supplementation. Whole blood and erythrocyte manganese are sometimes preferable as index of manganese status because their concentration is higher than in serum.

**FUNCTIONAL INDICES**

Functional indexes may suggest more strongly than static markers, the mechanism of deficiencies. The measurement of enzymes such as Mn SOD, Cu-Zn SOD, Se GPx, in plasma and erythrocytes, platelets and tissues is now currently done as well as some markers useful in estimating the response to a supplementation (immunity for Zn or Se, or HbA1C for Cr).

**Conclusions**

Considering the biological and clinical consequences of trace element disturbances, more attention should be devoted to trace element status in human and animals. Trace element intakes and status are frequently marginal in large segments of the population, resulting in an higher risk of nutrition-related diseases. Regarding the essential protective roles of zinc and selenium against oxidative damage and decline of immune functions, or the beneficial effects of chromium on glucose tolerance, there is now increasing evidence that appropriate supplemntations, restoring marginal trace element status, could reduce in human the risk of degenerative diseases including cardiovascular diseases, cancer, diabetes and dementia, and, in pets could participate to the improvement of functions like reproduction, immunity, or vision and taste. Surprisingly, little information is available concerning the real mineral requirements of pets and additional research also needs to be done to evaluate the efficiency of supplemntations. Numerous questions need to be answered about the nature and forms of supplementation, the doses administrated and the duration. Interpretation of the studies is also often limited by, mainly, use of inappropriate indicators of status. Most of the reported parameters reflect biological modifications and few studies focused on clinical or functional signs, such as number of infections, overall health or incidence of diseases.

**References**


