Review Article

# Leptin and zinc relation: In regulation of food intake and immunity

**Abdulkerim Kasim Baltaci, Rasim Mogulkoc**

*Department of Physiology, Selcuklu Medical School, Selcuk University, Konya, Turkey*

## ABSTRACT

Leptin is synthesized and released by the adipose tissue. Leptin, which carries the information about energy reserves of the body to the brain, controls food intake by acting on neuropeptide Y (NPY), which exercises a food-intake-increasing effect through relevant receptors in the hypothalamus. Zinc deficiency is claimed to result in anorexia, weight loss, poor food efficiency, and growth impairment. The fact that obese individuals have low zinc and high leptin levels suggests that there is a relation between zinc and nutrition, and consequently also between zinc and leptin. Leptin deficiency increases the predisposition to infections and this increase is associated with the impairments in the production of cytokines. Zinc has a key role in the sustenance of immune resistance against infections. Dietary zinc deficiency negatively affects $CD_4^+$ cells, Th functions, and consequently, cell-mediated immunity by causing a decrease in the production of IL-2, IF-γ, and TNF-α, which are Th1 products. The relation between zinc and the concerned cytokines in particular, and the fact that leptin has a part in the immune responses mediated by these cytokines demonstrate that an interaction among cellular immunity, leptin and zinc is inevitable. An overall evaluation of the information presented above suggests that there are complex relations among food intake, leptin and zinc on one hand and among cellular immunity, leptin and zinc on the other. The aim of the present review was to draw attention to the possible relation between zinc and leptin in dietary regulation and cellular immunity.

**Key words:** Dietary regulation, cellular immunity, leptin and zinc

## Introduction

Leptin is a recently described hormone with protein structure. It is synthesized and released by adipose tissue.[1] Leptin, which carries the information about energy reserves of the body to the brain, controls food intake by acting on NPY, which exercises a food-intake-increasing effect through relevant receptors in the hypothalamus.[1] There is an increasing evidence highlighting the importance of leptin, which is a key hormone in the regulation of body weight and nutrition in animals and humans alike.[1,2] Zinc, which is known to play extensive and pivotal roles in the mammalian system is accepted as a trace element that is crucial in the growth of humans and many animal species.[3] Zinc is said to be involved in the fat metabolism, insulin resistance and obesity, whereas zinc deficiency in animals is claimed to result in anorexia, weight loss, poor food efficiency, and growth impairment.[3,4] Zinc, an essential trace element, also has a role in the regulation of appetite.[3-5] The fact that obese individuals have low zinc and high leptin levels suggests that there is a relation between zinc and nutrition, and consequently also between zinc and leptin.

Due to the similarity of the structure of leptin and leptin receptors with cytokines, leptin may also be classified as a cytokine.[6] Therefore, leptin deficiency increases the predisposition to infections and this increase is associated with the impairments in the production of cytokines.[7] Cellular immune response to infections is marked with Th1 cell activation and elevated levels of IL-2, IF-γ, and TNF-α.[8] Leptin plays an active role in these immune responses.[6,7] Zinc has a key role in the

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**Corresponding Author:** Dr. Abdulkerim Kasim Baltaci, Department of Physiology, Selcuklu Medical School, Selcuk University, 42075, Konya, Turkey. E-mail: baltaci61@yahoo.com

sustenance of immune resistance against infections.[9] Its catalytic, structural and regulatory functions make this element indispensable in the development of immune response.[9] According to a currently held view, the deficiency of no other element causes a more serious impairment than that of zinc and it is accepted that zinc deficiency in humans is among the most common nutritional causes of immunodeficiency.[9] Dietary zinc deficiency negatively affects $CD_4^+$ cells, Th functions, and consequently, cell-mediated immunity by causing a decrease in the production IL-2, IF-γ, and TNF-α, which are Th1 products.[9,10] The relation between zinc and the concerned cytokines in particular, and the fact that leptin has a part in the immune responses mediated by these cytokines demonstrate that an interaction among cellular immunity, leptin and zinc is inevitable.

An overall evaluation of the information presented above suggests that there are complex relations among food intake, leptin and zinc on one hand and among cellular immunity, leptin and zinc on the other. The presence of reports indicating that zinc might be a mediator of leptin production is significant evidence lending support to this view. The aim of the present review was to draw attention to the possible relation between zinc and leptin in dietary regulation and cellular immunity.

## Leptin in Regulation of Food Intake

Although significant advances have been made regarding the biological controls over food intake and body fat tissue regulation, the increasing prevalence of obesity continues to pose a critical health problem.[11] Leptin, which was first described by Zhang, *et al.*,[12] and has been widely researched since then, is the 167-amino-acid hormonal protein product of the obesity gene. Leptin, which was originally described in relation to satiety and energy balance was later claimed to be an anti-obesity factor that exercised a feedback effect from adipocytes to hypothalamus. Therefore, many studies have focused on the effect of leptin on the regulation of food intake. The major target organ for leptin to act is hypothalamus.[13] Leptin controls food intake through its receptors in the hypothalamus by inhibiting the release of NPY which has an augmentative effect on food intake. Leptin administration reduces body fat mass and food intake. Leptin deficiency and a change in leptin receptors associated with any reasonable increase the synthesis and release of NPY in the hypothalamus, which leads to the manifestation of obesity.[14] Besides, both NPY and NPY messenger ribonucleic acid (mRNA) concentrations are elevated in leptin-deficient obese rats whose leptin levels drop after leptin administration.[14]

Melanocyte-concentrating hormone (MCH) is an neuropeptide that acts to increase nutrition.[15] MCH mRNA level is elevated in obese rats and is restored to normal after leptin administration.[15]

Leptin receptors were shown in the neurons of corticotropin releasing hormone (CRH) in the paraventricular nucleus (PVN) which has an inhibiting effect on food intake. Leptin increases CRH mRNA in PVN and stimulates the production of CRH.[16]

It is known that the increase in noradrenalin secretion after the stimulation of the sympathetic system leads to weight loss. Leptin causes an increase in the energy consumption by playing a key role in the stimulation of the sympathetic system.[17]

There is also a relationship between insulin and leptin. Circulating amounts of leptin drop during hunger, whereas leptin levels were observed to increase in rats fed with carbohydrates. Presence of leptin receptors in the β cells of pancreas indicates that leptin influences insulin synthesis through negative feedback.[18]

## Zinc in Regulation of Food Intake

Zinc has an important part in the regulation of nutrition. Marginal zinc deficiency is associated as much with decreased appetite as with low body mass and both of these negative situations can be corrected with zinc supplementation.[19] Changes in the sense of taste are accepted as the significant effect of zinc on appetite.[19] However, the most widely accepted mechanism is that the alterations in appetite results from the general or local changes in neurotransmitter concentrations at the hypothalamic level associated with the adjustments in zinc levels.[20] Zinc deficiency is known to cause specific and deep anorexia in experimental animals. More importantly, zinc supplementation to rats fed on a zinc-deficient diet brings about an increasing effect on fat-free body mass.[19,20] Features observed in zinc deficiency like lack of appetite, weight loss, growth retardation, and amenorrhea are all seen in anorexia nervosa (AN) patients.[21] Therefore, it was reported that zinc deficiency contributed to AN symptoms.[21] Restoration of the body weight in the recovery process of AN should necessarily include adequate zinc in the diet. As a matter of fact, zinc levels in the hypothalamus were shown to decrease in AN, whereas zinc supplementation increased body weight.[21]

There is a substantial relationship between NPY and galanin regulation in the case of anorexia induced by zinc deficiency.[22] Selvais *et al.*[22] showed that NPY mRNA

increased in the hypothalamus of zinc-deficient rats, but this increase was not detectable in NPY levels. Similarly, Lee *et al.* found that NPY mRNA increased by 100% whereas NPY levels increased by 50% in zinc deficiency.[23] In any case, there is no study reporting decreased NPY levels in zinc deficiency.[22,23] Reduced food intake despite elevated NPY levels in zinc deficiency is described as NPY resistance.[22,23] It is speculated that this resistance may be caused by factors such as the impairment of the transformation of pro-NPY to active NPY, decreased NPY secretion from the neurons and reduced NPY signal generation. The concentration of galanin, a hunger-stimulating peptide like NPY, is also significantly reduced in zinc deficiency.[22,23] Galanin mRN in the hypothalamus was reported to be low in zinc deficiency, whereas Kennedy *et al.*[24] demonstrated that galanin concentration in PVN in zinc-adequate rats was 120 times higher than that in zinc-deficient rats. Galanin reduces the effect of NPY during anorexia.[24] Failure to increase food intake despite elevated NPY levels during zinc deficiency may be attributed to the inhibition of the galanin concentration.

Dynorphin is an opioid peptide whose intracerebrovascular infusion stimulates food intake in rats.[25] In a study, infusion of 1 and 10 μg dynorphin to their right ventricle caused zinc-adequate rats to respond to food intake with a dose-dependent increase. Zinc-deficient rats did not respond to 1 μg dynorphin infusion, whereas their response to 10 μg dynorphin was found to be quite low in comparison to the response of zinc-adequate rats.[25] In a study which evaluated the relation between naloxone and zinc as an indicator of the opioid peptide receptor sites, a high affinity for naloxone was demonstrated in the brain tissue membranes of zinc-deficient rats.[25]

Zinc is a strong modulator of amino acids' binding to receptors associated with neurotransmission.[25] The presence of zinc is a requisite for the synthesis of proteins that are necessary for the production of γ-aminobutyric acid (GABA) which is known to stimulate food intake. Receptors that are formed from the α and β subunits of GABA are particularly sensitive to zinc. Essatera, *et al.*[25] investigated the relationship between the central effects of muscimol, a γ-aminobutyric acid (GABA) agonist, and zinc and nutrition. Administration of this substance did not bring about any stimulating effect on food intake in zinc-deficient rats. Consequently, the concerned researchers concluded that reduced food response in these rats was associated with the decreased response of receptors in the brain due to zinc deficiency.[25]

Zinc is required for the synthesis of serotonin, which is a critical neurotransmitter.[26] Serotonin stimulates the sensation of satiety and reduces food intake.[26] Similarly, dopamine activation decreases food intake.[27] However, high-dose zinc administration was shown to inhibit the binding of dopamine to $D_1$ and $D_2$ receptors, which are important in dopamine's food intake-inhibiting effect.[26] These seemingly contradictory results in the relationship between neurotransmitters and zinc suggest that zinc may be playing a regulator role in food intake through neurotransmitters.

Zinc is also associated with thyroid hormones which have critical effects on the metabolic rate.[28] Zinc deficiency inhibits TSH release in the anterior hypophysis and brings about a decrease in thyroid hormone levels.[28] Zinc is also involved in the structure of 1,5-deiodinase enzyme which transforms $T_4$ to $T_3$.[28]

Zinc is found in the α and β cells of pancreas.[29] Zinc is particularly necessary in β cells for the production, storage and release of insulin.[29] Insulin secretion was shown to drop in zinc deficiency.[29] Zinc increases the activity of insulin signaling pathway.[29] *In vivo* zinc deficiency causes both a decrease in insulin secretion and lessened cellular reaction to insulin.[30] Therefore, zinc deficiency may reduce the ob gene expression stimulated by insulin.

## Leptin and Zinc Relation in Food Intake

Recent studies exploring the relationship between zinc and leptin demonstrate that zinc may critically impact leptin secretion.[31] Chen, *et al.*[32] found elevated leptin and reduced zinc levels, as well as a significant increase in the urinary zinc excretion in mice with sucrose-induced obesity.[32] Zinc supplementation to the obese mice in the same study caused a further increase in leptin levels and restoration of obesity induced by sucrose.[32] The authors suggested in their study that leptin resistance that occurred in obesity might have resulted from zinc deficiency.[32] In this case, zinc may either directly affect leptin gene expression or indirectly cause leptin production by increasing glucose use of the fatty tissue. It was reported that zinc deficiency inhibited leptin secretion from the fatty tissue, whereas supplementation of a physiological dose of zinc increased both leptin levels and glucose intake in mice with hyperglycemia induced by streptozotocin (STZ).[33] Zinc deficiency also inhibited IL-6 secretion of the fatty tissue in these mice.[33] This is an interesting result as leptin and leptin receptors are structurally similar to IL-6.[33] In conclusion, it was demonstrated that metabolic defects that arise in mice with hyperglycemia induced by STZ could be restored by supplementation of zinc in physiological doses.

Maybe the most important study about the relationship between zinc and leptin is the one by Ott and Shay.[34] These researchers examined how zinc deficiency affected leptin gene expression and leptin secretion in the fatty tissue.[34] A decrease was found in the ob mRNA content of the fatty tissue in rats fed on a zinc-deficient diet with a concomitant and significant decrease in leptin secretion from the fatty tissue.[34] More interestingly, a significant decrease was observed in the leptin secretion per gram of fatty tissue in zinc-deficient rats, when compared to their controls.[34] It was noted in the same study that insulin levels were also significantly inhibited in zinc-deficient rats and it was concluded that decreased insulin levels and response might be responsible for the lessened Ob gene expression.[34] The major question that needs to be clarified in this relation is whether the decrease in leptin gene expression is caused by a decrease in transcription as zinc is also involved in the structure and function of RNA polymerase.[35] Zinc deficiency specifically alters the composition of mRNA synthesis of the cell.[35] Proteins are either found in smaller amounts or are not found at all in zinc-deficient systems, when compared to systems with adequate zinc.[35]

The relationship between zinc and leptin was examined in nine healthy individuals who had zinc deficiency induced by diet.[36] It was established that zinc deficiency significantly inhibited leptin secretion from the fatty tissue and IL-2 and TNF-α levels decreased parallel to inhibited leptin levels. Zinc supplementation to these individuals was observed to result in a significant increase in leptin secretion together with a critical increase in the concentrations of IL-2 and TNF-α. It was concluded in the concerned study that there was a positive correlation between zinc and leptin and that this effect of zinc on leptin might be mediated by elevated IL-2 and TNF-α levels.[36] This view which argues that zinc is a regulator of leptin concentration in humans is supported by similar results in the study by Chen, *et al.*[37] Consequently, there is a positive correlation between zinc and leptin. These results may have important implications in the clinic.

## The Role of Leptinin Immunity

Due to the similarity of leptin and leptin receptors to cytokines, leptin may also be classified as a cytokine.[38] It was argued that leptin might have a fundamental part in the production and maintenance of the immune response. Leptin structurally resembles IL-2 and IL-6 and is a critical T-cell growth factor.[39] Therefore, leptin deficiency increases predisposition to infections and this increase is associated with impairments in the production of cytokines.[40] Presence of leptin receptors in $CD_4^+$ and $CD_8^+$ lymphocytes is also evidence of the relation between leptin and immune functions.[41] Leptin stimulates thymic functions and the proliferation of $CD_4^+$-T cells, and has a stimulating effect on Th1 cells and an inhibiting effect on Th2 cells.[41] It plays a substantial role in Th1 cell activation and elevated levels of IL-2, IFN-γ, and TNF-α, which are Th1 products, in cellular immune response to infections.[41,42] Leptin exercises a crucial stimulating effect on the production of the concerned cytokines by Th1.[40-42] The fact that naturel killer (NK) NK cell activation responds to leptin stimulation also demonstrates that leptin is critically involved in the NK cell activation.[41,42]

## The Role of Zinc in Immunity

Many diseases in humans are accompanied by changes in the zinc metabolism.[43,44] Just like the animals with zinc deficiency, humans were also found to catch infections more readily in the case of zinc deficiency.[45,46] The most typical example of this situation is infants with Acrodermatitis enteropathica who have hereditary zinc deficiency and who easily acquire infections and may even die.[47] Immunological reactions are events which require an increase DNA, RNA and protein synthesis.[43] One of the major roles of zinc is to stimulate the synthesis of DNA, RNA and protein through enzymes.[44] Zinc-containing enzymes like DNA, RNA, polymerase and thymidine kinase take a part in these events.[43,44] Consequently, zinc is inevitably involved in immune reactions. According to the currently held view, the deficiency of no other element causes as serious an impairment as that of zinc and the deficiency of zinc is considered among the major causes of immunodeficiency.[43,44] Dietary zinc deficiency negatively affects cell-mediated immunity by bringing about a decrease in $CD_4^+$- cells, Th1 functions in particular, and consequently a fall in the production of IL-2, IFN-γ, and TNF-α, which are Th1 products.[48] Thymuline hormone, which is secreted from the thymus and required for the production and maintenance of cellular immune functions, is a zinc-dependent hormone.[49] Thymuline needs zinc for its biological activity.[49] Thymuline which is not bound to zinc is inactive and exercises an inhibitive effect on active thymuline.[49,50] Zinc-thymuline complex consists of thymicepithelial cells (TEC).[49] TEC acquires zinc from the circulation.[39] Thymuline binds zinc and carries it to T-lymphocytes at pg/ml levels.[49,50] Factors which stimulate the secretion of zinc-thymuline complex by TEC are zinc and IL-1.[49,50] IL-1 works in coordination with zinc-thymuline complex and supports IL-2 production and IL-2 receptor (IL-2 r) activity in T-lymphocytes.[49-51] It increases the production

of IFN-γ and TNF-α.[49,52] It is possible to say that a critical aspect of the thymic functions is the packaging and transfer of zinc to T-cell system and that this process is an excellent neuroendocrine control,[49] as zinc not only affects the Th1 cells and the cytokines secreted by them, but also the activation of NK cells.[49,53]

## Leptinand Zinc Relation in Immunity

It is observed that the effects of zinc and leptin on cellular immunity in particular focus on Th1 cells and cytokine secretions. It is known that thymuline hormone is necessary for the Th1 cell and cytokine secretion and that thymuline is a zinc-dependent hormone.[49-51] Therefore, zinc must have a substantial role in the effect of leptin on immune functions.

However, the scarcity of studies about the relation between the immune system on one hand and leptin and zinc on the other is striking. *Toxoplasma gondii* infection caused an increase in leptin secretion without significant changes in the body weights of rats.[54] However, 4-week zinc deficiency resulted in a significant decrease in both the body weight and leptin levels of infected animals. The same study reported that 4-week zinc supplementation increased leptin secretion without changing the body weight of infected rats (unpublished data).

## Conclusion

On the basis of the reports published on this topic, it can be concluded that there are complex and critical relationships between zinc and leptin in terms of the regulation of both food intake and cellular immune responses, but that zinc may be playing a more important role in the regulation of the effects of leptin hormone.

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