Linking Zinc and Leptin in Chronic Kidney Disease: Future Directions

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Abstract Anorexia is a common complication in patients
with chronic kidney disease (CKD) and is associated with
the development of malnutrition and an increased risk of
mortality. Several compounds are linked to anorexia in
these patients; however, the mechanisms are unknown. Zinc
(Zn) deficiency is associated with decreased food intake
and has been observed in CKD patients. In addition, leptin
is an anorexigenic peptide, and patients with CKD present
generally high levels of this hormone. Studies have
suggested an association between Zn and leptin status in
human and rats; however, the results are inconsistent. Some
claimed that Zn supplementation does not change leptin
release or that there is no significant relationship between
Zn and leptin. Others have reported that Zn might be a
mediator of leptin production. CKD patients have hyper-
leptinemia and hypozincemia, but the relationship between
Zn deficiency and leptin levels in CKD patients has been
poorly understood until now. The aim of this review is to
integrate knowledge on leptin and Zn actions to provide a
cohesive clinical perspective regarding their interactions in
CKD patients.

Keywords Leptin · Zinc · Anorexia · Chronic kidney
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Introduction

Patients with chronic kidney disease (CKD) frequently
experience a loss of appetite (anorexia), which increases in
severity during disease progression [1]. Anorexia reduces
oral energy and protein intake, thus contributing to the
development of malnutrition and cachexia [2]. The exact
causes of anorexia among patients with CKD are not yet
fully characterized, and it is likely that myriad of factors
contribute.

The impact of zinc (Zn) on this process is poorly studied
in the renal population despite the facts that this mineral has
a wide spectrum of biological activities, and its deficiency
has been related to various dysfunctions and alterations of
normal cell metabolism such as anorexia. Anorexia results
in decreased food intake with subsequent weight loss,
suggesting that Zn status might affect the complex
mechanisms underlying normal food intake [3–5].

The most widely accepted mechanism for Zn-induced
changes in appetite is an alteration in the hypothalamic
neurotransmitter metabolism by influencing the leptin
system [6]. Leptin is an anorexigenic peptide that is
primarily known for its role as a hypothalamic modulator
of food intake, body weight and fat stores. Leptin levels are
directly correlated to white adipose tissue mass or the
energy balance of adipocytes, and after crossing the blood
brain barrier, leptin activates specific receptors at the

hypothalamic central level [7]. CKD patients have inappropriately high serum leptin levels; it has been speculated that hyperleptinemia in these patients may be one of the factors mediating anorexia and wasting [8].

Some researchers have tried to investigate the Zn status and its action on plasma leptin levels in experimental animals and humans [6, 9, 10]. In CKD patients, the relationship between Zn deficiency and leptin levels is poorly understood to date. Therefore, the intent of this review is to integrate knowledge on leptin and Zn actions to provide a cohesive clinical perspective regarding their interactions in CKD.

Zinc

The anorexia resulting from Zn deficiency consistently results in decreased food intake with subsequent underweight results. Although changes of taste acuity and altered membrane fluidity may contribute to Zn's effect on appetite, the most widely postulated mechanism for Zn-induced changes in appetite is an alteration in the concentrations of neurotransmitters either in the circulation or locally in the hypothalamus [11].

Communication from the periphery to the brain involves neural feedback, e.g., by the vagus nerve, as well as blood-borne factors, including both metabolites and hormones, which can affect brain function [12]. Neuropeptide Y (NPY) is one of the most potent appetite-regulating neuropeptides and stimulates food intake behavior; this peptide has received much attention with regard to food intake regulation in Zn deficiency [13], which might therefore cause anorexia because Zn deficiency inhibits the release of NPY that is required for orexigenic receptor activation [14, 15].

Taken together, some other peptides might be responsible for the loss of appetite in Zn deficiency, such as cholecystokinin, calcitonin gene-related peptide, galanin and serotonin [16–18]. However, the most widely accepted mechanism for Zn-induced changes in appetite is an alteration in the hypothalamic neurotransmitter metabolism by influencing the leptin system [6]. Tallman et al. [19] suggested that an association between the Zn status and adiposity may also be due, in part, to the relationship between Zn metabolism and leptin.

Leptin

The hormone leptin was originally discovered in 1994 due to its involvement in the homeostatic regulation of body weight [20]. This 16 kDa protein encoded by the obese gene is primarily synthesized in adipose tissue and was first linked to obesity when its importance in controlling body mass size via inhibition of appetite was discovered [20, 21]. Circulating leptin levels are proportional to adipose tissue mass. Therefore, leptin levels can be considered as a signal to the body of its energy reserves [7].

This hormone acts through the leptin receptor (OB-R), which is expressed in the nervous system and peripheral tissues such as adipose tissue, skeletal muscles, pancreatic β cells and liver, thus suggesting that leptin has both an autocrine and a paracrine function in adipose tissue. This ubiquitous distribution of OB-R leptin receptors in almost all tissues underlies the pleiotropic roles of leptin [22]. After binding to its receptors in the hypothalamus, leptin stimulates a specific signaling cascade that results in the inhibition of several orexigenic peptides (NPY, melanin-concentrating hormone, orexins, agouti-related peptide-AgRP) while stimulating several anorectic peptides (α-MSH, cocaine- and amphetamine-related transcript) and corticotropin-releasing hormone [23].

Studies have investigated the regulation of leptin levels and concomitant Zn deficiency in rats and in humans; however, results of these studies are contradictory.

Bribiescas [24] argued that Zn supplementation did not change leptin secretion, and Olusi et al. [25] showed that there was no significant relation between Zn and leptin in healthy individuals. In contrast, Chen et al. [26] reported an inverse correlation in plasma values between Zn and leptin.

Although recent experimental evidence demonstrates that Zn deficiency decreases leptin levels while Zn supplementation increases leptin levels, the relationship between Zn status and the leptin system in humans remains unknown.

Association Between Zn and Leptin Levels in Observational Studies

Zn deficiency leads to reduced serum leptin concentrations in rats and humans and reduced leptin secretion by rat adipocytes, while Zn repletion reverses this effect [10]. Kwun et al. [27] showed that leptin mRNA levels in rats were decreased by Zn deficiency independently of food intake, suggesting that Zn targeted one or more factors affecting energy utilization efficiency and leptin gene expression.

Mantzoro et al. [6] studied nine healthy men with marginal Zn deficiency and observed that leptin levels decreased in response to Zn depletion and increased after Zn supplementation. They concluded that Zn may influence serum leptin levels, possibly by increasing the production of IL-2 and TNF-α.

In addition, it is notable that leptin levels may be reduced during Zn deficiency because anorexia caused by Zn deficiency can lead to weight loss and consequently to a reduction in body fat, as reported by Mangian et al. [9], who showed that leptin levels were reduced in Zn-deficient rats because anorexic rats had less body fat compared with controls. Other studies also showed that leptin levels were reduced in rats receiving a Zn-deficient diet [13, 28].

In contrast, results obtained by other researchers were different from the findings cited above. Chen et al. [26] suggested that there was an inverse correlation between Zn and leptin levels in both obese and lean individuals. Chen and Lin [29] observed that Zn supplementation reduced sucrose-induced obesity in mice. In 2003, Lee et al. [30] found that Zn deficiency increased serum leptin levels but that Zn supplementation decreased those levels. In addition, they also indicated that the regulation of leptin expression by Zn deficiency or sufficiency was tissue-specific.

Researchers studied the effects of dietary Zn deficiency and supplementation on adiposity, serum leptin and fatty acid composition of adipose tissue in mice fed low-fat or high-fat diets. The high fat-fed mice had reduced adipose Zn concentrations. Furthermore, serum leptin concentration was positively correlated with body weight and body fat and negatively correlated with adipose Zn concentration. These results support an interrelationship among obesity, leptin and Zn metabolism [19].

Konukoglu et al. [31] studied the relationship of plasma Zn and leptin in obese diabetic and non-diabetic patients and suggested that hypozincemia observed in obese diabetic patients contributes to the resistance to leptin and that this phenomenon does not appear to be associated with mechanisms related to the hormone receptor.

Some studies suggest that the low Zn concentration in plasma, associated with an increase in certain tissues, could be related to hyperinsulinemia and to insulin resistance [19, 32].

Several potential mechanisms have been suggested for Zn affecting insulin action, including a role for Zn in the modulation of the activity of the insulin receptor tyrosine kinase. Zn has been shown to enhance tyrosine kinase phosphorylation compared with other cations [31]. Based on these findings, Zn deficiency could lead to insulin resistance, which subsequently is related to increased plasma concentrations of leptin under high dietary fat or sucrose.

On the other hand, changes in leptin concentrations resulting from deficiencies in specific micronutrients may result in changes in adipose tissue mass and increased activation of the inflammatory response. In fact, Zn deficiency can lead to increased oxidative stress and an inflammatory response as well as reduced lean body mass and increased body fat, which may be risk factors for obesity and increased leptin levels [33].

Zn and Leptin in CKD

Many studies have shown a high prevalence of Zn deficiency in CKD patients [34–39]. Lower levels of Zn might occur because of reduced renal function, proteinuria, leading to losses of protein-bound elements, alterations in gastrointestinal absorption, inflammation, hypoalbuminemia and the dialysis procedure per se [36, 40].

Zn deficiency can also cause anorexia in CKD patients; however, the mechanisms by which Zn deficiency induces anorexia are unclear. Studies have investigated the regulation of leptin levels are altered during Zn deficiency.

In contrast to Zn, CKD patients present high leptin plasma levels [41–43]. This elevation occurs due to uremic retention, hyperproduction or both, and acquired leptin resistance is thought to be present in uremic individuals. It has been speculated that uremic patients might show a downregulation of hypothalamic leptin receptors associated with the high circulating leptin levels [44, 45]. The effects

Fig. 1 Hypothetical relationship between Zn deficiency and high leptin levels in CKD patients
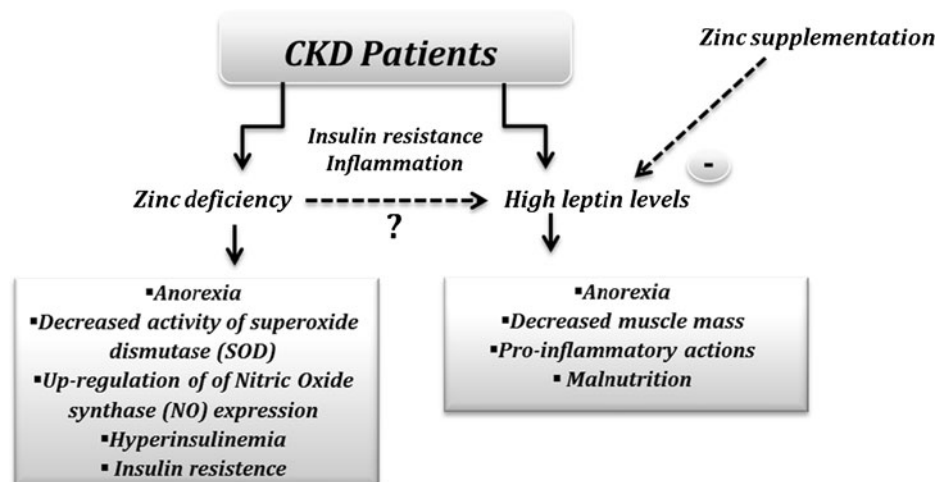
of hyperleptinemia on malnutrition in the CKD population have been of much interest. Data derived from cross-sectional studies tend to support the hypothesis that high serum leptin levels may contribute to anorexia and malnutrition in these patients [1, 45].

Castaneda et al. [46] showed that high leptin levels were associated with decreased muscle mass CKD patients, leading to the development of malnutrition. Studies, such as Stenvinkel et al. [47] and Lam et al. [48] in patients on peritoneal dialysis, also found higher leptin levels in patients with a loss of muscle mass, confirming that the increased leptin contributes to malnutrition in these patients. Leptin has several additional effects on peripheral tissues. It increases the inflammatory response by stimulating the production of cytokines, enhances the proliferation of endothelial cells, vascular smooth muscle cells and neovascularization [49]. Then the pro-inflammatory actions of leptin can promote anorexia, wasting and malnutrition in CKD patients. Accordingly, in CKD patients and other inflammatory states, inflammation and increased leptin levels participate in a vicious cycle, exerting an influence on each other [42].

In conclusion, CKD patients have hyperleptinemia and hypozincemia and, according to the data described above, it seems reasonable to speculate that an interactive connection may exist between Zn and leptin.

Linking Zn and Leptin in CKD: Future Directions

The relationship between Zn deficiency and leptin in CKD patients is poorly documented. As far as we know, there is only one study on renal populations that addresses leptin and Zn, and this study did not find any correlation between plasma leptin and Zn levels in hemodialysis patients [50]. Additionally, there is a high prevalence of Zn deficiency in patients with CKD, as previously discussed, which is also correlated with signs of malnutrition.

Most of the previously mentioned studies involving Zn, leptin and food intake conclude that Zn may be a mediator of the effects of leptin, but there are no studies that correlate the levels of Zn with leptin in patients with CKD. Therefore, considering the effects of anorexia and the consequences of malnutrition on morbidity and mortality of hemodialysis patients, our hypothesis is that the Zn deficiency could increase the leptin levels and lead the patients to anorexia and consequently malnutrition (Fig. 1).

Recently, we evaluated 48 hemodialysis patients and compared them with 21 healthy subjects. We observed that the leptin levels were significantly higher in the hemodialysis patients than in subjects who were healthy individuals, whereas the serum Zn levels were significantly lower, and plasma leptin was correlated negatively with plasma Zn

levels [51]. These preliminary data may shed a new light on the determinants of food intake and body composition in CKD.

Thus, further studies regarding the molecular and biochemical basis are required to investigate the regulatory pathways by which Zn and leptin interact to regulate energy intake and body composition to study whether there is any relationship between Zn, leptin and malnutrition in the hemodialysis patients.

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