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REVIEW

Systemic zinc redistribution and dyshomeostasis in cancer cachexia

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Abstract Cachexia affects up to two thirds of all cancer patients and is a significant cause of morbidity and mortality. It is a complex metabolic syndrome associated with the underlying illness and characterized by loss of skeletal muscle tissue with or without loss of fat mass. Cachexia's other prominent clinical symptoms include anorexia, systemic inflammation, pediatric growth failure, and hypogonadism. The relationship between the symptoms of cancer cachexia and the underlying illness is unclear, and there is an urgent need for a better understanding of the pathophysiology of this syndrome. Normal Zn metabolism is often disrupted in cancer patients, but the possible effects of systemic Zn dyshomeostasis in cachexia have not been investigated. We propose that the acute phase response can mediate Zn redistribution and accumulation in skeletal muscle tissue and contribute to the activation of the ubiquitin–proteasome pathway that regulates protein catabolism. This chronic redistribution deprives Zn from other tissues and organs and compromises critical physiological functions in the body. The cardinal symptoms of Zn deficiency are anorexia, systemic inflammation, growth failure in children, and hypogonadism. These symptoms also prominently characterize cancer cachexia suggesting that the role of systemic Zn dyshomeostasis in cachexia should be investigated.

Keywords Cachexia muscle wasting · Zinc · Systemic Zn dyshomeostasis · Anorexia · Systemic inflammation · Hypogonadism · Growth failure

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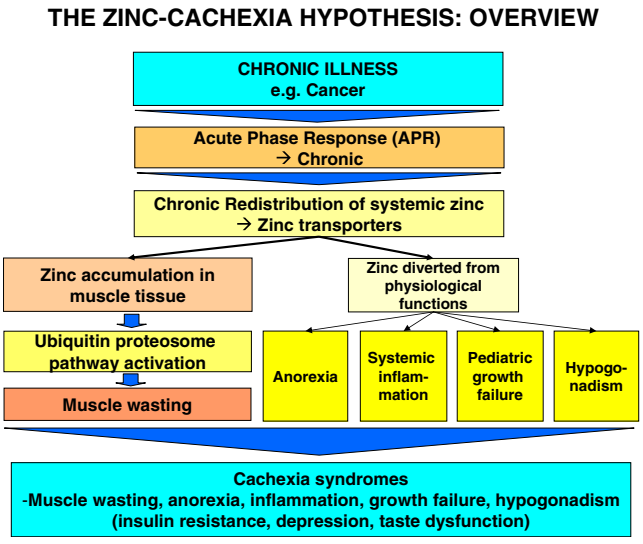
1 Introduction

Cachexia affects up to two thirds of all cancer patients and is directly responsible for one fifth of all cancer-related deaths [1]. Muscle wasting is one of the most devastating, complex, and enigmatic aspects of cancer, but it is also common in other conditions such as chronic heart failure [2], chronic obstructive pulmonary disease [3], chronic kidney disease [4], chronic inflammation [5], severe trauma [6], AIDS [7], and sepsis [8]. The 2008 Cachexia Consensus Conference defined cachexia as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass." Other prominent clinical features of cachexia include anorexia, systemic inflammation, pediatric growth failure, and hypogonadism [9]. It is unclear how these symptoms are related to each other or to the underlying illness, and as Lainscak and colleagues recently noted, there is an urgent need for effective therapies and a precise definition of this common and deadly syndrome [10].

We propose that systemic Zn dyshomeostasis is a salient characteristic of cancer cachexia, and that Zn redistribution is mediated by the acute phase response (APR) as a host defense mechanism in response to infection, inflammation, trauma, or cancer. We hypothesize that chronic APR can induce significant Zn accumulation in skeletal muscle tissue resulting in ubiqui-

tin–proteasome pathway mediated protein catabolism and functional systemic Zn deficiency associated with anorexia, inflammation, growth failure, and hypogonadism.

Zn is a critical trace element that has a broad range of vital catalytic and structural functions in all eukaryotic cells and higher organisms, and it is of exceptional biologic importance for humans [11]. As Maret points out, "Zn ions are essential for all forms of life. In humans, they have catalytic and structural functions in an estimated 3,000 zinc proteins" [12]. Zn homeostasis is often disturbed during cancer, and in certain malignancies Zn uptake appears to be an index of tumor viability [13]. Zn can also upregulate telomerase activity that is associated with the unlimited proliferation of cancer cells [14, 15]. However, Murakami and Hirano note that while tumors need Zn to survive and grow, "excess Zn may induce tumor cell apoptosis, although the sensitivities of the different types of tumors are likely to vary" [16]. Low Zn levels have been reported in cancer patients [17–22], but we are aware of only one clinical study that specifically examined the link between serum Zn levels and cancer-induced muscle wasting [23]. In 1989, Westin and colleagues showed in a small pilot study with 6 patients that cachectic subjects with head and neck cancer had significantly lower serum Zn levels compared to controls ($p<0.025$). The results should be viewed with caution due to the small size of the cohort and the fact that the patients were alcoholics. Alcohol abuse has been associated with abnormal Zn metabolism. It is important to note that while Zn is commonly measured from serum, normal levels can be found in patients suffering from Zn dyshomeostasis due to Zn released from catabolic muscles, hemolysis, protein binding, hormone-mediated redistribution, and postprandial effects [23, 24]. Future studies should consider an alternative method suggested by Prasad and colleagues for determining Zn status in humans that is not affected by these processes [25].



There are other important clinical mechanisms that can contribute to systemic Zn dyshomeostasis in cancer patients. These include low dietary intake of Zn, hypoalbuminemia, and fecal losses of Zn. The adult body contains 2–3 g of Zn [26], of which 57% is found in skeletal muscle and 29% in bone [27]. However, there is no functional reserve or store for Zn. The body uses a small rapidly exchangeable pool of Zn which is dependent on constant nutritional replenishment. The recommended daily allowance (RDA) for Zn is 15 mg [28], and low daily intake of Zn rich food stuffs such as shellfish, beef, lamb, veal, and poultry [29] can contribute to Zn deficiency in cancer patients. The majority (75–85%) of plasma Zn is bound to serum albumin [30], and hypoalbuminemia can compromise Zn transport. Finally, fecal losses of Zn due to gastrointestinal surgery associated with cancer can contribute to low Zn levels [31].

2 APR and Zn redistribution

We hypothesize that systemic Zn redistribution and dyshomeostasis play a central role in cancer cachexia. However, Zn metabolism is vital for human health and is normally tightly regulated. There is no systemic store for Zn [32], yet the body seems to be able to accommodate tenfold changes in Zn intake by adjusting the rate of absorption and excretion of the metal [27]. Considering how vigilantly physiological Zn homeostasis is maintained, we investigated if there is an identifiable mechanism that can initiate and sustain the redistribution of Zn in pathological situations.

APR is a host defense mechanism triggered in response to trauma, inflammation, infection, and cancer. Gabay and Kushner explain that "a large number of changes, distant from the site or sites of inflammation and involving many organ systems, may accompany inflammation [and] these systemic changes [are] referred to as the acute phase response, even though they accompany both acute and chronic inflammation" [33]. APR seems to play an important role in cancer cachexia and as Stephens, Skipworth, and Fearon note, "at the time of diagnosis, around half of all cancer patients will demonstrate an APR" [1]. The proportion of patients with APR increases with the progression of the disease, and in certain malignancies, the presence of APR is a significant predictor of survival [34].

One of the main functions of APR is the orchestrated acceleration of hepatic production of specific plasma proteins used during the defense response. To achieve this increased rate of protein production, APR initiates the hepatic amino acid uptake and the large increase in the synthesis of acute phase proteins by the liver [35]. The liver

of cancer patients and tumor-bearing animals incorporates amino acids at a significantly ($p<0.025$) higher rate compared to healthy controls [36]. The persistent hepatic synthesis of acute phase reactants may represent a nutritional sink that sucks amino acids mobilized from skeletal muscle tissue that is aggressively broken down during APR. Indeed, 2.6 g of muscle protein must be catabolized to produce 1 g of fibrinogen [1], one of the most important acute phase proteins [37]. The correlation between muscle wasting and increased hepatic protein synthesis is known, but the mechanism behind APR-mediated protein catabolism in skeletal muscle is poorly understood.

The redistribution of systemic Zn and hypozincemia are prominent characteristics of APR [33, 35, 38]. Clinical data indicate that APR-induced hypozincemia is in part due to internal Zn redistribution [39, 40], the liver being a major target [41]. However, Zn can also be redistributed into skeletal muscle during APR. A rat model of chronic heart failure that uses aldosterone to induce a persistent APR showed Zn^{65} uptake not only in the liver, but also in uninjured skeletal muscle where Zn^{65} increased nearly twofold after 1 week of aldosterone administration and remained 50% higher than controls at week 4 [42].

The pro-inflammatory cytokines, in particular tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) that are central to the induction of the APR [1], significantly reduce systemic Zn levels. The administration of TNF-α ($p<0.01$; [43]), IL-6 ($p<0.001$; [44]), and lipopolysaccharide (LPS; $p<0.0001$; [39]) results in the significant decrease of serum Zn levels. The chronic administration of IL-1 to rats resulted in significantly reduced plasma Zn levels (<70 μg/dl vs. >110 μg/dl, $p<0.01$), severely diminished appetite ($p<0.0001$), increased protein breakdown and decreased synthesis ($p<0.05$), and over a tenfold increase in IL-6 plasma levels ($p<0.001$; [45]). IL-6 significantly ($p<0.01$) upregulates the Zrt/IRT-like protein (ZIP) 14 Zn influx transporter that has a central role in inducing hypozincemia during APR [35]. The Zn transporters are divided into the ZIP influx and the Zn-transporter efflux transporter groups [46]. They move Zn into and out of cells and organelles and are responsible for Zn redistribution in pathological situations such as inflammation and cancer [47]. Key APR factors directly regulate Zn homeostasis, and chronic APR can lead to perpetual systemic Zn redistribution. These results also help to explain why cancer patients, who commonly demonstrate chronic APR, also suffer from systemic Zn dyshomeostasis.

3 Zn accumulation in muscle tissue

We suggest that systemic Zn dyshomeostasis observed in cancer is in part due to the accumulation of Zn in skeletal muscle tissue that constitutes ~40% of human body mass (BM). Malignant growth disturbs the Zn metabolism in the body [16], but we know of only two pre-clinical studies that specifically examined the relationship between cancer-induced muscle wasting and Zn accumulation in muscle tissue. A 1987 fibrosarcoma study with rats showed that Zn is significantly accumulated into cachexic skeletal muscle tissue ($p<0.05$; [48]). Zn levels in the tumor tissue doubled in the same 12-day period. We recently examined the role of Zn in the cachexia-inducing murine adenocarcinoma-16 (MAC-16) model and showed that Zn levels in skeletal muscle tissue correlate with muscle wasting [49]. The Zn concentration in the gastrocnemius muscle of mice with more than 20% weight loss was twice as high as that in controls ($p<0.05$). The extracellular Zn chelating compound D-myo-inositol 1,2,6-triphosphate (Alpha trinositol, AT; Bioneris Ab; [50]), a polyanionic isomer of myo-inositol phosphate that forms a mononuclear 1:1 complex with Zn and binds the ion to phosphates P1 and P6 in its inositol ring structure [51], reduced Zn accumulation ($p<0.05$) in skeletal muscle tissue while significantly attenuating muscle atrophy ($p<0.001$; [49]). We have previously shown that AT attenuates both the loss of lean body mass ($p<0.001$) and tumor growth ($p<0.01$) in the MAC-16 model. The anti-cachexic effect of AT was not dependent on tumor suppression. [52]. Also another metal chelator, curcumin (diferuloylmethane), that binds Zn through its beta-diketone group and forms a mononuclear (1:1) complex with Zn [53], attenuates weight loss ($p<0.05$) in the MAC-16 model [54].

A 1986 Lewis Lung Carcinoma (LLC) study showed that 21 days after tumor implantation Zn concentration in murine skeletal muscle tissue had doubled compared to the controls ($p<0.01$). The study did not measure muscle wasting [55], but LLC is known to cause cachexia and is commonly used as an animal model for the syndrome [56–58]. Interestingly, a 1987 study on hamsters with muscular dystrophy showed an 82% increase in the skeletal muscle Zn levels compared to controls ($p<0.001$; [59]). A recent study in mice with dystrophic muscle wasting reported similar results [60].

A recent clinical pilot study with 26 cancer cachexia patients showed that Zn progressively and significantly ($p<0.01$) accumulates in the skeletal muscle tissue of cachexic patients. In patients with more than 9.5% weight loss, the Zn concentration in skeletal muscle tissue more than doubled compared to healthy controls (Siren et al., unpublished results). To our knowledge this is the first clinical measurement of Zn concentrations in cachexic skeletal muscle tissue. Considering that in healthy individuals, approximately 60% of total body Zn is found in skeletal muscle tissue [27], that constitutes ~40 % of total BM, the doubling of Zn levels in cachexic muscle indicates that these patients suffer from severe systemic Zn dyshomeostasis.

Cachexic muscle tissue can significantly accumulate Zn, and the clinical usefulness of this trace element as a diagnostic biomarker for muscle wasting should be investigated.

4 Zn and the ubiquitin–proteasome pathway

It is unclear if Zn accumulation in cachexic skeletal muscle is a cause or an effect of protein catabolism. However, the fact that Zn chelators can significantly attenuate muscle wasting in vivo and also attenuate both increased protein degradation and decreased protein synthesis induced by diverse cachexic factors in vitro suggests that the ion may be a causative factor in the catabolic process.

In cachexia, increased protein degradation and decreased protein synthesis occur simultaneously and result in muscle wasting. The activation of the ubiquitin–proteasome pathway seems to be essential for protein catabolism [61–63] and has been implicated in a variety of pathological conditions [64]. According to Tisdale, "studies in animal models of cancer cachexia, as well as in cancer patients, suggest that the ubiquitin–proteasome pathway plays the predominant role in the degradation of myofibrillar proteins, particularly in patients with a weight loss of >10%" [65]. Double-stranded RNA-dependent protein kinase (PKR) seems to play an important in role the activation of the ubiquitin–proteasome pathway. Phosphorylation of PKR leads to the induction of eukaryotic initiation factor 2α (eIF2α) phosphorylation resulting in depressed protein synthesis. PKR also activates IκB kinase, leading to the degradation of the inhibitors IκBa and IκBb and the concomitant release of nuclear factor-κB (NF-κB) that is a central regulator of protein degradation [66]. Eley and Tisdale conclude that the "activation of PKR may provide the link between the inhibition of protein synthesis and induction of muscle protein degradation, leading to muscle atrophy in response to diverse cellular stress in a range of conditions in addition to cancer cachexia, including HIV-AIDS, sepsis, burns, and weightlessness" [67].

AT is an extracellular Zn chelator that effectively attenuates both the increased protein degradation and decreased protein synthesis induced by TNF-α, TNF-α+interferon-gamma, LPS, proteolysis-inducing factor (PIF), and angiotensin II (Ang II; all $p<0.001$; [68]). Tisdale notes that the activation of PKR is thought to be critical for both the depression protein synthesis and the increase in protein degradation, and that AT likely inhibits a common step leading to the activation of PKR. The effect of AT on protein degradation is accompanied by the attenuation of the increased expression and activity of the ubiquitin–proteasome pathway. AT completely attenuated the activation of PIF-induced phosphorylation of both PKR and eIF2α and the nuclear accumulation of NF-κB (all $p<0.001$). AT also inhibited the activation of caspase-3 and -8 ($p<0.001$), which are thought to lead to the activation of PKR. The ability of increasing concentrations Zn to reverse the attenuation by AT of the increased activity of the ubiquitin–proteasome pathway induced by PIF and Ang II, as well as the depression of protein synthesis induced by PIF (all $p<0.001$), indicates that Zn may be involved in the signaling process.

5 Effects of systemic Zn dyshomeostasis

We argue that chronic functional Zn deficiency in specific tissues and organs contributes to the salient clinical symptoms of cancer cachexia such as anorexia, systemic inflammation, pediatric growth failure, and hypogonadism. Zn dyshomeostasis associated with cancer may have serious implications for systemic Zn metabolism. As King and colleagues note, "because plasma must provide Zn to all the tissues, maintaining relatively constant plasma Zn concentrations is essential to sustaining normal function and health" [27]. Physiological signs of Zn depletion are not evident until a drop in plasma Zn concentration occurs, but clinical symptoms manifest rapidly thereafter. Zn deficiency has been studied for nine decades and is characterized by symptoms that are strikingly similar to those commonly found in cachexia. Against this background, it is indeed surprising that the possible link between systemic Zn dyshomeostasis and cancer cachexia has not been investigated.

However, nutritional factors such as leucine and other branched chain amino acids, arginine, glutamine, polyunsaturated fatty acids [69], creatine [70], and cystine [71] have been studied in relation to cancer cachexia. These factors have limited metabolic functions, and they cannot account for the severe and multifaceted symptoms that saliently characterize cachexia.

6 Anorexia in cachexia

Anorexia, broadly defined as the loss of appetite or desire to eat, is common in cancer cachexia patients. However, anorexia appears to be a distinct syndrome as it does not cause loss of lean body mass by itself [72]. The relationship between cachexia and anorexia is unclear, but it has been argued that cancer anorexia may result from the signaling defects of orexigenic factors such as neuropeptide Y (NPY; [65]). There is a demonstrated decrease in hypothalamic NPY immunostaining in tumor-bearing rats [73], and in anorexic cancer patients, the mean NPY serum levels are significantly ($p<0.004$) lower compared with healthy controls [74]. Zn deficiency is thought to induce anorexia by impairing the release of NPY from the terminals in the paraventicular nucleus of the hypothalamus that is required for receptor activation [75].

It is well known that Zn deficiency causes anorexia in many animal species [76, 77]. Chesters and Quarterman observed already 40 years ago that "a fall in food intake is highly characteristic of Zn deficiency" [78]. Young rats are very responsive to a Zn-deficient diet and exhibit decreased food intake within 3–5 days of Zn deprivation. Decreased appetite is the first visible sign of Zn deficiency, and it generally occurs in advance of other symptoms [79].

The correlation between anorexia and low systemic Zn levels has also been extensively studied in humans. Patients with eating disorders may develop Zn deficiency for a variety of reasons, such as low dietary intake of Zn, impaired Zn absorption, vomiting, diarrhea, and binging on low Zn foods [80]. Anorexia patients may also suffer from diminished absorption of dietary Zn [81]. A study with 30 hospitalized anorexic patients who had lost 34% of the height/age adjusted weight, found that the mean plasma Zn level was considerably lower compared to healthy controls ($p<0.01$). Eight patients had plasma Zn levels below 60 μg/dl [82]. Another clinical study with 24 anorexic patients showed that 54% had biochemical evidence of Zn deficiency [83]. In several open trials, Zn supplementation has improved weight gain in anorexia patients [84–86]. In a randomized, double-blinded clinical study, the rate of increase in the body mass index (BMI) of the Zn supplemented group was twice that of the placebo group ($p>0.03$) [87]. Still, the role of Zn deficiency in the onset and progression of anorexia is both unappreciated and underestimated [79]. Several authors advocate the use of Zn supplementation as a cheap, effective and safe treatment for anorexia [88–90].

We compared the serum Zn levels in anorexia patients with those of cancer patients to investigate the possible role of Zn dyshomeostasis in cancer-induced anorexia. Three clinical studies with anorexia patients who lost between 15% and 50% of their original body weight reported mean serum Zn levels between 71.9 μg/dl and 73.9 μg/dl [24, 82, 91]. Patients with a variety of malignancies (carcinoma of the bronchus, lung, breast prostate, bladder, cervix, gallbladder and mouth) reported mean serum Zn levels between 59.6 μg/dl and 77.2 μg/dl. The corresponding range in healthy controls was 95.5–99.3 μg/dl [18, 92, 93]. These results indicate that cancer patients can have serum Zn levels as low as or lower than patients with advanced anorexia.

We know of only one clinical study that specifically examined the relationship between cancer cachexia-induced anorexia and serum Zn levels [94]. The average weight of 10 small cell lung carcinoma patients declined from 81.7 to 74.1 kg during a 7 month period. The patients suffered from diminished appetite, and their mean caloric intake was 72% of the RDA. The mean serum Zn concentration in the study group was 71 μg/dl. The authors of the 1986 study characterize this level as low but normal, and conclude that Zn does not appear to be an anorexigenic factor. We suggest that this conclusion is incorrect, because studies in non-cancer anorexia patients show that anorexia is associated with Zn serum levels below 75 μg/dl. Cancer cachexia patients with anorexia may suffer from functional systemic Zn deficiency, and Zn should be evaluated as a possible clinical biomarker in these patients.

7 Systemic inflammation in cachexia

Immunodeficiency is associated with many types of malignancies, including head and neck, lung, esophagus and breast cancer, but the underlying mechanisms are poorly understood [95]. The correlation between systemic inflammation and cancer cachexia was first demonstrated by Simons and colleagues in 1999 [96]. Recently, Fearon noted that systemic inflammation, defined as C-reactive protein >10 mg/l, is a key feature of cancer cachexia [97]. The correlation between chronic systemic inflammation and progressive loss of lean body mass has been observed in several clinical studies [98].

Altered Zn metabolism may contribute to systemic inflammation observed in cancer cachexia because Zn homeostasis is critical for efficient immune function [99]. Haase and Rink observe that "zinc is essential for the immune system, and zinc deficiency affects multiple aspects of innate and adaptive immunity" [100]. Already mild forms of Zn deficiency adversely affect immunity [101], and Zn deficiency is constantly observed in clinical cases of chronic systemic inflammation [102]. Mouse models have demonstrated that 30 days of suboptimal intake of Zn can lead to 30–80% losses in the host's immune defense capacity [103]. Patients with diminished systemic Zn levels show a diminished immune response and a far greater susceptibility to infection. Zn supplementation reduces both spontaneous inflammatory activity ($p<0.001$) and defects in the termination of inflammatory activity in elderly subjects [104]. The results from the past three decades indicate that Zn deficiency diminishes antibody- and cell-mediated immune responses in both humans and animals [105–107].

Zn has a broad impact on key immunity mediators, such as enzymes, thymic peptides, and cytokines, and regulates lymphoid cell activation, proliferation, and apoptosis [108]. The activity of practically all immune cells is modulated by Zn in vitro and in vivo, and Zn affects the expression of hundreds of genes in immune cells. Inflammation disrupts Zn homeostasis on both a systemic and cell level, and Zn deficiency that is a secondary characteristic of many diseases may aggravate the underlying condition [109]. The integrity of the human immune system can be severely impaired by functional Zn deficiency, and chronic Zn

dyshomeostasis deficiency may contribute to the systemic inflammation observed in cachexia patients.

8 Growth failure in cachexia

Growth failure is commonly observed in pediatric patients suffering from cancer cachexia [9, 110]. The specific reasons for cancer associated growth failure are unknown, but it has been suggested that the reasons are multifactorial and include increased metabolic rate and lipolysis, decreased nutrient intake, and changes in carbohydrate and protein metabolism [111, 112]. The metabolic changes associated with cancer cachexia are complex, and it is unlikely that one factor by itself could explain impaired growth in pediatric patients. However, we suggest that Zn redistribution and dyshomeostasis may contribute to growth failure in cachexic children.

Zn is essential to the function of a large number of macromolecules and for over 300 enzymic reactions [113], and as MacDonald notes, "the inhibition of growth is the cardinal symptom of zinc deficiency" [114]. Raulin demonstrated in 1869 that Zn is necessary for the growth of the fungus *Aspergillus niger* [115]. Since then, its critical role in the normal development of higher plants [116], animals [117–119], and humans [120] has been established. Zn deficiency adversely and seriously affects growth in animals and humans [121, 122]. Reduced energy intake is not the limiting factor in growth because force feeding a Zn-inadequate diet to animals fails to maintain growth [114]. Zn deficiency is often the result of insufficient dietary intake or poor absorption through the digestive tract. Not surprisingly, growth failure caused by Zn deficiency is recognized as a serious nutritional health issue in many developing countries [123].

Zn deficiency results in retarded growth in infants and children [124–126]. Already moderate Zn deficiency causes growth retardation and delayed puberty in adolescents [121]. Prenatal Zn supplementation correlates significantly ($p<0.001$) with infant weight [127]. Children who suffered from stunted growth and who received Zn supplementation significantly ($p<0.001$) increased in both height and weight compared to the placebo group [128]. Pediatric geophagia patients who suffered from marked growth failure had subnormal serum Zn levels compared to controls (73.9 μg/dl vs. 110.5 μg/dl; $p<0.001$). The growth failure was significantly attenuated by Zn supplementation [129]. Interestingly, the mean serum Zn levels in the geophagic patients were comparable to those of patients with serious anorexia (71.9–73.9 μg/dl) and advanced cancer (59.6–77.2 μ/dl).

We propose that Zn dyshomeostasis may contribute to the growth failure in pediatric cancer patients. If functional Zn deficiency is verified as a causative factor in cachexic growth failure, it could provide clinicians with a novel biomarker and improve pediatric care.

9 Hypogonadism in cachexia

Hypogonadism refers to a defect of the gonads that results in the underproduction of testosterone and is common in cancer patients, especially in those suffering from weight loss. A recent clinical study noted that "hypogonadism is a frequent condition in patients with advanced, incurable cancer and is associated with negative mood, fatigue, and symptoms related to anorexia/cachexia" [130]. Chlebowski and Heber studied 44 patients with lung cancer, adenocarcinoma of the colon and rectum, and prostate carcinoma with proven metastatic spreads [131]. The mean ideal body weight of patients with low testosterone and low or normal luteinizing hormone was significantly lower ($p<0.05$) than in patients with normal testosterone levels. The authors conclude that "hypogonadism is a relatively common biochemical abnormality in men with cancer, particularly in patients experiencing weight loss."

The metabolic link between hypogonadism and cachexia is unresolved, but the critical role of Zn in gonad function and steroidogenesis is well known. Zn is essential for spermatogenesis and testosterone steroidogenesis [132], and hypogonadism is a classic symptom of Zn deficiency [133]. The first study linking Zn and testosterone metabolism by the prostate gland was published in 1971 [134]. Karaca and colleagues succinctly note that "hypogonadism is a major manifestation of Zn deficiency in both humans and animals" [135].

Several possible molecular mechanisms linking Zn and hypogonadism have been proposed. Hypogonadism associated with Zn deficiency seems to result from changes in testicular steroidogenesis or indirectly from Leydig cell failure [136]. A study with young rams showed that Zn deficiency completely blocked testicular growth [137]. The Zn-specific effect on gonad function is localized within the testis where it reduces the capacity to produce testosterone, leading to low intratesticular concentrations of testosterone, a critical factor for the growth, development, and function of the seminiferous tubules. This mechanism seems to be related to the biochemical disruption of Leydig cell function.

Zn can directly modulate serum testosterone levels, and in rats, Zn supplementation results in a considerable increase in testosterone levels ($p<0.05$; [138]). In the clinical study on healthy males, testosterone concentrations declined significantly ($p=0.005$) after 20 weeks on a Zn-deficient diet serum [139]. It is known that diminished levels of anabolic hormones, e.g., testosterone, can lead to

the loss of skeletal muscle mass [97], indicating that Zn dyshomeostasis could exacerbate muscle wasting also through a secondary mechanism. Cancer cachexia patients with functional Zn deficiency may suffer from impaired steroidogenesis and gonad activity since Zn is critical for both functions.

10 Conclusion

Cachexia is a complex metabolic syndrome, and the debate regarding its definition is ongoing. In this paper, we have examined the link between cancer cachexia and systemic Zn redistribution. Zn dyshomeostasis has been associated with malignant growth, but the pathophysiological consequences of chronic Zn redistribution during cancer cachexia have been ignored. We suggest that Zn dyshomeostasis is associated with the salient symptoms of cachexia such as muscle catabolism, anorexia, inflammation, growth failure, and hypogonadism. To our knowledge, this is the first report implicating systemic Zn redistribution and dyshomeostasis as central causative mechanisms in cancer cachexia.

The APR plays an important role in cachexia, and it is known to disrupt the carefully maintained Zn homeostasis and to mediate the systemic redistribution of Zn. This redistribution is mediated by Zn transporters that are significantly upregulated by APR factors such as IL-6. The primary purpose of muscle protein catabolism associated with APR seems to be the supply of amino acids for the production of hepatic proteins deployed in the defense response. We suggest that Zn accumulation into skeletal muscle tissue may be associated with protein catabolism and that this link should be further investigated.

Cancer cachexia is characterized not only by muscle wasting, but also by anorexia, systemic inflammation, pediatric growth failure, and hypogonadism. Zn homeostasis is essential for the normal function of all these processes and functional Zn deficiency compromises them. We hypothesize that Zn is accumulated in certain tissues and deprived from others resulting in severe systemic Zn dyshomeostasis and that as a result, cachexia may require completely new therapeutic approaches. Skeletal muscle Zn levels may provide the first practical and cost-effective diagnostic biomarker for cachexia, and we urge research centers to measure the Zn levels in their cachexic muscle biopsy samples.

The Zn–cachexia hypothesis has parsimonious explanatory power, but clearly the correlation and causality of Zn dyshomeostasis in cancer cachexia need to be further investigated. However, it is well established that Zn metabolism is critical for normal health and function and that systemic and chronic Zn dyshomeostasis has serious pathophysiological implications.

Other cachexia symptoms, such as insulin resistance, depression, and taste dysfunction are also associated with Zn deficiency [140–142] and should be further explored in light of the zinc-cachexia hypothesis. The possible role of systemic Zn dyshomeostasis in other cachexia-inducing conditions such as AIDS (originally known as ‘Slim Disease’), chronic heart failure, chronic obstructive pulmonary disease, chronic kidney disease, rheumatoid arthritis, severe injury, chronic inflammation, and sepsis should also be investigated. We propose that systemic Zn redistribution and dyshomeostasis play a central and thus far unappreciated role in cancer cachexia.

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Conflict of interest Siren PMA and Siren MJ are directors of Bioneris Ab. There are no other conflicts of interest.

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