Molecular mechanisms of zinc in alleviating obesity: Recent updates (Review)

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Abstract. Obesity has become a global health concern, and the number of individuals with obesity continues to increase significantly worldwide. Obesity increases the risk of developing chronic diseases, resulting in increases morbidity and mortality rates in humans. Zinc (chemical symbol, Zn) has been found to be associated with obesity. Zinc participates in several physiological processes, having been shown to play roles in energy balance, lipid metabolism, appetite regulation, insulin resistance, the regulation of the serum leptin concentration, as well as in inflammatory responses. However, in terms of alleviating obesity, the molecular mechanisms underlying the role of zinc in this process remain poorly understood. Therefore, the present review aimed to provide a comprehensive analysis of what is currently known regarding the molecular mechanisms of zinc supplementation in alleviating obesity, with a focus on lipid metabolism, appetite regulation, insulin signalling and the inflammatory response.

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1. Introduction

The marked increase in the number of individuals being overweight and obese in numerous geographical regions worldwide has led to these conditions being currently considered a global pandemic; obesity has become one of the major public health concerns globally (1,2). Obesity is marked by a body mass index (BMI) ≥30 kg/m^2, and this abnormal accumulation of fat may contribute to an increased risk of developing chronic diseases, including diabetes, hypertension, cancer and neurological disorders (3). In addition, obesity is still the leading risk factor for osteoarthritis (OA), affecting weight-bearing (knee) and non-weight-bearing (hand) joints (4,5). OA is considered to stress the joints caused by the excess weight, resulting in the degradation of articular cartilage. Numerous additional factors, among these being adipose deposition, insulin resistance (IR) and immunological responses, may contribute to the commencement and development of obesity-associated OA (5). Metabolic syndrome (MetS), which comprises a range of conditions, including obesity, hypertension, diabetes and dyslipidaemia, induces the release of inflammatory cytokines, including oxidized low-density lipoprotein (ox-LDL). This results in the destruction of cartilage and synovitis, which subsequently leads to the development of OA, thereby triggering pain. Moreover, there is often a limitation of activity and exercise that will also contribute to obesity, further worsening MetS, setting off a vicious cycle that is most likely triggered by the oxidative stress environment in OA (6). Obesity should not merely be considered as excess weight; along with its comorbidities, particularly diabetes and cardiovascular disease, it is a leading cause of morbidity and mortality in humans (7). Moreover, childhood and adolescent have been linked to adulthood premature mortality (8).

Although obesity is largely preventable, it is challenging to treat due to its multifactorial origin. A positive energy balance is the most crucial determinant in the development of

obesity, although imbalances in micronutrients can also play a role. Individuals who are overweight or obese have a higher prevalence of micronutrient deficiencies compared with those who are of normal weight, even if their energy intake is excessive (9). A number of different states of overweight and obesity conceal other health issues, including vitamin and mineral deficiencies, potentially as a result of a poor-quality diet that is lacking in sufficient micronutrients to meet the physiological and metabolic demands of the individual (10).

The micronutrient status, particularly regarding zinc (chemical symbol, Zn) and vitamins A, B and D, may influence the energy balance, and may thus play a role in obesity (11). Additionally, new evidence has identified a link between zinc, obesity and diabetes, particularly in the modification of lipid and insulin characteristics, oxidative stress, inflammatory responses, IR, adiposity and the serum leptin concentration (10).

The most notable characteristic of obesity is inflammation, which is manifested as a chronic, low-grade inflammatory state known as metabolic inflammation, which is distinct from the essential acute inflammation (3). Obese individuals with limited rates of zinc intake are known to have a diminished ability to respond to inflammation. In addition, zinc supplementation has been shown to stimulate insulin secretion and enhance sensitivity to this hormone (12). In a previous study, in rats fed a high-fat diet (HFD), zinc supplementation was found to reduce weight gain and visceral adiposity, as well as increasing insulin sensitivity (13). Furthermore, a previous double-blind, placebo-controlled study revealed that taking a 30 mg supplement of zinc gluconate daily for 4 weeks led to a marked reduction in body weight, BMI and waist circumference in obese adults (14).

The main role of zinc supplementation in weight loss is possibly exerted through its influence on appetite regulation, its ability to improve IR, and its anti-inflammatory effects associated with cytokine signalling pathways, as evidenced by the suppression of interleukin (IL)-6, tumour necrosis factor α (TNF-α) and C-reactive protein (CRP) (15).

The role of zinc in lipid metabolism, appetite control, IR and obesity, as well as its contribution to insulin production and action, has already been largely well-established; However, the underlying molecular mechanisms have yet to be fully elucidated. The present review aimed to provide a comprehensive discussion of the molecular mechanisms through which zinc supplementation alleviates obesity, particularly through lipid metabolism, appetite regulation, insulin signalling and the inflammatory response. The present review aimed to provide new insight that may contribute to the further development of zinc as a novel target in obesity treatment.

For the purposes of the review, a comprehensive literature study as performed on the PubMed, Scopus and Google Scholar databases using several key words and phrases, including 'zinc AND obesity', 'zinc AND body weight', 'zinc AND lipid metabolism', 'zinc AND appetite regulation', 'zinc AND insulin signalling' and 'zinc AND inflammatory response'.

Articles were analysed from the aforementioned databases to obtain a comprehensive understanding of the molecular mechanisms that explain how zinc supplementation diminishes obesity. Moreover, the focus of the present review was further sorted according to how zinc supplementation modulates the following: i) Lipid metabolism; ii) appetite control; iii) the insulin-signalling pathway; and iv) the inflammatory response. In terms of the article selection process, note that the majority of these articles were published in the most recent decade, and were restricted to the English language.

2. Molecular mechanisms of zinc and obesity

In terms of its pathogenesis, obesity shares several risk factors with those of type 2 diabetes mellitus. Molecularly, zinc exerts a beneficial effect on improving obesity through several mechanisms. First, zinc participates in the process of maturation of the insulin hormone, which forms an insulin hexamer composed of six insulin molecules and two zinc molecules (16). Insulin and zinc molecules associate in a complex to form insulin granules in the cytosol of the pancreatic β-cells. This association both maintains the crystal structure of insulin and protects it from being broken down by the proteolytic enzyme, peroxidase (17). A lack of zinc will impede the hexamerization process, as well as hinder insulin maturation and impair the structural stability of insulin.

Secondly, zinc limits the activity of protein tyrosine phosphatase 1B (PTP1B), a protein that initiates negative feedback signalling in the P13K/Akt insulin-signalling pathway (16). PTP1B has the physiological function of inhibiting the insulin receptor through mediating its dephosphorylation, thereby weakening the insulin signal transduction process (17). The P13K/Akt pathway fulfils a crucial role in the insulin-signalling pathway, and the dysregulation of this pathway is linked to the development of obesity and IR (18). Zinc-induced inhibition of PTP1B activity therefore leads to the enhancement and stimulation of the PI3K/Akt insulin-signalling pathway, which impedes the advancement of obesity (16).

The third mechanism through which zinc is associated with obesity is that it functions as a key mineral for activating antioxidant enzymes, such as catalase and superoxide dismutase (SOD). These enzymes are crucial for the protection of pancreatic β-cells from oxidative stress in people with type 2 diabetes and obesity (16). In obesity, a lack of suitably functioning enzymatic and non-enzymatic antioxidant mechanisms may lead to the development of oxidative stress conditions. It has been well-established that obesity leads to a decrease in the production of SOD, catalase and the enzyme, glutathione peroxidase (17).

Furthermore, studies have shown that zinc influences the regulation of leptin, a hormone that suppresses appetite. The ability of zinc to decrease the levels of neuropeptide Y (NPY), a substance that triggers hunger signals in the hypothalamus, may be responsible for this influence. However, further research in this area is warranted, as previous research has shown that zinc suppresses hunger by stimulating the release of serotonin, which leads to a feeling of satiety (12).

Zinc also participates in a further mechanism associated with obesity, in view of its capability to activate the peroxisome proliferator-activated receptor-γ (PPARγ) signalling pathway, leading to increases in the level of adiponectin and fatty acid oxidation. These processes lead to an increase in insulin sensitivity (19). Additionally, the formation of zinc-α2-glycoprotein (ZAG) has been shown to lead to increases in the rate of lipolysis, the adiponectin level and the thermogenesis of brown

adipose tissue, whereas there is a decrease in the rate of lipogenesis (20). Both processes will result in a reduction of free fatty acids (FFAs) and triglycerides (TGs), thereby reducing lipotoxicity, as well as the inflammatory process (12,19-21).

3. Molecular mechanisms of zinc in alleviating obesity: Effects on lipid metabolism

The imbalance of lipid levels may result in fat deposits or in the accumulation of lipids, leading to various complications, including obesity (1). The morphological substrate of obesity is an increase in adipose tissue mass, caused by the overaccumulation of lipids (22). The increased mass of adipose tissue, particularly in the visceral storage areas, leads to an increase in the transportation of fatty acid to the liver (23,24). Obesity further impairs lipolysis by reducing the mRNA expression levels of lipoprotein lipase (LPL) in adipose tissue and LPL activity in skeletal muscle, which leads to increased fatty acid transportation to the liver (23-25). Additionally, individuals with obesity have been found to exhibit an increased production of fatty acids in the liver, which may arise due to hyperinsulinemia observed in patients with IR. Insulin promotes the activity of sterol regulatory element binding protein-1c (SREBP-1c), which leads to increases in the expression of enzymes involved in fatty acid synthesis (24,26,27). Moreover, obesity has been shown to be associated with an increase in intestinal fatty acid production, as well as an increased secretion of chylomicron, which results in an increase in delivery of fatty acids to the liver (24).

Hypertriglyceridemia is a hallmark of dyslipidaemia in obesity. The hepatic accumulation of TGs occurs due to increases in the levels of hepatic fatty acids, including elevated rates of flux to the liver (24,25). In addition, both the protection of apolipoprotein (Apo)B100 from breakdown and the failure of insulin in suppressing ApoB secretion may contribute to the observed increases in the rate of synthesis of large very-low-density lipoprotein (VLDL) particles (24,28). An elevated concentration of large VLDL impedes chylomicron lipolysis due to competition, mostly at the level of LPL, with a larger remnant of TGs being delivered to the liver. Moreover, hypertriglyceridemia also causes an increase in the exchange of cholesterol esters and TGs mediated via cholesterol ester transfer protein (CETP) between VLDL, high-density lipoprotein (HDL) and LDL. This results in lower concentrations of HDL-cholesterol (HDL-C) and in a decreased content of TGs in LDL (25). In addition, the activity and mass of CETP also contribute towards increasing the level of obesity (29). Furthermore, hepatic lipase (HL) hydrolyses TGs from LDL and HDL, resulting in TG-depleted, small dense LDL and small HDL particles, respectively (24,25). Obese individuals with increased visceral adiposity have also been demonstrated to have an increased HL activity, leading to small lipoprotein particles (23-25). The lowered affinity of apolipoprotein (Apo)A-I for small HDL particles contributes to the disassociation of ApoA-I, as well as the clearance and degradation of ApoA-I by the kidneys (23). Furthermore, ApoA-I is the main protein of HDL, which contributes to reverse cholesterol transport and cellular cholesterol homeostasis, which, in turn, allows for greater cholesterol transport to, and elimination by, the liver (23,30). Hence, the alteration of Apo A-I results in lower levels of ApoA-I and HDL-C in obesity (23,24).

Additionally, increases in the level of ApoC-III have been observed in individuals with obesity due to IR (31). One effect of ApoC-III is to increase the concentration of plasma TGs by inhibiting LPL in the plasma, thereby inhibiting uptake of the triglyceride-rich lipoproteins remnant and stimulating VLDL secretion in liver, alongside its contributing to dietary TG trafficking in the intestine (32). For patients with obesity, decreases in the level of adiponectin and increases in resistin have also been shown to occur (24). A lower level of adiponectin is associated with an increased level of TGs and a reduction in the level of HDL-C, whereas increases in the level of resistin have been shown to be associated with increases in the rates of synthesis of ApoB, TGs and cholesterol, which subsequently result in the promotion of VLDL secretion and production (33,34). Moreover, resistin is associated with reductions in the levels of HDL-C and ApoA-I (28). Furthermore, the pro-inflammatory cytokine, resistin, plays a role in obesity by increasing the level of serum TGs, while decreasing the levels of HDL-C and ApoA-I (24).

In patients with obesity, it has been documented that they have lower blood zinc levels, which are also associated with changes in lipid profiles (22). Zinc supplementation elicits positive effects on plasma lipid parameters. A previously published meta-analysis revealed significant decreases in the levels of LDL-cholesterol (LDL-C), total cholesterol and TGs (reductions of 4.78, 10.72 and 8.73 mg/dl were recorded, respectively) (35). In non-healthy obese participants, including those with type 2 diabetes or end-stage renal failure and those undergoing haemodialysis, more prominent reductions were observed compared with the overall analysed data, with significant decreases in the levels of total cholesterol, LDL-C and TGs. Additionally, a significant increase in the level of HDL-C was observed in non-healthy patients (an increase of 6.15 mg/dl was determined following zinc supplementation) (35). However, as far as healthy subjects were concerned, although there was a slight reduction in the level of total cholesterol, zinc supplementation failed to elicit any significant decreases in LDL-C or TG; neither was there a significant change in HDL-c levels. Hence, these findings suggested that zinc supplementation may not have numerous significant advantages for healthy individuals (35).

Several studies have reported a negative association between zinc levels and BMI (10,36-38). An inverse association was also identified between the plasma zinc concentration and both waist circumference and BMI in obese individuals (38). Additionally, a lower zinc level in overweight and obese individuals was reported in one of these studies (10). The study by Laillou *et al* (39) found that zinc deficiency affected 61.1% of Vietnamese women of reproductive age with overweight/obesity. Additionally, the prevalence of zinc deficiency in obesity has been reported to be in the range 14-30% (40). Although no marked changes have been observed with respect to glucose levels or lipid profiles, the administration of a zinc supplement may become a promising therapy for healthy obese individuals. The administration of a zinc supplement has previously been shown to significantly increase the zinc concentration, as well as significantly reducing the TG concentration, weight, waist circumference and BMI in

healthy obese patients (14). Furthermore, the administration of zinc supplementation for obese or overweight individuals may also become a promising means of therapy. Zinc supplementation has been shown to reduce BMI, waist circumference, hip circumference, body weight, inflammatory markers and IR, as well as to improve cognitive performance (15,41). However, further studies are still required to verify the precise effects of zinc supplementation for obese individuals who are without zinc deficiency.

Several mechanisms are considered to be involved in the reduction of serum lipids following zinc supplementation. Previous studies have demonstrated that an adequate amount of zinc in adipose tissue is essential for normal adipocyte functioning and leptin production; zinc has been shown to trigger leptin-mediated negative feedback (22), which contributes to the regulation of adipose tissue mass (42). Zinc supplementation has also been shown to be associated with an increase in serum leptin levels in obese leptin-resistant subjects, alongside improvements in weight and other metabolism-associated parameters. Finally, it has also been suggested that zinc may reduce the rate of leptin resistance (22).

Zinc has also been shown to promote the oligomerization of higher-molecular-weight forms of adiponectin *in vitro* by reducing the rate of disulfide bond formation (43). The study by Asghari *et al* (44) found that the administration of a zinc supplement at a concentration of 30 mg/day for 12 weeks in diabetic patients led to a marked increase in the level of circulating adiponectin in the treatment group compared with the baseline, although this was not found to be significantly different compared with the control group at the end of the study. A similar study by Soheylikhah *et al* (45) revealed a significant increase in adiponectin levels following the administration of zinc supplementation at a concentration of 50 mg/day for 12 weeks. It is considered that zinc may regulate PPARγ signalling, and that an elevated zinc level would increase PPARγ activity (44). PPARγ is predominantly found in adipose tissue, where it contributes to the differentiation and function of brown and white adipocytes, as well as stimulating lipid accumulation in adipocytes. This receptor appears to be associated with genes responsible for fatty acid transport, lipid droplet formation and TG synthesis and breakdown (19). PPARγ has also been shown to promote an increase in adiponectin levels in the plasma, leading to the stimulation of fatty acid oxidation in liver and skeletal muscle, improved insulin sensitivity in liver and skeletal muscle, and a reduced level of glucose production in the liver (19). This will result in a lowering of the concentration of FFAs, TGs and glucose levels in the liver (19,44).

In obesity, the protein ZAG is downregulated, which leads to an inhibition of ZAG function, affecting lipid metabolism (20,46). Zinc has been shown to have a role as a regulator of ZAG homeostasis (46). Zinc contributes to the formation of ZAG, facilitating its binding to fatty acids and β3-adrenergic receptors. Therefore, ZAG is able to contribute to lipid metabolism by stimulating lipolysis, hindering lipogenesis, and promoting thermogenesis of brown adipose tissue and other peripheral tissues, alongside increasing adiponectin secretion (20). The interaction between ZAG and β3-adrenergic receptors stimulates the cyclic adenosine monophosphate (cAMP) pathway, thereby promoting lipolysis in adipose tissue (20). In addition, lipolysis is regulated by hormone-sensitive lipase (HSL), and ZAG increases the activity of HSL, which has a direct effect on lipid mobilization (22,47). Furthermore, ZAG triggers thermogenesis through an increase in lipid oxidation by regulating the gene expression of mitochondrial uncoupling protein 1 (UCP-1) in brown and white adipose tissue (20,47). ZAG promotes the expression of PPARγ and early B-cell factor 2; subsequently, this will increase binding of these molecules to PR domain-containing 16 (Prdm16) and UCP-1, which serves to trigger the browning of white adipose tissue as well as energy consumption, resulting in an increase of lipolysis (46,48).

Furthermore, by catalysing the hydrolysis of diverse substrates, such as TGs, diacylglycerol, cholesteryl ester, as well as other lipid substrates, ZAG plays a role in releasing FFAs from adipose tissue, which enter into the circulation as an important source of energy for the majority of tissues (49). ZAG has also been shown to reduce the synthesis of fatty acids and acetyl-CoA carboxylase-1 (ACC-1) (47). It has been documented that ACC-1 is highly expressed in lipogenic tissue, including liver and adipose tissue, in which it exerts a function in lipogenesis. ACC-1 is the first rate-limiting enzyme in the fatty acid synthesis pathway, thereby having an important role in fatty acid synthesis (50). Moreover, it has been suggested that the overexpression of ZAG in 3T3-L1 adipocytes promotes an increased number of adiponectin transcripts, and the resultant higher expression of adiponectin may decrease IR (22,46). Adiponectin stimulates glucose uptake and the oxidation of fatty acids in skeletal muscle, as well as decreasing vascular inflammation through the activation of AMP-activated protein kinase (46).

In summary, zinc has been identified to perform numerous roles in lipid metabolism (Fig. 1). Moreover, zinc levels are lower in obese individuals, which consequently affects the lipid profile. Zinc supplementation may be beneficial in terms of improving lipid metabolism via the various mechanisms outlined in the preceding paragraphs.

4. Molecular mechanisms of zinc in alleviating obesity: Effects on appetite regulation

Leptin, a hormone produced by adipocytes, fulfils several roles in regulating numerous neuroendocrine processes. The expression of leptin receptors (LEPRs) is prevalent in the central nervous system (CNS), particularly in specific parts of the hypothalamus that are responsible for regulating appetite. The activation of LEPR in the arcuate nucleus (ARC) allows leptin to activate the melanocortin pathway. This regulation involves increasing the production of α-melanocyte-stimulating hormone (α-MSH), which is derived from proopiomelanocortin (POMC), while simultaneously reducing the synthesis of NPY and agouti-related protein (AgRP). These actions ultimately lead to the activation of the melanocortin 4 receptor (MC4R) axis, which results in an anorectic effect. On the other hand, the stimulation of AgRP neurons results in hyperphagia and subsequent weight gain. Obesity is considered to result from the overexpression of AgRP, a neuropeptide that promotes adipogenesis and inhibits lipolysis in adipocytes through antagonizing the action of α-MSH on the hypothalamic melanocortin receptor (18).

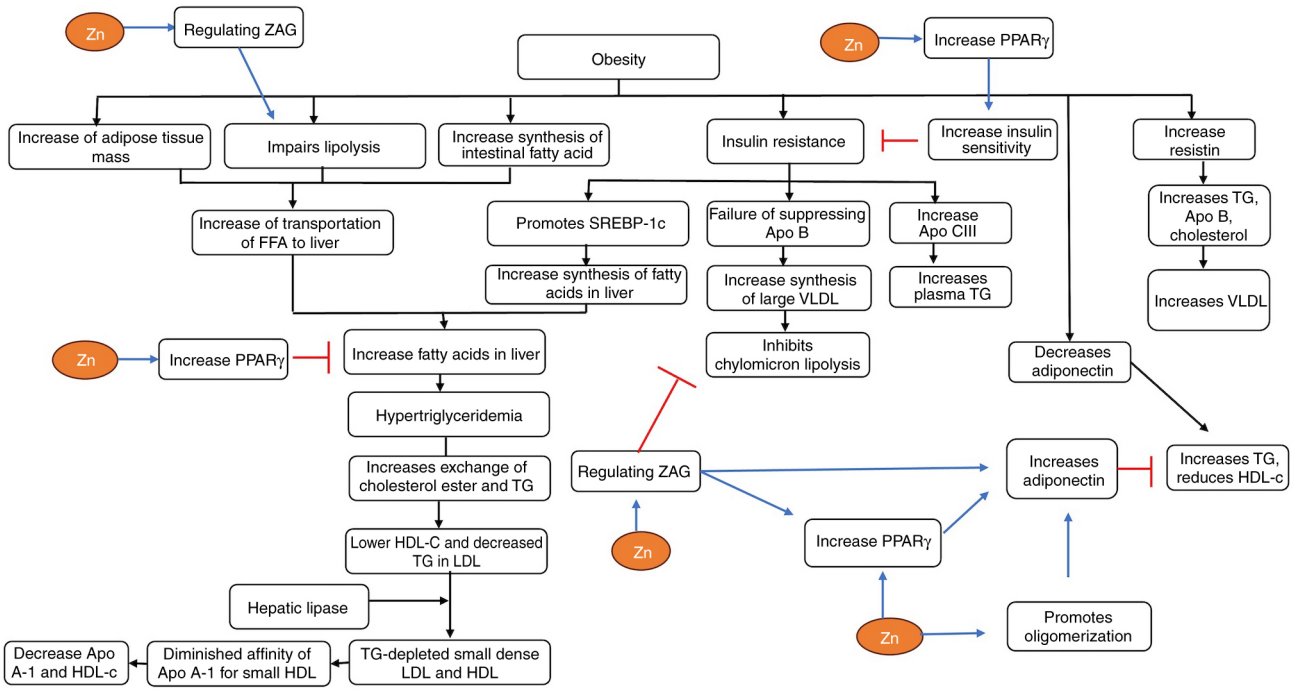

Figure 1. The molecular mechanisms of Zn in alleviating obesity through its effects on lipid metabolism are shown. In obesity, several mechanisms contribute to the imbalance of lipids, among which are increases in the levels of fatty acids in the liver, an impairment of lipolysis, the development of insulin resistance and decreases in the level of adiponectin. Zinc has demonstrated beneficial effects with regard to lipid metabolism. Zinc is able to promote adiponectin oligomerization, which increases the level of adiponectin, further affecting the levels of TG and HDL-c. Moreover, zinc increases the activity of PPARγ, which, in turn, increases the levels of adiponectin, insulin sensitivity and fatty acid oxidation in the liver and skeletal muscle. Therefore, the levels of FFAs and TGs are likely to be decreased. Moreover, zinc contributes to the regulation of ZAG, which has roles in promoting lipolysis, inhibiting lipogenesis and promoting thermogenesis of brown adipose tissue, as well as increasing adiponectin and PPARγ. ZAG also triggers the release of FFAs into the circulation, where they provide a source of energy, and reduces fatty acid synthesis. Hence, this suggests that zinc has a potentially important role in managing obesity through these mechanisms of lipid metabolism. The blue line shows the mechanism of Zn in affecting lipid metabolism. ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; ApoCIII, apolipoprotein C-III; FFAs, free fatty acids; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; PPARγ, peroxisome proliferator-activated receptor-γ; SREBP-1c, sterol regulatory element-binding protein-1c; TG, triglyceride; VLDL, very-low-density lipoprotein; Zn, Zinc; ZAG, zinc-α 2-glycoprotein.

NPY is a highly potent brain neuropeptide that possesses orexigenic properties, serving a crucial function in the hypothalamus-adipose tissue axis. NPY and noradrenaline play key roles in regulating energy balance and stress responses, often co-localized within sympathetic nerves. The synthesis of NPY has been found to originate from adrenergic and noradrenergic cells. It has been demonstrated that male Sprague-Dawley rats administered a HFD become obese and this is associated with an increase in the NPY serum level (51). NPY is a protein that modulates energy homeostasis through promoting appetite stimulation (51). In an indirect manner, NPY also induces the storage of lipids in white adipose tissue through the activation of NPY receptor 2 (NPY2R). This process further facilitates the proliferation of adipocyte precursor cells, the differentiation of preadipocytes into fully mature adipocytes, as well as the synthesis of lipids and the accumulation of adipose tissue. In the presence of chronic stress, the release of NPY via sympathetic axons occurs concurrently with catecholamines, hence promoting the accumulation of adipose tissue (52). It has been proposed that the involvement of catecholaminergic NPY signalling is crucial in the augmentation of adipose tissue volume that results from dietary factors and prolonged stress, as well as in the enhancements of lipogenic capability and corticosterone levels that occur in response to stress. Moreover, it has been shown that the occurrence of NPY release from sympathetic nerves, and subsequent activation of NPY2R in response to stress, have been found to induce angiogenesis and macrophage infiltration in adipose tissue. This, in turn, leads to the differentiation and proliferation of new adipocytes, ultimately contributing to the development of abdominal obesity and MetS (51).

The AgRP neurons are a well-defined cellular subtype that fulfil a crucial role in the regulation of food intake. The activity of AgRP neurons is modulated by hormones that provide information regarding the nutritional status of the body, and their activation is significantly enhanced during periods of food shortage. The stimulation of AgRP neurons by optogenetic or chemogenetic methods has been found to induce both an acute increase in food consumption and the initiation of appetitive behaviours that facilitate the discovery of food. Conversely, the suppression of these neurons results in a reduction or even complete absence of food intake, a condition known as aphagia (53). Therefore, AgRP neurons play a crucial role in terms of establishing a link between nutritional signals and the motivational mechanisms that regulate feeding behaviour (53). The regulation of hunger is strongly dependent on the presence of AgRP neurons, and the activation of the mechanisms underlying AgRP neuronal activity occurs in response to a deficit in calorific intake. When these mechanisms are either naturally or artificially triggered, they

exert a prominent effect by triggering a heightened sense of hunger, subsequently increasing food consumption (54). The activation of neurons encoding AgRP has been shown to occur in response to fasting, resulting in the sensation of hunger, which drives individuals to search for and consume food (55). A process of inhibiting or ablating AgRP neurons leads to a significant reduction in food intake. The activation of AgRP/NPY neurons is prompted by peripheral signals that are associated with hunger, such as ghrelin; conversely, the activity of these neurons is suppressed by peripheral signals associated with satiety, such as leptin (56).

The neurons of the hypothalamus, particularly the ARC, have been shown to have a significant expression level of LEPRs (54). Leptin interacts with the long form of LEPRs, known as Ob-Rb, located on the ARC neurons. This interaction leads to both the activation of the JAK2/STAT3 signalling pathway and the suppression of the AMP-activated protein kinase activity. The activation of hypothalamic leptin signalling leads to an increase in the neuronal activity of POMC/cocaine- and amphetamine-regulated transcript (CART) neurons, while concurrently reducing the activity of NPY/AgRP neurons (57). In the condition of obesity, it has been observed that, despite the presence of leptin elevated circulating levels, leptin is unable to effectively reduce food intake. This phenomenon may be attributed to the insensitivity of the ARC of the hypothalamus neurons, which play a crucial role in regulating the energy balance, ensuring that changes in the level of leptin are adequately responded to. This insensitivity is likely due to the impaired signalling of the leptin receptor (LepRb), indicating a potential malfunction in the signalling pathway mediated by LepRb (56).

The occurrence of hyperphagia accompanied by morbid obesity has been observed in both rodents and humans as a result of mutations in the leptin protein (e.g., ob/ob mice) or the LEPR (e.g., db/db mice), as discussed in a previous study (58). Leptin resistance has been identified in obese individuals, who do not exhibit the typical reduction in food consumption following the administration of exogenous leptin that is commonly observed in lean individuals (59). The potential underlying mechanisms that contribute to the development of leptin resistance encompass various factors, including compromised leptin signalling in neurons located in the hypothalamus and other regions of the CNS, the hindered transport of leptin across the blood-brain barrier, inflammation in the hypothalamus, endoplasmic reticulum stress and autophagy (60,61).

The previous paragraphs have provided a description of the molecular mechanisms underlying the regulation of appetite and its perturbation in an environment of obesity. The potential for zinc supplementation to enhance obesity management through its impact on appetite regulation has been observed in a range of different studies. The findings from studies performed both *in vitro* and *in vivo* suggest that an insufficient level in zinc may lead to a decrease in leptin gene expression. The systematic review by Khorshidi *et al* (62) reported that a deficiency in zinc resulted in a reduction in the expression of the leptin gene, its synthesis and its secretion, which was associated with the mass of adipose tissue in rats (62). It was also demonstrated that the mRNA expression level of leptin was markedly decreased in response to zinc deficiency in rats (63).

Zinc has been suggested as a potential modulator of leptin synthesis in humans and animals. Both the levels of leptin in circulation and the expression of leptin mRNA in white adipose tissue are reduced in a state of zinc deficiency. The administration of zinc supplements to mice with obesity and diabetes have been found to result in an increase in the leptin levels in their bloodstream (63). In a previous study, in cases of acute zinc deficiency accompanied by reduced food intake, as was expected, the reduction in adipose tissue consequentially led to reductions in the synthesis and release of leptin (63).

In another study, the 8-week supplementation of zinc sulphate ($ZnSO_4$; 15 mg/kg per body weight) led to a marked decrease in the leptin concentration, and this may have been associated with the effects of the zinc supplement in terms of improving leptin resistance in HFD-induced obese rats (64). One potential mechanism that has been proposed is a potential connection between the enhancement of zinc status and the regulation of leptin, which may lead to an inhibition of eating behaviours through reducing the levels of NPY, as was noted in a study by Costarelli *et al* (12). A potential consequence of zinc deficiency and obesity is the occurrence of leptin resistance, which has been observed to increase the levels of NPY in the hypothalamus of both rodents and humans (65). Another study (66) indicated that an insufficient amount in zinc may result in as much as a 50% increase in NPY levels. However, despite the augmented NPY levels that have been observed in rats with zinc deficiency, their food consumption was shown to be diminished due to the development of resistance to NPY (15). Moreover, zinc plays a crucial role in the regulation of appetite, and other underlying mechanisms may be responsible for the reduction in food consumption, such as an enhancement of leptin synthesis and subsequent reduction of hypothalamic NPY levels. The subgroup analyses from the meta-analysis of randomized controlled trials performed by Abdollahi *et al* (9) revealed that zinc supplementation resulted in a reduction of ~0.5 kg in body weight among overweight or obese, but otherwise healthy, human individuals. The aforementioned meta-analysis concluded that a dose of ≥40 mg zinc supplement/day with a duration of ≥8 weeks would be able to reduce the weight of obese patients by 0.5 kg (9).

It is plausible to suggest that the level of zinc may play a crucial role in the regulation of body weight and appetite among obese individuals. The molecular mechanism of zinc in alleviating obesity through its effects on modulating appetite regulation are illustrated in Fig. 2.

5. Molecular mechanisms of zinc in alleviating obesity: Effects on enhancing insulin production and the insulin-signalling pathway

Insulin plays an essential role in the pathophysiology of obesity. It is noteworthy that serum insulin levels are elevated in obese individuals, which is ultimately manifested as IR (14). IR is defined as the lack of ability of insulin-sensitive tissues, including skeletal muscle, the liver and adipose tissue, to respond properly to the physiological effects of circulating insulin in regulating glucose uptake and its utilization (67). It has been suggested that a reduced glucose uptake in insulin-sensitive tissues impairs the functioning of insulin-signalling pathways. The PI3K/Akt pathway is a crucial

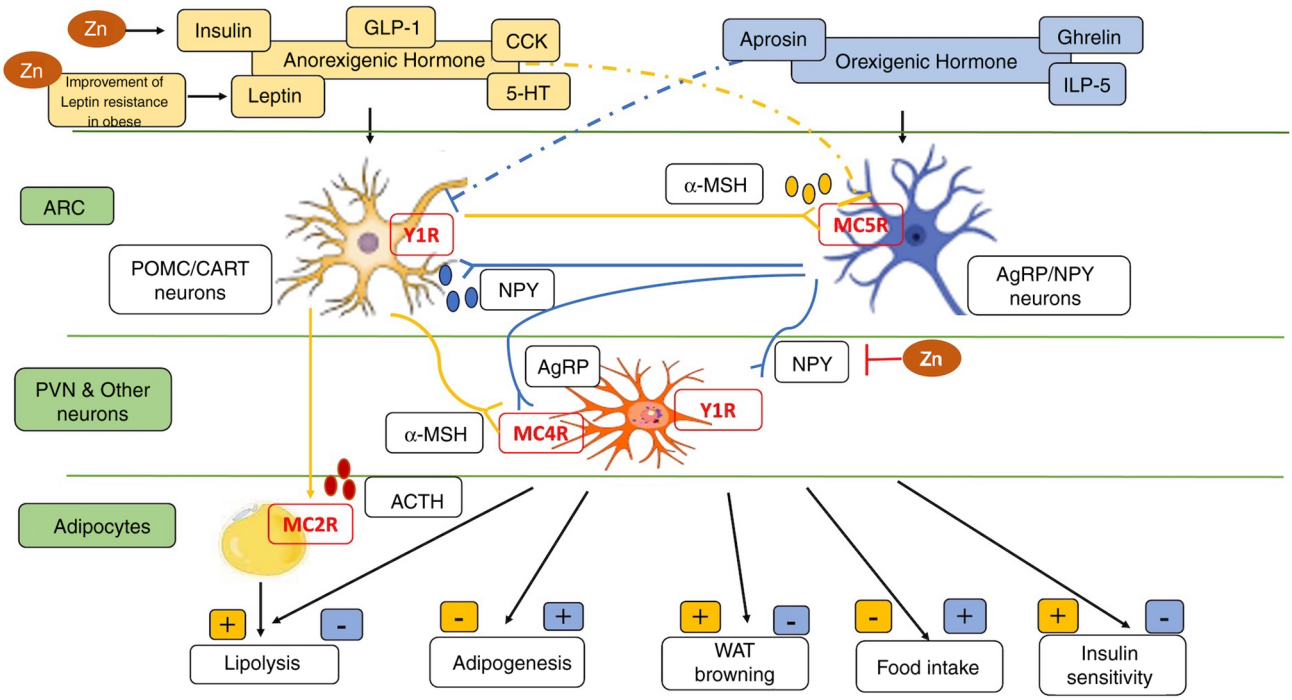

Figure 2. Illustration of the molecular mechanisms of Zn in alleviating obesity through its effects on appetite regulation. The pathophysiology of obesity involves the melanocortin network, which consists of various components, including POMC, MC1R-MC5R, agouti and AgRP. The POMC/CART neurons located in the ARC of the hypothalamus are subject to stimulation by anorexigenic hormones (GLP-1, leptin, CCK, and 5-HT). Conversely, these neurons are inhibited by orexigenic hormones (ghrelin, ILP-5, and asprosin). Following activation, POMC/CART neurons release POMC neuropeptides, specifically α-MSH and ACTH. The α-MSH is secreted into the PVN and interact with MC4R, which stimulates the activation of PVN neurons, resulting in anti-obesity properties (inhibition of adipogenesis, induction of lipolysis and WAT browning, reduction in food intake, and enhancement of insulin sensitivity). The activities of ACTH, which is released by POMC/CART neurons, on adipocytes occur through direct binding to MC2R, thereby enhancing the process of lipolysis. Nevertheless, those effects can be inhibited by AgRP, an endogenous antagonist of POMC that is released by AgRP/NPY neurons in the ARC. By contrast, the activation of AgRP/NPY neurons can be induced by orexigenic hormones, and their activity is suppressed by anorexigenic hormones. This demonstrates that a reciprocal interaction occurs between POMC/CART and AgRP/NPY. The expression of the NPY receptor Y1R has been observed in POMC/CART neurons, and its activation has been found to result in the inhibition of POMC neurons. On the other hand, the expression of MC3R in AgRP/NPY neurons appears to enhance food intake. Interestingly, zinc has been found to have a beneficial effect on various important aspects of appetite regulation within the melanocortin pathway. Specifically, it has been observed to improve insulin and leptin resistance, hence stimulating the POMC/CART neuron and promoting anorexigenic activities. Zinc was found to downregulate NPY, hence attenuating its role as an inducer of the orexigenic process. These findings implied that Zn has a potentially important role of in managing obesity through its impact on appetite regulation. ACTH, adrenocorticotropic hormone; AgRP, agouti-related protein; ARC, arcuate nucleus; CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; 5-HT, serotonin; ILP-5, insulin-like peptide-5; MC1R-MC5R, melanocortin receptors; α-MSH, α-melanocyte-stimulating hormone; POMC, pro-opiomelanocortin; POMC/CART, the pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript; PVN, paraventricular nucleus; WAT, white adipose tissue; Zn, zinc.

signalling pathway that regulates the metabolic effects of insulin, with Akt (a serine/threonine protein kinase) functioning as a major effector molecule, as previously reviewed by Yudhani *et al* (68). The presence or extent of IR can be determined on the basis of a diminished insulin-induced activation of the PI3K/Akt pathway that governs glucose absorption (69).

In comparison to other cell types, pancreatic β-cells are known to contain high levels of zinc molecules. In particular, insulin secretory granules have the highest zinc concentration found among cells (16). Zinc plays a crucial role in the processing, crystallization and storage of insulin within pancreatic β-cells via the pancreatic zinc transporter (ZnT8), which facilitates the transportation of zinc into cells responsible for insulin secretion (70,71). The ZnT8 transporter has been shown to be essential for zinc deposition inside insulin secretory granules (72). In a previous study the pancreatic β-cells of a mouse model wherein the ZnT8 gene was knocked out exhibited impaired glucose tolerance, aberrant β-cell morphology, diminished processing of insulin inside the islets, a decrease in the overall quantity of insulin granules, and an increase in the numbers of empty atypical granules present (70). Taken together, these findings suggest perturbed insulin crystallization and packaging (70). In addition, zinc is essential for the insulin hexamerization process, since the structure of insulin comprises a hexamer composed of six insulin molecules, in addition to two zinc molecules. Zinc has also been shown to be crucial for the conversion of proinsulin into insulin in the Golgi compartment; therefore, zinc has been demonstrated to be required for the appropriate synthesis, storage and structural stability of insulin (16).

Zinc functions as an insulin-mimetic, activating intracellular signalling pathways that control cellular homeostasis and other physiological reactions. A previous study established an association between impaired zinc signalling and various pathological conditions, including cancer, type 2 diabetes and obesity. As an insulin mimetic, zinc has been found to stimulate crucial molecules that participate in cellular signalling to regulate glucose homeostasis in both mice and human skeletal muscle cells (73).

Zinc also has the ability to enhance glucose absorption by L6 myotubes through the modulation of proteins involved in the insulin-signalling pathway. The study by Wu *et al* (74) revealed that the administration of zinc at concentrations of 20, 50 and 100 μmol/l led to a significant enhancement of glucose consumption, Akt^{Ser473} and glycogen synthase kinase-3β (GSK-3β) phosphorylation, as well as glucose transporter-4 (GLUT4) translocation in a dose-dependent manner. These results demonstrated that the ability of zinc to modulate glucose consumption was mediated via its effects on activating the Akt protein and facilitating GLUT4 translocation. Additionally, zinc was observed to activate phosphorylation of the GSK-3β protein, hence increasing glucose absorption and glycogen formation (74).

A previous *in vitro* study on the adipocyte 3T3-L1 cell line revealed that the administration of zinc resulted in an enhancement of tyrosine phosphorylation in the β-subunit of the insulin receptor, as well as the phosphorylation of Akt. This occurrence coincided with an augmentation of glucose transport, which was observed to be independent of the availability of insulin (75). Supporting this finding, the study by Norouzi *et al* (73) reported that the phosphorylation of Akt was observed in both the mouse skeletal C2C12 cell line and human skeletal muscle cells within 15 min of treatment when exposed to 20 μM $ZnSO_4$ in the presence of 10 μM pyrithione.

Previous studies have also demonstrated the involvement of zinc in the activity of signalling pathways that are regulated by insulin (76). Zinc compounds exert 'insulin-like' effects by activating several crucial insulin-signalling pathways, including the PI3K/Akt pathway (77). In the PI3K/Akt pathway, zinc has been shown to induce the phosphorylation of the insulin receptor β-subunit, thereby facilitating the activation of PI3K and Akt, which, in turn, enhances the transport of glucose into cells (76). Interestingly, zinc has been also shown to directly stimulate PI3K in the HNN8 and Swiss 3T3 cell lines (77).

The activation of Akt has the direct consequence of phosphorylating and inactivating the Rab-GTPase activating protein, AS160. This process then initiates the translocation of GLUT4 to promote glucose uptake. Furthermore, the activation of Akt has been observed to increase glycogen production in skeletal muscles via the inhibition of GSK-3β (68). In another study, a significant ($P<0.001$) increase in the level of GSK-3β protein was observed in mouse skeletal muscle cells (C2C12 cells) that were treated with $ZnSO_4$ compared with the control group. Although zinc has been shown to stimulate the upregulation of GSK-3β expression, it has also been shown to promote the serine phosphorylation of GSK-3β, leading to its inactivation. Consequently, this process promotes glycogenesis (73).

A previous review regarding the biochemical and molecular aspects of zinc related IR by Cruz *et al* (76) concluded that Zinc induces the phosphorylation GSK-3β and the transcription factor forkhead box protein O1 (FoxO1), in a process that bears some similarities to the mechanism of insulin action. The inhibitory effect on the action of GSK-3β is mediated through the phosphorylation of GSK-3β serine residues, which promotes the its dephosphorylation and subsequent activation of glycogen synthase, a key enzyme involved in the process of glycogen production. The process of FoxO1 phosphorylation results in the relocation of FoxO1 from the nucleus to the cytoplasm, which thereby impedes its ability to activate the transcription of genes involved in gluconeogenesis. Therefore, zinc promotes the conversion of glucose into glycogen for storage, and hinders the process of gluconeogenesis, thereby performing a role in maintaining glucose homeostasis (76).

Moreover, mounting evidence has identified a link between the insulin-sensitizing effects of zinc and the suppression of tyrosine phosphatase activity on PTP1B. Zinc ions inhibit the enzymatic activity of PTP1B by non-covalently binding to its essential cysteine residues (16). The activity of PTP1B was found to be hindered by zinc ions due to their direct interaction with the enzyme (78). PTP1B has been extensively investigated as a prominent target for the insulin-mimetic properties of zinc. The phosphatase fulfils a crucial role in controlling insulin action by dephosphorylating the insulin receptor, as well as insulin receptor substrates-1 and -2. This dephosphorylation process effectively inhibits the insulin-signalling cascade, thereby reducing the overall insulin response (79). Knockout mice lacking PTP1B have been demonstrated to have heightened insulin sensitivity, reduced levels of adiposity, and are protected against obesity induced by dietary factors (80).

The ability of zinc to regulate insulin-signalling pathways suggests that this specific element may be strategically utilized in experimental interventions to improve the management and/or treatment of IR as a prominent characteristic of obesity (73). The molecular mechanisms of zinc governing how this element alleviates obesity through its effects on enhancing insulin production and the insulin-signalling pathway are illustrated in Fig. 3.

6. Molecular mechanisms of zinc in alleviating obesity: Effects on ameliorating the activity of the inflammatory pathway

It is known that obesity can be characterized as a state of chronic low-grade inflammation accompanied by systemic alterations resulting from an excess of visceral adipose tissue. Obesity is often associated with significant systemic alterations in the human body. The presence of abdominal (or visceral) obesity is linked to an increased release of FFAs from the visceral fat stores and metabolic dysfunction, such as the development of IR. Intra-abdominal adipocytes that have experienced hypertrophy have the potential to undergo hyperlipolysis, resulting in an increased rate of release of FFAs to multiple organs, including the liver. The increase in circulating FFAs has the potential to negatively impact liver function, resulting in elevated hepatic glucose synthesis and the development of IR (7). Moreover, obese individuals are known to exhibit increased levels of circulating FFAs, which can accumulate in non-adipose tissues. This accumulation leads to lipotoxicity, a significant contributor to the development of IR (67).

Adipocytes play a complementary role in the development of obesity-induced inflammation by increasing the secretion of various pro-inflammatory chemokines and cytokines (51). Adipose tissue also serves as a significant origin for various regulatory molecules, including leptin, a hormone associated with satiety that is predominantly synthesized by adipocytes (81). In obesity, adipose tissue secretes higher levels of leptin, with the goal of reducing hunger and increasing energy

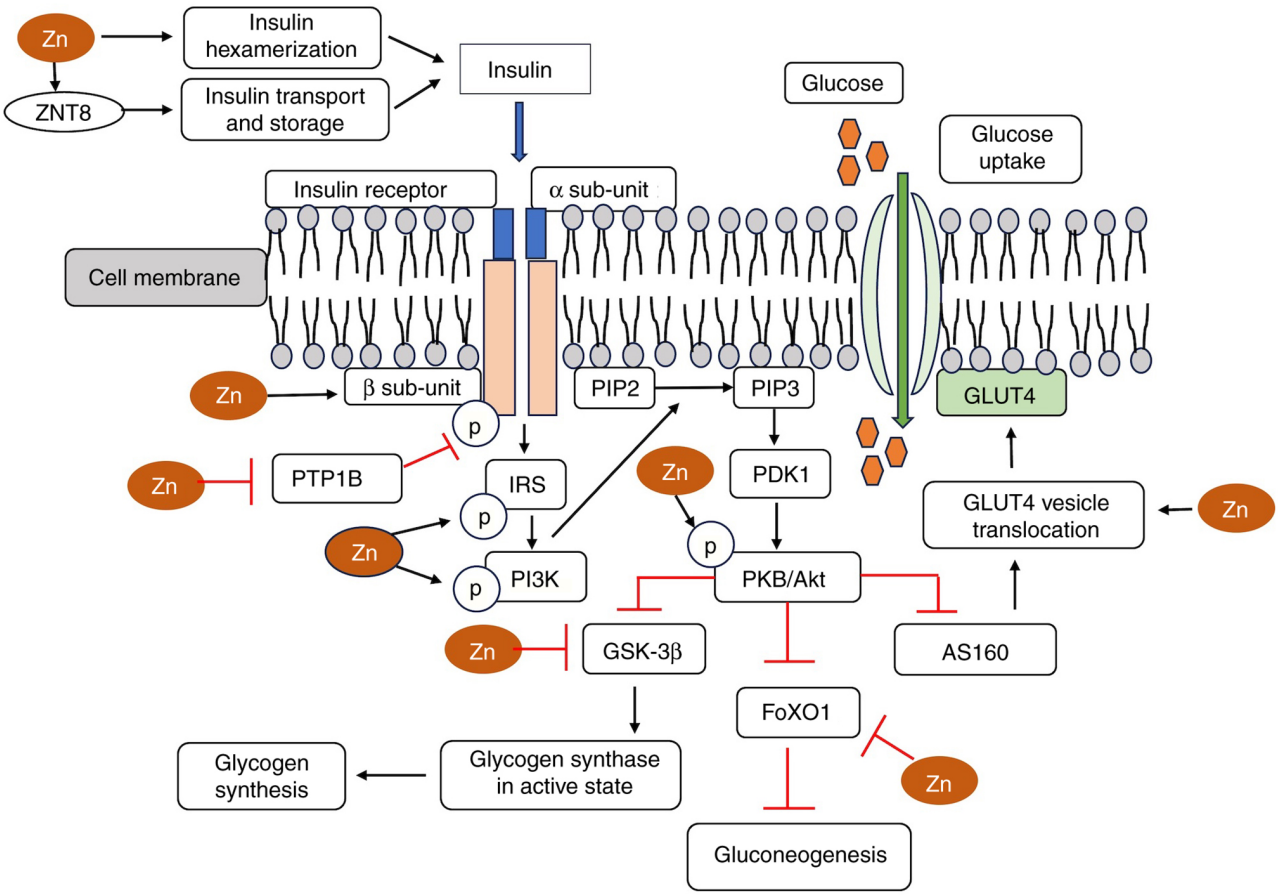

Figure 3. The molecular mechanisms of Zn in alleviating obesity through its effects on enhancing insulin production and the activity of the insulin-signalling pathway are shown. Zinc is required for the appropriate synthesis (insulin hexamerization), storage and structural stability of insulin. It also increases the activity of insulin-signalling pathways, especially the PI3K/Akt signalling pathway, through its abilities as an insulin-mimetic, inducing the phosphorylation of the β-subunit of the insulin receptor, IRS and PI3K, which results in Akt activation. The translocation of GLUT4 is also affected by Zn, which further promotes glucose uptake. Notably, Zn exerts a negative effect on PTP1B, GSK-3β, and FoXO1. PTP1B and GSK-3β are known as inhibiting factors for the activation of insulin receptor and glycogen synthesis, respectively; hence, FoXO1 is the transcription factor for gluconeogenesis. FoXO1, forkhead box protein O1; GLUT4, glucose transporter 4; GSK-3β, glycogen synthase kinase-3β; IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; PTP1B, protein tyrosine phosphatase 1B; Zn, zinc.

expenditure to facilitate weight loss. However, a number of obese individuals exhibit insufficient brain responsiveness to elevated leptin levels, resulting in dysregulation of hunger and energy balance, a condition referred to as leptin resistance (82). Leptin governs the synthesis of pro-inflammatory cytokines, including TNF-α, IL-1 and IL-6, in which contribute to a chronic inflammatory state. Additionally, IL-6 and TNF-α stimulate the synthesis of leptin in adipose tissue. The combination of high leptin resistance, along with the increased of free fatty acids level and inflammatory cytokines may result in lipotoxicity and IR (83).

The various aspects of the role of leptin in inflammation can be briefly described as follows: i) Leptin exhibits pro-inflammatory properties, ii) it enhances T-cell activation and proliferation, as well as the release of cytokines; iii) it promotes the Th1 immune response; iv) it increases the activation of natural killer cells; v) it enhances the activation of macrophages and their release of cytokines, including TNF-α and IL-6, and activates neutrophils, augmenting their chemotaxis and oxidative stress (84). Obese individuals exhibit an infiltration of macrophages within adipose tissue, leading to the development of a persistent, low-grade inflammatory state. Additional factors that could potentially contribute to the modified metabolic profile observed in individuals with obesity include proinflammatory molecules, including IL-6 and TNF-α (85). Elevated levels of TNF-α have been observed to restrict the production of adiponectin, which subsequently results in a decrease in the secretion of anti-inflammatory cytokines, including IL-1 and IL-10. Consequently, adiponectin loses its ability to impede the NF-κB pathway, thereby impairing insulin signalling (7). The anti-inflammatory effects of adiponectin have been established, including its innate anti-inflammatory properties, and its abilities to reduce the activation and proliferation of T-cells, to hinder the release of cytokines and reduce the expression of molecules dependent on NF-κB (including TNF-α/IL-6), to enhance the production of IL-10, and to impede oxidative stress during phagocytosis (84).

The presence of chronic inflammation and stress in obesity affects the synthesis of glucocorticoids, and this, in turn, stimulates the expression of genes coding for metallothionein and zinc transporters. These proteins promote the absorption of zinc by adipocytes, so that the homeostasis of the mineral will consequently be changed, thereby reducing its concentrations

in the serum or plasma (51). A significant reduction in zinc levels has been identified among obese individuals with an inflammatory condition; moreover, there is a greater likelihood of developing complications associated with obesity (22).

As previously demonstrated, Italian adults who were obese and who had a lower zinc dietary intake (5.66 mg/day) exhibited comparatively lower plasma levels of zinc, as well as higher levels of plasma CRP and IL-1β compared with obese individuals with a normal zinc intake (12.2 mg/day) (12). Additionally, that study also disclosed an inverse association between dietary zinc intake and inflammatory markers, including CRP, IL-6 and IL-1β (12). In addition, a previous randomized, double-blinded, placebo-controlled study was conducted to investigate the effects of zinc supplementation on 40 healthy elderly individuals (aged 56-83 years) (21). It was reported in that study that a daily dose of 45 mg zinc gluconate administered for 6 months led to an increase in plasma zinc concentrations, with concomitant decreases in the concentrations of plasma high-sensitivity CRP (hs-CRP), IL-6, macrophage chemoattractant protein 1 and vascular cell adhesion molecule 1. Zinc supplementation with zinc gluconate at concentrations of 30 mg/day for 8 weeks in obese young adult women (BMI ≥25 kg/m^2) led to significant increases in serum zinc of ~15%, while the levels of hs-CRP and IL-6 were reduced (86). In accordance with the earlier findings by Kim *et al* (86), a substantial decrease in hs-CRP levels was observed subsequently to the administration of a daily 20 mg zinc supplement over a time period of 8 weeks in obese Iranian children with MetS (87).

The potential molecular mechanism underlying the anti-inflammatory actions of zinc appears to involve the modulation of NF-κB through the activation of the anti-inflammatory protein A20 and the PPARα signalling pathway. NF-κB has been shown to upregulate the expression of adhesion molecules, thereby increasing the concentrations of CRP and inflammatory cytokines, such as IL-1β and TNF-α (86,88). *In vitro* studies have also demonstrated that zinc administration results in the suppression of TNF-α, IL-1β and NF-κB, whereas the expression levels of A20 and PPAR-α are increased in zinc-sufficient human monocytic cells and vascular endothelial cells in comparison with zinc-deficient cells (21).

The other mechanism by which zinc may suppress inflammation in obesity is associated with the capability of zinc to upregulate the expression of adiponectin. In their study, Briggs *et al* (43) identified an increase in adiponectin oligomerization, which was associated with a reduced rate of disulfide bond formation following zinc administration. The initial reduction in disulfide formation rates may facilitate the interaction of adiponectin subunits prior to their complete oxidation, which would have the effect of locking the conformation, rendering it incapable of further oligomerization (43).

The ability of zinc to regulate inflammatory pathways in a low-grade inflammation state of obesity indicates that this specific element may be strategically utilized in experimental interventions in the development of novel strategies for obesity management. The underlying molecular mechanisms of zinc in alleviating obesity through its effects on ameliorating the activity of the inflammatory pathway are illustrated in Fig. 4.

In summary, the present review has discussed how zinc is an essential trace element that exerts a substantial role in alleviating obesity. The molecular mechanisms through which zinc has been shown to alleviate obesity are associated with its effects on modulating lipid metabolism, appetite regulation, insulin hexamerization and insulin signalling (particularly the PI3K/Akt pathway), as well as ameliorating the inflammatory response in the chronic low-grade inflammation state of obesity. Zinc therefore has a highly significant role in the pathogenesis of obesity, suggesting that zinc supplementation would have a positive effect in suppressing the progression of disorders associated with obesity. The proposed molecular mechanisms of zinc in alleviating obesity are summarized in Table I.

7. Future perspectives of zinc supplementation for obesity

Several clinical trials have provided evidence to support the potential use of zinc supplementation in the management of obesity. In a previous double-blind clinical trial with 40 obese people, restricting calories by 300 kcal less than their estimated energy needs and consuming zinc sulphate supplements (30 mg/day) for 15 weeks led to significant reductions in their body weight, BMI, waist circumference, hip circumference and appetite (15). There were also significant decreases in the levels of CRP, the homeostasis model assessment for IR (HOMA-IR) and appetite scores, which suggested a decrease in inflammation and IR compared with the placebo group (15). Payahoo *et al* (14) performed another double-blind clinical trial involving 60 healthy obese individuals, which demonstrated that administering a daily dose of 30 mg zinc glucoronate for 1 month caused a significant reduction in body weight, BMI and TG levels. However, the zinc supplementation did not affect the lipid profile or blood glucose levels (14). The study by Kelishadi *et al* (87) on 60 overweight children in Iran found that consuming $ZnSO_4$ supplements at a dose of 20 mg/day for 8 weeks led to a significant improvement in the HOMA-IR and Apo-B/ApoA-1 ratios. Additionally, compared with a placebo, this supplementation led to a reduction in the levels of ox-LDL, malondialdehyde and LDL-C.

A previous study by Kadhim *et al* (89) demonstrated that a daily dose of 50 mg zinc acetate taken for >3 months by individuals with type 2 diabetes mellitus resulted in positive outcomes in terms of their lipid profile. This included a decrease in total cholesterol, TGs and LDL-C levels, as well as an increase in the levels of HDL-C. Consistently with these findings, Khan *et al* (90) observed that administering a daily dose of 50 mg $ZnSO_4$ for 3 months to individuals with type 2 diabetes mellitus resulted in a decrease in TG levels, and an increase in HDL-C levels.

The aforementioned preclinical studies, and the systematic review by Abdollahi *et al* (9) have decisively shown that zinc supplementation at a daily dose ≥40 mg for a minimum of 8 weeks may be beneficial for both healthy and obese individuals with comorbidities. However, another systematic review by Jafarnejad *et al* (91) concluded that the daily intake of a 20 mg zinc supplement was the most effective treatment for enhancing metabolic parameters. Therefore, to determine the optimal zinc supplementation dose and duration for treating obesity in a larger obese population, further clinical

Table I. Summary of the molecular mechanisms of zinc in alleviating obesity.

No.	Authors/year of publication	The affected pathway of zinc in alleviating obesity	Molecular mechanism	(Refs.)
1.	Ranasinghe *et al*, 2015	Lipid metabolism	Zn supplementation significantly decreases level of LDL-C, total cholesterol, and TG by a reduction of 4.78, 10.72 and 8.73 mg/dl, respectively. Zn supplementation rise HDL-C by 6.15 mg/dl in non-healthy patients.	(35)
	Olechnowicz *et al*, 2018		Zinc may reduce the rate of leptin resistance. Zinc is, also, related with an increase in serum leptin levels in obese leptin-resistant subject, as well as improvement of weight andmetabolic parameters.	(22)
	Asghari *et al*, 2019		Zn supplementation (30 mg/day) for 12 weeks in diabetic patients increases circulating adiponectin in the treatment group compared to the baseline, although it was not significantly difference compared to control group during the end of the study.	(44)
	Soheylikhah *et al*, 2012		Zn supplementation (50 mg/day) for 12 weeks increases adiponectin levels.	(45)
	Monsalve *et al*, 2013		Zinc may regulate PPARγ signaling and increase PPARγ, that will increase of adiponectin levels, leading to the stimulation of oxidation of fatty acid and improvement of insulin sensitivity, resulting in lower free fatty acids and triglycerides.	(19)
	Severo *et al*, 2020		Zinc contributes to the formation of ZAG, that can stimulate lipolysis, hinders lipogenesis, promotes thermogenesis of brown adipose tissue, and increases adiponectin secretion.	(20)
2.	Hasani *et al*, 2021	Appetite regulation	The 8-week supplementation of Zn sulfate (15 mg/kg body weight) significantly reduced the leptin concentration and this effect may be related to its effects on improving leptin resistance in rats with high-fat diet-induced obesity.	(64)
	Costarelli *et al*, 2010		The enhancement of Zn status, improved leptin regulation, which may lead to the inhibition of eating behaviours by reducing the levels of NPY mRNA.	(12)
	Baltaci *et al*, 2012		Zn deficiency related to obesity may be due to the occurrence of leptin resistance, which has been observed to elevate NPY levels in the hypothalamus of both rodents and humans.	(65)
	Wen *et al*, 2022		The downregulation of NPY by Zn, attenuating its role as an inducer of the orexigenic process.	(18)
3.	Wijesekara *et al*, 2010 Chimienti *et al*, 2004	Insulin production and insulin signalling pathway	Zinc plays a crucial role in the processing, crystallization, and storage of insulin within pancreatic β-cells, via the pancreatic Zn transporter (ZnT8), which facilitates the transportation of Zn into cells responsible for insulin secretion.	(70,71)
	Fukunaka and Fujitani 2018		Zinc is required for the appropriate synthesis, storage, and structural stability of insulin since it essentials for the insulin hexamerization (insulin structure is a hexamer composed of six insulin molecules along with two Zn molecules). Zinc also crucial for the conversion of insulin from proinsulin in the Golgi compartment.	(16)
	Norouzi *et al*, 2018		$ZnSO_4$ at concentration 20 μM in the presence of 10 μM pyrithione serves as an insulin mimetic, which stimulates Akt phosphorylation within 15 min of treatment in both mouse and human cell lines.	(73)

Table I. Continued.

No.	Authors/year of publication	The affected pathway of zinc in alleviating obesity	Molecular mechanism	(Refs.)
	Wu *et al*, 2016		The administration of Zn at concentrations of 20, 50, and 100 μmol/l significantly enhanced glucose consumption ang glycogen synthesis via Akt^{Ser473} and GSK-3β phosphorylation, as well as GLUT4 translocation in a concentration-dependent manner.	(74)
	Vardatsikos *et al*, 2013		Zn compounds exert insulin-like effects by activating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathways.	(77)
	Cruz *et al*, 2018		Zn induces the phosphorylation of the insulin receptor β subunit and facilitates the activation of PI3K and Akt, thereby enhancing the transport of glucose into cells.	(76)
	Cruz *et al*, 2018		Zinc induces the phosphorylation of glycogen synthase kinase 3β (GSK-3β) and the transcription factor forkhead box protein O1 (FoxO1), exhibiting a mechanism of action similarly to the effects of insulin (promoting glycogenesis while inhibiting gluconeogenesis).	(76)
	Fukunaka and Fujitani, 2018		The insulin-sensitizing effect of Zn is related to the suppression of tyrosine phosphatase activity on the protein tyrosine phosphatase 1B (PTP1B), which blunts the PI3K/Akt pathway.	(16)
4.	Olechnowicz *et al*, 2018	Inflammatory pathway	A significant reduction in Zn levels has been identified among obese individuals with an inflammatory condition. There is a greater likelihood of developing complications related to obesity.	(22)
	Costarelli *et al*, 2010		Italian adults who were obese and had a lower Zn dietary intake (5.66 mg/day) exhibited lower plasma Zn levels, as well as higher levels of plasma CRP and IL-1β vs. obese individuals with a normal Zn intake (12.2 mg/day). There was also an inverse association between dietary Zn intake and inflammatory markers, including CRP, IL-6, and IL-1β.	(12)
	Bao *et al*, 2010		Daily dose of 45 mg Zn gluconate for 6 months increased the plasma Zn level, while simultaneously decreasing the concentrations of plasma hsCRP, IL-6, MCP-1 and VCAM-1.	(21)
	Kim and Ahn, 2014		Zinc supplementation (30 mg/day Zn gluconate) for 8 weeks in young adults obese women (body mass index ≥25 kg/m^2) significantly increased serum Zn by 15% while reducing hs-CRP and IL-6.	(86)
	Kelishadi *et al*, 2010		A substantial decrease in hs-CRP levels was observed subsequent to the administration of a daily 20 mg Zn supplement during 8 weeks in obese Iranian children with metabolic syndrome.	(87)
	Bao *et al*, 2010		Zn administration suppresses TNF-α, IL-1β, and NF-κB while increases the expression of A20 and PPAR-α in zinc-sufficient human monocytic cells and vascular endothelial cells in comparison with zinc-deficient cells.	(21)
	Briggs *et al*, 2012		Zn has ability in up-regulating adiponectin since it increases the adiponectin oligomerization.	(43)

Table I. Continued.

No.	Authors/year of publication	The affected pathway of zinc in alleviating obesity	Molecular mechanism	(Refs.)
	Hasani *et al*, 2021		The 8-week supplementation of Zn sulfate (15 mg/kg body weight) significantly reduce the leptin concentration and may be related to its effects on improving leptin resistance in rats with high-fat diet-induced obesity.	(64)

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Zn, zinc; PPARγ, peroxisome proliferator-activated receptor-γ; ZAG, zinc-α2-glycoprotein; NPY, neuropeptide Y; $ZnSO_4$, zinc sulphate; GSK-3β, glycogen synthase kinase-3β; GLUT4, glucose transporter-4; CRP, C-reactive protein; MCP1, monocyte chemoattractant protein 1; VCAM-1, vascular cell adhesion protein 1.

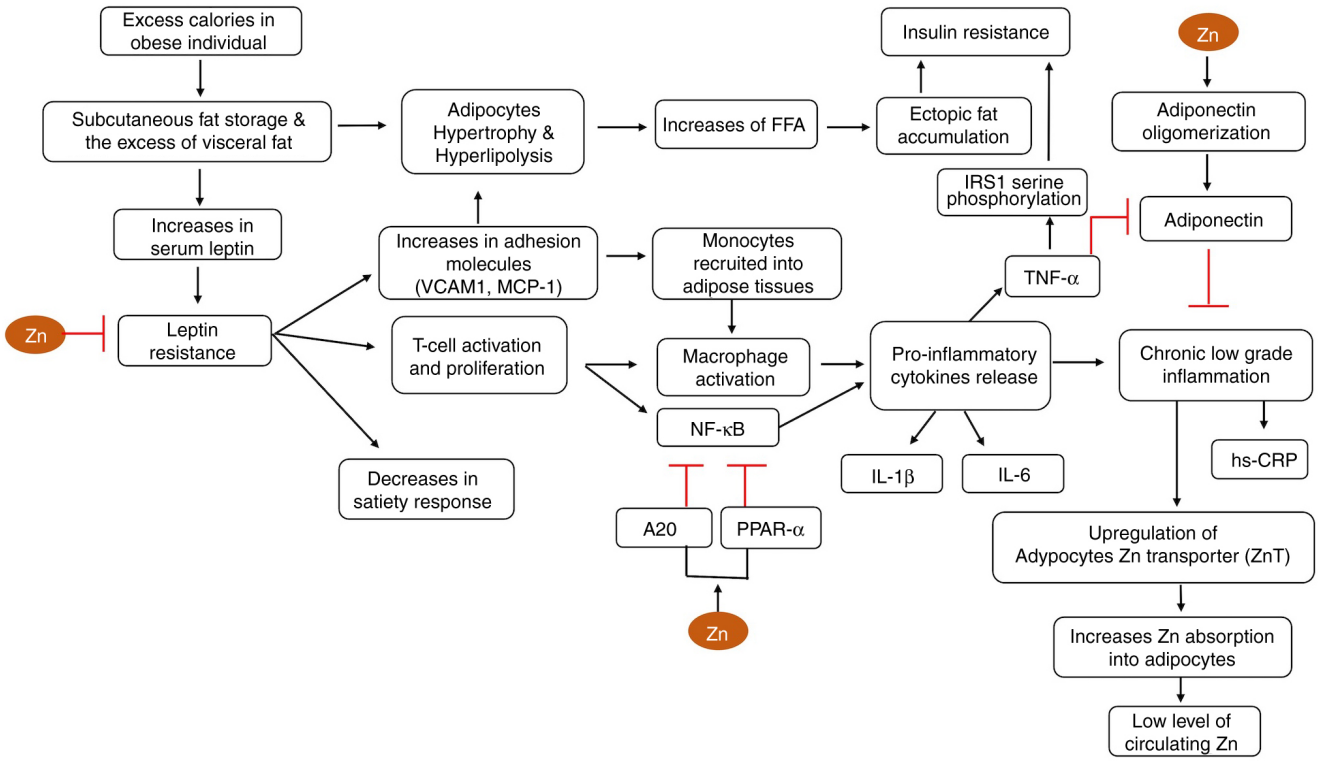

Figure 4. The molecular mechanisms of Zn in alleviating obesity through its effects on ameliorating the activity of the inflammatory pathway is shown. The Zn anti-inflammatory actions in obesity appear to involve several crucial elements, including the downregulation of NF-κB through the activation of anti-inflammatory proteins A20 and PPAR-α, reducing leptin resistance while inducing adiponectin oligomerization. NF-κB is known to upregulate the expression of adhesion molecules, which serves to increase the level of CRP and inflammatory cytokines, including IL-1β and TNF-α. Leptin resistance promotes the up-regulation of the adhesion molecules ICAM1 and MCP1 and increases T-cell activation, while decreasing the satiety response. Adiponectin has beneficial effects in suppressing the inflammatory process by reducing the activation and proliferation of T cells, hindering the release of cytokines and inhibiting the expression of molecules dependent on NF-κB. CRP, C-reactive protein; ICAM1, intercellular adhesion molecule 1; IL-1β, interleukin-1β; MCP1, monocyte chemoattractant protein 1; PPARα, peroxisome proliferator-activated receptor-α; TNF-α, tumour necrosis factor-α; Zn, zinc.

trials aimed at identifying various dosages and durations are required.

According to the Netherlands Food and Nutrition Council, the Recommended Dietary Allowance (RDA) for daily zinc intake to meet the nutritional requirements of healthy adults is 7-10 mg for males and 6-9 mg for females (92). However, certain clinical trials investigating zinc supplementation for obesity and type 2 diabetes mellitus used higher doses than the recommended upper limit, exceeding 40 mg/day (91). A previous meta-analysis reported that zinc supplementation at a dose of 50 mg/day for >3 months could reduce the level of plasma HDL-C (93). Furthermore, excessive amounts of zinc may potentially lead to a copper deficiency, which could adversely affect the functioning of antioxidant enzymes such as SOD (94). Moreover, prolonged consumption of high amounts of zinc gives rise to the risk of causing a serious neurological disorder associated with copper deficiency (95). Therefore, before implementing zinc supplementation in a wide range of obese populations, it is necessary to perform further studies, both *in vitro* and *in vivo*, to investigate the potential harmful

effects and risk of toxicity associated with zinc. Additionally, clinical studies need to be performed to analyse the probable adverse effects of long-term zinc supplementation.

8. Conclusions

Further investigations of the associations between zinc and lipid metabolism, appetite regulation, insulin production, storage and transport, insulin-signalling pathways and inflammatory pathways are required to gain in-depth and comprehensive information regarding the insights that have been gleaned thus far. The modulation of the zinc status may become a novel target in the prevention and treatment of obesity. It appears that obtaining more detailed knowledge regarding both the physiological functions of zinc and the ability to control lipid metabolism, appetite regulation, insulin production, storage and transport, insulin-signalling pathways and inflammatory pathways in cases of obesity may prove to be an important factor in developing novel strategies for obesity management.

The present study provided a comprehensive literature review in an aim to obtain a more in-depth understanding of the underlying molecular mechanisms of zinc supplementation in diminishing obesity. However, the data are still limited, and this prevents the drawing of firmer conclusions, particularly as regards the mechanisms of zinc supplementation affecting the leptin and lipid profiles. One of the proposed mechanisms is that zinc supplementation may reduce leptin resistance. However, there is an ongoing debate as to whether zinc supplementation increases or decreases the production of leptin in controlling the regulation of appetite. Similarly, several studies have obtained differential results on the levels of lipid profiles. Therefore, further studies are required to obtain a more in-depth understanding regarding this mechanism. Additionally, further studies on the optimal dose, duration and possible chronic toxicity of zinc supplementation, as well as on the effects of zinc on obese individuals without zinc deficiency, are required before zinc supplementation may be implemented on larger-scale obese populations.

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Availability of data and materials

Not applicable.

Authors' contributions

RDY was involved in the conceptualization of the study and in funding acquisition. RDY and DNP were involved in the design of the study and in the collection of data from the literature. BW and NW were involved in the interpretation of the study and in reviewing the literature. RDY and DNP were involved in the writing and preparation of the first draft of the manuscript. BW and NW contributed to the critical revision of the article. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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