Zinc and Lifestyle-Related Disease - with Focus on Diabetes Mellitus and Osteoporosis

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Abstract

In recent years, more people worldwide have suffered from diseases such as cancer, myocardial infarction, hypertension, osteoporosis, and diabetes mellitus. Diabetes mellitus and osteoporosis, well known as lifestyle-related diseases, have been considered serious problems in particular because full recovery is difficult. In 2007, the number of diabetes mellitus patients worldwide was reported to be approximately 200 million. Osteoporosis patients also amounted to approximately 200 million people worldwide. Against this background, many kinds of minerals have been used in the treatment and/or prevention of these lifestyle-related diseases. In particular, though the abundance of zinc in the body is very large, thus it is presumed to have a wide safety margin. Known as the second messenger, zinc has a wide variety of physiological functions, and attracts attention as an alternative to drug biological components. In this review, we outline the effect of zinc on the lifestyle-related diseases diabetes and osteoporosis.

Keywords: Osteoporosis; Diabetes; Biomolecules; Autoimmune disease

Introduction

The number of lifestyle-related diseases has been increasing globally as a result of recent drastic changes in lifestyle, diet, and increased possession of driver's licenses. In particular, it is an important problem that the lives of diabetes mellitus (DM) patients may be shortened when such patients are associated with other diseases (hypertension or hyperlipidemia) [1]. DM is a disease associated with absolute or relative insulin deficiency, and various types of medicines to treat DM have been developed worldwide. The World Health Organization (WHO) has classified DM into 2 types, namely, type 1 and type 2 DM. Type 1 DM is an autoimmune disease characterized by β-cell destruction, and insulin injections are administered for its management, whereas type 2 DM refers to adult-onset DM caused by defective insulin sensitivity, which is managed by the administration of several types of organic medicines [2-5]. A very important aspect of DM is that it leads to serious life-threatening complications, causing severe damage to the heart, eyes, kidneys, blood vessels, nerves, gums, teeth, feet, and legs [6,7]. There is also the fear of an increase in the incidence of osteoporosis as the population ages [8]. The WHO defines osteoporosis as a systemic degeneration of the skeleton, characterized by the loss of bone mass (in both organic and mineral bone components) and the structural degeneration of bone tissue that leads to an increase in bone fractures [9]. The risk of fracture is also increased by factors such as lifestyle, drug treatments, family history, and other conditions that cause secondary osteoporosis. About 40% of women in developed countries will experience an osteoporosis-related fracture in the course of their lifetime, with men facing approximately one-third to one-half the risk of women [10]. In recent years, it has been reported that adequate calcium and vitamin D intake are essential if a specific treatment is established. Insufficient calcium intake and/or poor vitamin D status represent the most common condition of non-responders to conventional anti-osteoporotic therapies [11]. Recently, medicines containing metals, such as cisplatin with platinum, auranofin with aurum, and promac with zinc, have been developed and used clinically [12-14]. Among them, zinc is known as one of the most important essential trace elements of all biological systems, and is less toxic than the other trace elements [15]. Among the many physiological and nutritional roles of zinc, zinc ions have been found to stimulate lipogenesis in rat adipocytes in a manner similar to the action of insulin. Zinc also plays an important role in infant development.

Furthermore, it has been demonstrated that zinc plays an important role in bone metabolism-regulating factors [16].

Anti Diabetic Activity of Zinc and its Complexes

At present, therapy for type 2 DM relies mainly on several medicines intended to reduce high blood glucose in addition to diet and exercise. For instance, the therapy may include medicines such as dipeptidyl peptidase IV inhibitors, which enhance insulin secretion; sulphonylureas, which increase insulin release from the pancreatic islets; thiazolidinediones, which enhance insulin action; and a-glucosidase inhibitors, which interfere with glucose absorption in the small intestine [17-20]. These medicines have limited efficacy and significant mechanism-based side effects such as hypoglycemia and hepatopathy. In the course of the search for new pharmaceuticals, several metal ions and their complexes have been found to exhibit an antidiabetic effect in vitro and in vivo systems. Currently, the most consistent finding, which has been observed in diabetic animal models such as rats and mice as well as in human diabetic patients, is the increased urinary excretion of zinc in diabetic subjects compared to controls. In DM studies, many researchers have thus recognized very clearly that zinc is an essentially important factor. In 1980, zinc was found to stimulate rat adipocyte lipogenesis similar to the action of insulin [21], which was followed by observations on the in vivo antidiabetic effects of oral zinc chloride (ZnCl2) in streptozotocin (STZ) rats and ob/ob mice in 1992 and 1998, respectively [22,23]. Simon and Taylor [24] reported that dietary zinc supplementation decreased high blood glucose in db/db mice, but that these administration doses were very high doses that exceeded the median lethal dose. As the bioavailability of ZnCl2 is relatively low, the complexation of zinc has been attempted. Metal complexes as metallo drugs are required to possess high bioavailability, to which there are...
many important contributing factors involving low molecular weight, neutral charge, coordination mode around the metal center, moderate stability constant, and moderate partition coefficient, high stability in the presence of many proteins and other biomolecules, and non-toxicity. Since then, we have proposed a wide variety of zinc complexes with different coordination modes. Zinc complexes with Zn(NO₃)₂, Zn(O₂), Zn(S₂O₃), Zn(N₄)₂, and Zn(S₄)₂ coordination modes have been prepared [25-26]. For example, we have synthesized zinc complexes with the Zn(N₄)₂ coordination mode. Bis(2-aminothiophenolate)Zn [(Zn(2-ampy)₂)], bis(2-aminoethylpyridinato)Zn [(Zn(2-aepy)₂)], and (1,5,8,12-tetraazadodecanato)Zn [(Zn(1,5,8,12-td)] complexes have been proposed [27]. Saha et al. [28] found that water-soluble (meso-tetakis[4-sulfonatophenyl]porphyrinato)Zn [(Zn(tpps)₂)], in which the zinc coordination sphere is Zn(N₄)₂, was a potential insulin-mimetic Zn–porphyrin complex to treat KKAα mice when introduced by oral gavage. Bis(pyridoxal dithiocarbamato)Zn [(Zn(pdcs)₂)] complex with the Zn(S₄)₂ coordination mode exhibited high hypoglycemic activities when orally administered to KKAα mice [29]. On the other hand, we have focused on bis(hinokitiolato)Zn ([(Zn(hkt)₂)], a complex with a Zn(O₄) coordination mode that has been reported to have higher insulin-mimetic activity relative to zinc complexes with the Zn(O₂) coordination mode [30]. Hinokitiol is a ligand of [Zn(hkt)₂], and is known to be a tropolone-related compound with an aromatic 7-member ring. It was reported that the hinokitiol and tropolone obtained from Aomori cypress tar acids have antibacterial and antioxidant activities [31,32]. In our study, tropolone-related zinc complexes with the Zn(O₂) coordination mode, including hinokitiol or tropolone, were converted into complexes with the Zn(S₂O₃)₂ coordination mode, and their insulin-mimetic activity (IC₅₀ value) was evaluated by measuring the inhibition of free fatty acid (FFA) release and enhancement of glucose uptake in isolated rat adipocytes (EC₅₀ value), and their antidiabetic effect in vivo. Among the complexes, the bis(historopropolonato)Zn [(Zn(trpp)₂)] complex with the Zn(S₂O₃)₂ coordination mode was identified from among several prepared complexes by in vitro evaluations, in which the [Zn(trpp)₂] complex exhibited 10-fold higher activity than that of the [Zn(trpp)₂] complex in regard to the suppression of FFA release in the adipocytes (Figure 1) [33]. In addition, blood glucose levels were improved, and hemoglobin A1c (HbA1c), which is indicative of average blood glucose levels, was also improved when [Zn(trpp)₂] was administered to type 2 diabetic KKAα mice for 25 days [33]. Other interesting anti-diabetic zinc complexes have recently been proposed (Figure 2). For example, zinc as a component of prostate extract enhanced glucose utilization in STZ-diabetic rats and improved their diabetic condition, which indicates that other substances present in the prostate extract, such as [Zn(cyclo[His-Pro])], might also contribute to the positive effects on the diabetic state [34]. Moreover, it has been reported that bis(N-hydroxy-4-[(trifluoromethylsulfonamido)methyl]benzamidato)Zn ([(Zn(h-4-tmn-b)₂)] complex activates Akt phosphorylation and exhibits insulin-like activity [35]. An especially interesting finding regarding the antidiabetic effect of zinc complexes was obtained in 2013 by us. Based on past studies, we synthesized a new zinc complex based on lipophilicity, stability, and the hard and soft acids and bases rule. The complex was a bis(2-selenopyridine-N-oxidato)Zn ([(Zn(spno)₂]) complex, which is an analog of bis(2-hydroxypropidine-N-oxidato)Zn ([(Zn(hpno)₂]) with a Zn(O₂) coordination mode or bis(2-mercaptopyridine-N-oxidato)Zn ([(Zn(mpno)₂]) with a Zn(S₂O₃)₂ coordination mode, and has a Zn(SeO₃)₂ coordination mode. Analyses of the structure–activity relationships between their insulin-mimetic activity and the coordination modes of their related complexes showed that [Zn(spno)₂] had highest insulin-mimetic activity (Figure 3) [36].

We evaluated the antidiabetic effects of [Zn(spno)₂] using a lower oral dose (1.25–2.5 mg Zn/kg body weight), unlike previous studies on KKAα mice [36]. The HbA1c levels in the treatment group decreased considerably compared to those in the control group (Figure 4). These results indicate that [Zn(spno)₂] has the most effective hypoglycemic effects among the known zinc complexes. Conducting a human study involving the use of zinc complexes by diabetic patients would be a future research aim.

Implication of Zinc and Bone Metabolism in Osteoporosis

Osteoporosis is a disease involving genetics, endocrine function, exercise, and nutritional considerations. In this disease, the bones become porous, brittle, and susceptible to breaking. Osteoporosis itself is not a disease that threatens a person’s life as cancer, stroke, and myocardial infarction, but many people require nursing care due to osteoporosis-related bone fractures. The quality of life of such individuals decreases remarkably. Thus, many approaches are being employed to reduce bone fracture risks in patients with osteoporosis [37,38]. An example of drug therapies is as follows. Bisphosphonates are potent inhibitors of bone resorption used mainly in the treatment of osteoporosis [39]. Other treatments such as teriparatide, raloxifene,
or strontium ranelate are now also available, and new medicines are currently being developed for osteoporosis patients [40]. However, these medicines have severe side effects. Thus, the development of drugs with fewer side effects and accessible supplements is expected. In recent years, it has been reported that various metal ions take an interest in bone metabolism. Tucker et al. [41] reported that magnesium intakes were significantly associated with bone mineral density in 2001 and Zhu et al. [42] also reported that potassium intake shows positive association with bone mineral density in 2009. In addition, many researchers have investigated the influence of zinc on bone metabolism [43-46]. For example, the bone mineral content of the jawbone and bone mechanical strength of the femur in zinc-deficient osteoporosis Sprague Dawley rats were reportedly restored by 12-week administration of zinc [47]. Yamaguchi and other investigators have reported that the amounts of DNA, an indicator of bone growth, and alkaline phosphatase (ALP) increase after zinc administration, and have proven that zinc effectively treats diabetic abnormal bone metabolism [48,49]. In contrast, the influence of other metals (copper, cobalt, magnesium) on bone metabolism has been noted, but high doses were required to demonstrate the effect of these metals. Thus, the high toxicity of metal ions was apprehended. Zinc was the metal that exerted the best effects on bone metabolism in these reports [50]. In a recent study, when we bred SAMP6 mice (a senescence-accelerated model mouse) treated with ZnSO4 (25 mg Zn/kg body weight) from 7 weeks to 15 weeks of age, the ZnSO4-treated group exhibited improved bone strength, increased ALP activity, and increased bone zinc density compared with the non-treated group (Figure 5) [51]. This result is considered to be related to the osteoplasty promotion effect of zinc and the reinforcement of material strength of the osseous tissue by zinc incorporation into the bone. It was reported that the stability of the collagenous triple helix is increased by metals in artificial collagen model peptides [52]. Thus, enhancement of zinc uptake to the bone stabilizes the collagen, and zinc may strengthen bone that has thinned due to osteoporosis. The world awaits the development of zinc compounds with an anti-osteoporosis effect.

**Conclusion**

Zinc is an essential element in the body and is present in amounts of approximately 2 g. Thus, its toxicity is very low and it is easy to use. It has a number of physiological effects and closely relates with human health, as discussed previously. In particular, zinc is closely related to the lifestyle-related diseases diabetes or osteoporosis, and a number of other researchers and we have focused on its effects on these conditions. The zinc complexes we have plans to synthesize will have high bioavailability, and we expect them to have a major effect on these lifestyle-related diseases. Zinc will play an important role in maintaining the health of the body.

**Acknowledgement**

The authors are grateful to the members of the Department of Analytical and Bioinorganic Chemistry, Division of Analytical and Physical Chemistry, Kyoto Pharmaceutical University and Department of Sports, Health and Nutrition, Faculty of Health and Welfare, Kobe Women's University.

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