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Zinc

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Abstract

Since the discovery of manifest Zn deficiency in 1961, the increasing number of studies demonstrated the association between altered Zn status and multiple diseases. In this chapter, we provide a review of the most recent advances on the role of Zn in health and disease (2010 – 20), with a special focus on the role of Zn in neurodegenerative and neurodevelopmental disorders, diabetes and obesity, male and female reproduction, as well as COVID-19. In parallel with the revealed tight association between ASD risk and severity and Zn status, the particular mechanisms linking Zn^{2+} and ASD pathogenesis like modulation of synaptic plasticity through ProSAP/Shank scaffold, neurotransmitter metabolism, and gut microbiota, have been elucidated. The increasing body of data indicate the potential involvement of Zn^{2+} metabolism in neurodegeneration. Systemic Zn levels in Alzheimer's and Parkinson's disease were found to be reduced, whereas its sequestration in brain may result in modulation of amyloid β and α--synuclein processing with subsequent toxic effects. Zn^{2+} was shown to possess adipotropic effects through the role of zinc transporters, zinc finger proteins, and Zn-α2-glycoprotein in adipose tissue physiology, underlying its particular role in pathogenesis of obesity and diabetes mellitus type 2. Recent findings also contribute to further understanding of the role of Zn2 + in spermatogenesis and sperm functioning, as well as oocyte development and fertilization. Finally, Zn^{2+} was shown to be the potential adjuvant therapy in management of novel coronavirus infection (COVID-19), underlining the perspectives of zinc in management of old and new threats.

1. Introduction

Zinc is a IIB group metal and is the 23rd most abundant element in the Earth's crust. The history of investigation of Zn essentiality dates back for more than 150 years. For example, its essentiality for *Aspergillus niger* was demonstrated in 1869, for plants in 1926, for laboratory rodents in 1933, for pigs in 1955, and for humans in 1963 (King, 2011; Prasad, 2014a, 2014b). The essential role of Zn in living organisms is mediated by its involvement in a plethora of physiological processes. More than 300 enzymes and proteins were considered as Zn-dependent, being regulated by more than 2000 transcription factors (Prasad, 2014a, 2014b). Particularly, Zn plays a significant role in regulation of cell cycle, DNA replication

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and reparation, cell proliferation and differentiation, apoptosis, metabolism of lipids and carbohydrates, as well as other processes (Chasapis, Ntoupa, Spiliopoulou, & Stefanidou, 2020; Maret, 2017a).

A significant part of biological effects of Zn is mediated through by antioxidant and anti-inflammatory role (Jarosz, Olbert, Wyszogrodzka, Młyniec, & Librowski, 2017). Zinc ions are considered as key regulators of redox homeostasis. Antioxidant activity of Zn^{2+} may be mediated by its direct interaction with amino acid residues preventing oxidative modification of protein molecules, its structural role in enzymatic antioxidants (Cu, Zn-superoxide dismutase) and metallothionein synthesis, as well as modulation of Nrf2 signaling. At the same time, at increasing concentrations Zn^{2+} may possess prooxidant activity (Maret, 2019; Oteiza, 2012). Zn-dependent modulation of redox homeostasis results in regulation of redox-sensitive transcription factors including NF-κB. Specifically, the anti-inflammatory effect of Zn^{2+} has been shown to be dependent on NF-κB inhibition with subsequent downregulation of target genes of proinflammatory cytokines, including TNF-α and IL-1β (Jarosz et al., 2017). In addition, Zn^{2+} may also modulate anti-inflammatory pathways including TGFβ, IL-2, and IL-4 downstream signaling (Gammoh & Rink, 2017). Taken together, these mechanisms result in a significant Zn-induced reduction in circulating C-reactive protein in human studies (Mousavi, Djafarian, Mojtahed, Varkaneh, & Shab-Bidar, 2018). Apart from modulation of inflammatory response, Zn is also known as an essential regulator of immune system development and functioning through regulation of proliferation and maturation of T- and B-lymphocytes, natural killers and dendritic cells, as well as B cell-mediated antibody production, phagocytosis, and antigen presentation (Wessels, Maywald, & Rink, 2017).

Due to involvement of Zn in a variety of physiological processes, deficiency in this trace element is associated with metabolic dysfunction and the resulting diseases. Zn deficiency as well as evidence of its essentiality was discovered by Prof. Ananda Prasad in the Middle East, where he described the case of Zn deficiency in 21 y.o. Iranian farmer characterized by hepatosplenomegaly, anemia, dwarfism, and hypogonadism (Prasad, Halsted, & Nadimi, 1961). Later studies by Prasad and coauthors further characterized the clinical manifestations of Zn deficiency (Prasad, 2013). Since then an increasing number of studies demonstrated the role of altered Zn status in a variety of pathological processes and diseases. Briefly, Zn deficiency was shown to be associated with neuropsychiatric and neurosensory disorders, skin lesions, acrodermatitis, hypogonadism and infertility, growth retardation, as well as thymic atrophy and immune dysfunction. In turn, excessive Zn intake may result in copper imbalance, gastrointestinal symptoms including nausea and vomiting, lymphocyte dysfunction, neurotoxicity, and respiratory symptoms in the case of Zn smoke inhalation (Plum, Rink, & Haase, 2010).

A state-of-the-art review on zinc biology and its particular health effects was described in a number of excellent reviews, summarizing the key findings in this field (Chasapis et al., 2020; King, 2011; Plum et al., 2010; Roohani, Hurrell, Kelishadi, & Schulin, 2013). Therefore, in this chapter, we provided a review of the most recent advances on the role of Zn in health and disease based on papers published in the last decade (2010–2020). In view of the high number of invaluable studies on molecular biology and pathology of Zn, we focused only on certain aspects of Zn biology that have been advanced over the last decade,

providing an insight into the data obtained on the role of Zn in neurodegenerative and neurodevelopmental disorders, diabetes and obesity, male and female reproduction, as well as COVID-19.

2. Zinc defiency worldwide: A 10-year update

Although the risk of low dietary Zn intake has significantly reduced from 22% to 16% in a period of 1992–2011, the prevalence of Zn deficiency is still significant (Kumssa et al., 2015). However, the existing data on Zn status in different regions on the edge of 2020s are highly variable. Zinc status was shown to be strongly related to economic development of the regions, achieving a prevalence of more than 20% in the majority of low- and middle-income countries (Gupta, Brazier, & Lowe, 2020). Despite reports on low prevalence of Zn deficiency in a number of countries including Afghanistan, Nigeria, and Chine, these outcomes may occur from the use of uncommon cutoffs (Hess, 2017).

High rate of Zn deficiency was observed in Latin America with the highest prevalence of inadequate Zn intake in Guyana (44%), Saint Vincent and Grenadines (42.9%), Bolivia (40.1%), Guatemala (38%), Paraguay (37.5%), Panama (36.5%), Peru (34.5%), El Salvador (34.5%), Nicaragua (33%), Honduras (31.6%), Suriname (31.6%), and Haiti (31.2%) (Cediel, Olivares, Brito, Cori, & López de Romaña, 2015). In Brazilian children the prevalence of dietary Zn insufficiency varies significantly from 16.6% to 46.0% (Pedraza & Sales, 2017), although certain regions (Southern Brazil) were characterized by low incidence of Zn deficiency in children (Sangalli, Rauber, & Vitolo, 2016). In Colombian 12- to 59-months-old children, the prevalence of Zn deficiency reached 49%, especially in poor families (Pinzón-Rondón, Hoyos-Martínez, Parra-Correa, Pedraza-Flechas, & Ruiz-Sternberg, 2019). Even higher rates of inadequate Zn status were detected in pregnant women from the Andean region (Ecuador) (Narváez-Caicedo, Moreano, Sandoval, & Jara-Palacios, 2018).

Analysis of national and subnational data from African countries demonstrated that the highest prevalence of Zn deficiency is observed in Nigeria (63%) followed by South Africa (39%) and Ethiopia (32%) (Harika, Faber, Samuel, Kimiywe, et al., 2017). Data from the same region demonstrated that in pregnant and non-pregnant women of reproductive age the prevalence of Zn deficiency is 46%–76% and 34%, respectively (Harika, Faber, Samuel, Mulugeta, et al., 2017). A recent meta-analysis demonstrated the prevalence of Zn deficiency in Ethiopian children and pregnant women of 38.4% and 59.9%, respectively (Berhe, Gebreareggay, & Gebremariam, 2019).

Middle East region is also characterized by high prevalence of Zn deficiency, although the existing data are highly variable. In a study originating from Bandar Abbas (Iran) the prevalence of Zn deficiency in 6-month to 12-year old children was estimated as 17.5% with higher rate in boys (20.94%) (Rahmati, Safdarian, Zakeri, & Zare, 2017). The results of the CASPIAN-V study which included more than 3500 children and adolescents (7–18 y.o.) revealed the prevalence of subclinical Zn deficiency of 4.9% in Iran (Azemati et al., 2020). In Turkey, subclinical Zn deficiency was observed in 27.8% of children and adolescents (6–

18 y.o.) (Vuralli, Tumer, & Hasanoglu, 2017). In an elderly population from Riyadh (Saudi Arabia) the rate of Zn deficiency was found to be 36% (Alqabbani & AlBadr, 2020).

The prevalence of Zn deficiency in India was shown to be highly variable due to differences in locations and the studied groups (Gonmei & Toteja, 2018). In Uttar Pradesh the prevalence of Zn deficiency in 4–6 y.o. children was estimated as 65.3 (Sharma & Yadav, 2019). In turn, 17.9% children from Ludhiana district of Punjab were characterized by low serum Zn levels (Bains et al., 2015), whereas in women from the same location the prevalence of suboptimal serum Zn was 31.4% (Bains, Kaur, & Bajwa, 2019). It has been also demonstrated that the prevalence of suboptimal Zn intake in India has significantly increased from 17.1% to 24.6% in a period of 1983–2012 (Smith, DeFries, Chhatre, Ghosh-Jerath, & Myers, 2019).

In contrast, Zn status in China was significantly improved during the last decades. Data from China Nutrition and Health Survey 2002 and 2012 demonstrated that the prevalence of Zn deficiency in schoolchildren has changed significantly from 44.4% to 10.2% (Liu, Piao, et al., 2017). Moreover, in younger children aged 3–5 y.o. the prevalence of Zn deficiency was even lower reaching 5.5% in rural and 2.4% urban children (Bi et al., 2020). 31% of Chinese adults were considered at high risk of Zn deficiency due to low dietary Zn intake during China Nutritional Transition Cohort Survey (CNTCS) 2015 (Wang et al., 2018).

Despite a high heterogeneity, the existing data demonstrate that the prevalence of Zn deficiency in developing countries is ~20%, although higher rates may be inherent to susceptible groups, such as infants, pregnant women, elderly, or low-income groups. A recent study also demonstrated that increased CO_2 production may promote the risk of zinc deficiency for additional 132–180 million predominantly in South Asia and Africa people by 2050. Particularly, the estimated CO2-associated Zn deficiency may affect up to 48 million people only in India (Myers, Wessells, Kloog, Zanobetti, & Schwartz, 2015). In contrast to developing countries, economically developed countries are characterized by higher micronutrient intake. However, systematic data on Zn status in the Western countries are less available.

The results of 2005–2012 NHANES demonstrated that 15% of adult US population are characterized by Zn inadequacy (Reider, Chung, Devarshi, Grant, & Hazels Mitmesser, 2020). More recent estimates (NHANES 2011–2014) of the prevalence of low serum Zn were 3.8%, 8.6%, and 8.2% in children, adult men and women, respectively (Hennigar, Lieberman, Fulgoni, & McClung, 2018). In Japan, the prevalence of marginal Zn status in adult men and women was estimated as 46% and 38.4%, whereas Zn deficiency was revealed in 0.4% men and 0.6% women (Yokokawa et al., 2020). The highest rate of Zn deficiency was observed in infants and elderly (Yasuda & Tsutsui, 2016). Correspondingly, high rate of Zn deficiency (10.1%) was also observed in Norwegian community-living elderly (65–87 y.o.) reaching 13.1% in men and 7.3% in women (Kvamme, Grønli, Jacobsen, & Florholmen, 2015). In 60- to 84-years-old people involved in Berlin Aging Study II low plasma Zn levels were found in 18.7% (Jung, Spira, Steinhagen-Thiessen, Demuth, & Norman, 2017). Therefore, existing data demonstrate that even in economically

developed countries the prevalence of Zn deficiency may reach 10%, especially in several risk groups.

A population-wide assessment of hair Zn levels in Russia demonstrated that increased risk of Zn deficiency may be observed in 18%–46% of the population depending on the region (Skalny & Kiselev, 2012).

Generally, the existing data on the prevalence of Zn deficiency are highly variable resulting in complicated assessment of the worldwide prevalence of low Zn status. It is proposed that Zn deficiency is observed in approximately 17% of the global population, although these values refer to 2012 (Chasapis et al., 2020).

3. Autism

3.1 Zinc status and autism

Recent studies provide evidence on significantly altered Zn stats in autism spectrum disorder (ASD). Correspondingly, systematic review and meta-analysis demonstrated lower serum Zn levels in autistic patients than those in the neurotypical children. Concomitantly, the difference in hair Zn content was found to be region-specific, being higher and lower in cases living in non-Asian and Asian regions (Saghazadeh, Ahangari, Hendi, Saleh, & Rezaei, 2017). However, the results of another meta-analysis demonstrated lack of significant group difference in hair, nail, and teeth Zn levels between autistic and neurotypical children (Babaknejad, Sayehmiri, Sayehmiri, Mohamadkhani, & Bahrami, 2016). A number of other studies failed to reveal any significant alteration of Zn levels in patients with ASD (Skalny et al., 2017; Sweetman, O'Donnell, Lalor, Grant, & Greaney, 2019; Tschinkel, Bjørklund, Conón, Chirumbolo, & Nascimento, 2018).

Despite the accumulating evidence of group difference in Zn status, its relationship to autism severity was demonstrated only in the last decade. An Italian study revealed an inverse association between hair Zn levels, defective play, and stereotype behavior in autistic children (Fiore et al., 2020). In addition, the presence of ADHD in children with ASD was characterized by a more profound decline in hair Zn (Skalny, Mazaletskaya, et al., 2020). This observation generally corroborated an earlier study which demonstrated inverse correlation between Zn concentration and hyperactivity, as well as fine motor skills severity (Russo et al., 2012). However, Priya and Geetha (2011) revealed a significant positive correlation between hair and nail Zn content and CARS values in children with ASD (Priya & Geetha, 2011). The observed contradictions may result from differences in clinical characteristics of the patients as well as background nutritional status of the studied populations.

Although an inverse association between maternal multivitamin multi-mineral supplementation and ASD risk in the offspring was proposed to be partially mediated by Zn (Guo, Li, Zhai, & Ding, 2019), the question of Zn supplementation in autism remains opened. A recent study demonstrated that 12-week Zn supplementation significantly reduced CARS values and improved locomotor and object control score in 3–8 y.o. children with

ASD that may be related to modulation of copper and metallothionein levels (Meguid et al., 2019).

3.2 Zinc and autism spectrum disorder pathogenesis

Recent advances in research on the particular role of zinc in autism demonstrated a role for the interplay between Zn and synaptic dysfunction in ASD pathogenesis, amplifying earlier reports on the involvement of Zn into regulation of neuroinflammation (Grabrucker & Grabrucker, 2017). The relationship between Zn and ASD stems from observations of behavioral deficits in Zn-deficient animals, demonstrating high rate of impaired social behavior, aggression, and anxiety (Hagmeyer, Haderspeck, & Grabrucker, 2014). Correspondingly, prenatal Zn deficiency was shown to induce autism-like behavior in adulthood (Grabrucker, Boeckers, & Grabrucker, 2016). Male but not female Znt3-deficient mice were demonstrated to have autism-like behavior, increased cortical volume, as well as MMP-9 and BDNF up-regulation (Yoo, Kim, Yoon, & Koh, 2016).

Prenatal LPS exposure was shown to induce maternal and offspring Zn deficiency and autism-like behavior, which was associated with impaired striatal dopaminergic signaling evidence by decreased striatal tyrosine hydroxylase and increased mTOR levels. These effects were shown to be reversed by Zn supplementation (Kirsten, Chaves-Kirsten, et al., 2015). In turn, Zn treatment was shown to ameliorate autism-like behavior and prevented increase in BDNF production in a rat model of autism induced by prenatal LPS exposure (Kirsten, Queiroz-Hazarbassanov, Bernardi, & Felicio, 2015). In a model of valproic acid (VPA)-induced autism Zn treatment also prevented repetitive and restrictive behaviors, impaired social interaction, and cognitive inflexibility, but not prevent VPA-induced reduction in striatal tyrosine hydroxylase protein expression (Cezar et al., 2018).

Grabrucker proposed that Zn^{2+} deficiency impairs synaptic ProSAP/Shank scaffold contributing to altered synapse plasticity, formation, and maturation, being associated with autism spectrum disorder-related behavior (Grabrucker, 2014; Grabrucker et al., 2014) (Fig. 1). Particularly, in a murine model of autism lacking Shank2 Zn mobilization significantly increased NMDAR signaling and improved social interaction (Lee et al., 2015). At the same time, in a Shank3 –/– mouse model of ASD, Zn supplementation prevented autism-like repetitive and anxiety behaviors, increased recruitment of Zn-sensitive SHANK2 to synapses, modulated postsynaptic NMDAR currents (Fourie et al., 2018) and presynaptic function at glutamatergic synapses (Vyas, Lee, Jung, & Montgomery, 2020). It is also notable that both models SHANK3-deficient mice and PZD mice are characterized by increased basal ganglia structures, whereas thalamus was differentially affected in genetic and non-genetic ASD models (Schoen et al., 2019). In turn, Zn supplementation was shown to significantly improve alterations in NMDAR subunits 1 and 2a, *Shank* gene expression, and decreased synaptic density associated with an ASD like biometal profile in a hippocampal cell culture (Hagmeyer et al., 2015).

Of note, patients with Phelan McDermid Syndrome (PMDS) characterized by ASD-related behavioral problems and SHANK3 mutations were found to have lower Zn levels due to the potential association between SHANK3 deficiency and enterocyte zinc transporter (ZIP2, ZIP4) expression (Pfaender et al., 2017). Therefore, the relationship between SHANK

family and zinc in shankopathies including autism may be possess significant effects not only in brain, but also in gut through alteration of Zn absorption and further aggravation of Zn dysregulation (Hagmeyer, Sauer, & Grabrucker, 2018).

Zinc was shown to improve dopamine uptake and amphetamine (AMPH)-induced, but not baseline dopamine efflux in ASD-associated human dopamine transporter (hDAT) mutation (Hamilton et al., 2015), suggesting a role for Zn in modulation of dopaminergic dysfunction in autism. Correspondingly, prenatally Zn deficient mice also considered as ASD model are characterized by altered brain lateralization, increased striatal volume, and impaired striatal lateralization of dopamine receptor 1 (DR1) expression (Grabrucker et al., 2018).

Several studies demonstrated the potential involvement of other Zn-dependent signaling mechanisms in ASD pathogenesis. Genetic deficiency of cytoskeleton-regulating cortactin binding protein 2 (CTTNBP2) results in altered synaptic plasticity and autism-like behavior, as well as reduced brain Zn levels, whereas Zn supplementation upregulated CTTNBP2-dependent synaptic proteins (Shih et al., 2020). Due to the role of purinergic system disturbances in ASD (Cheffer et al., 2018), downregulation of P2X7R-mediated signaling by Zn^{2+} may be at least partially involved in the role of Zn in ASD (Kovács et al., 2018). Modulation of gut-brain axis was also proposed as the potential mechanism of the role of Zn^{2+} in autism and other disorders (Vela et al., 2015).

Generally, the most recent human and laboratory data clearly demonstrate a significant role of altered Zn metabolism and autism pathogenesis. Although the potential benefits of Zn supplementation are widely discussed, further studies are required to evaluate clinical efficiency and the mechanisms of Zn supplementation in autism.

4. Zinc and Alzheimer’s disease

4.1 Zinc status and Alzheimer’s disease

Alzheimer’s disease (AD) pathogenesis is known to be tightly related to impaired metabolism of a number of toxic and essential metals including Zn^{2+} (González-Domínguez, García-Barrera, & Gómez-Ariza, 2014). Recent epidemiological and experimental studies further highlighted the potential role of Zn in Alzheimer’s disease. As results from systematic reviews and meta-analyses, the existing data demonstrate that circulating Zn levels were found to be reduced in patients with Alzheimer’s disease (Li, Zhang, Wang, & Zhao, 2017; Ventriglia et al., 2015). Of note, the use of acetylcholinesterase inhibitors in Alzheimer’s disease was shown to increase plasma Zn concentrations (Giacconi et al., 2019). At the same time, no significant increase in neocortical Zn levels was observed in AD patients (Schrag, Mueller, Oyoyo, Smith, & Kirsch, 2011). No significant association between dietary Zn intake and cognitive decline and/or Alzheimer’s disease risk was revealed (Loef, von Stillfried, & Walach, 2012). Moreover, in a group of AD patients with advanced age (70 y.o. and older) Zn supplementation was shown to reduce blood free Cu levels and afforded a protective effect against cognitive decline (Brewer & Kaur, 2013).

4.2 Zinc transporters in Alzheimer's disease

The observed alterations in Zn^{2+} handling in AD are mediated by aberrant expression of zinc transporters (Xu, Xiao, Liu, & Lang, 2019). In post-mortem brain samples mRNA levels of zinc transporters LIV1, ZIP1, ZnT1, ZnT4, and ZnT6 were found to increase in association with AD progression (Beyer et al., 2012). Laboratory studies also demonstrated increased expression of ZnT1, ZnT3, ZnT4, ZnT6, and ZnT7 expression in APPswe/PS1dE9 transgenic mouse brains, although the localization patterns were quite different. Specifically, ZnT7 was expressed in the core of the plaque, ZnT3, ZnT5, and ZnT6 expression was localized in the peripheral part of the plaques, whereas ZnT1 and ZnT4 were expressed in all parts of the plaques (Zhang et al., 2010). It is notable that human amyloid precursor protein-transgenic (Tg2576) mice are characterized by Zn^{2+} and ZnT3 localization in dystrophic neurites in a proximity to amyloid plaques, as well as in activated astrocytes (Lee, Cho, Seo, Hwang, & Koh, 2012). Correspondingly, Zn ions were found to be deposited in Aβ plaques in a APP/PS1 mouse model even after adjustment for tissue density (James et al., 2017).

Increased cerebrospinal fluid ZnT3 level was also shown to be associated with cognitive decline in AD (Enache et al., 2020). However, cerebral ZnT3 levels in AD patients with dementia were characterized by a significant reduction in association with increased tau tangle pathology and severity of delusions/agitation (Whitfield, Francis, Ballard, & Williams, 2018). In turn, in AD hippocampus, Zn^{2+} levels were found to be significantly increased in soluble fractions and synaptic vesicles in association with reduced ZnT3 expression (Bjorklund et al., 2012).

4.3 Direct interaction between zinc and amyloid β

Multiple studies have demonstrated direct interaction between Zn^{2+} cations and amyloid β, although the existing data are highly contradictory (Fig. 2). Several studies demonstrated that such interaction promotes amyloid aggregation and subsequent toxicity. Particularly, Zn^{2+} binding to Aβ metal-binding domain induced protein oligomerization (Istrate et al., 2016) and subsequent aggregation (Khatua et al., 2019), whereas inhibition of this interaction may prevent AD pathogenesis (Takeda & Tamano, 2015). Particularly, Zn^{2+} chelation by various agents was shown to prevent Zn-mediated Aβ aggregation and toxicity (Li, Xie, Dong, & Sun, 2018; (Liu, Dong, Liu, Zheng, & Sun, 2017); Tian, Wang, Wang, Li, & Wang, 2019). ZnAβ oligomers were proposed to be more neurotoxic, as well as more potent inducers of neuroinflammation through hippocampal microglia activation (Lee et al., 2018).

On the other hand, numerous studies revealed that Zn may alter Aβ aggregation and subsequent fibril formation. Nanomolar Zn^{2+} concentrations were shown to decrease the affinity of Aβ-Aβ interactions, whereas Cu^{2+} did not possess any significant effect (Hane et al., 2016). In addition, Zn was shown to irreversibly perturb formation of Aβ(1–40) and Aβ(1–42) amyloid fibers even at concentrations lower than the affinity threshold (Matheou, Younan, & Viles, 2016). Zn-induced reduction of amyloid fibril elongation was shown to be mediated by Zn^{2+} binding to Aβ40 monomer with subsequent folding of N-terminus around metal atom (Abelein et al., 2015). It is proposed that targeted Zn delivery to the brain may

reduce plaque size and neuroinflammation in a APP23 mouse model of AD (Vilella et al., 2018).

In addition, Zn^{2+} ions, unlike Cu2 + and Fe3 +, were also capable of promoting annular Aβ protofibril formation (Chen, Liao, Yu, Cheng, & Chen, 2011). In another study Zn^{2+} was shown to promote formation of smaller non-fibrillary Aβ42 aggregates with β-sheet structures (Zhang, Pauly, & Nagel-Steger, 2018). These findings generally corroborate earlier evidence of higher polymorphism of Aβ aggregates (Miller, Ma, & Nussinov, 2010).

It is also notable that Aβ1–42 uptake also alters intracellular Zn^{2+} handling that is responsible for at least of a part of the toxic effects (Tamano et al., 2020) and reduced systemic Zn levels (Baum et al., 2010). Specifically, Zn sequestration by amyloid was shown to prevent Zn^{2+} association with ProSAP2/Shank3 leading to impaired synapse maturation and decreased synaptic density in hippocampus (Grabrucker et al., 2011). In addition, direct interaction of extracellular Zn^{2+} with Aβ1–42 was shown to be essential for its uptake into rat hippocampus, whereas the uptake of both species was blocked by Ca2 +-EDTA (Takeda et al., 2017). At the same time, neither human Aβ1–40 nor rat Aβ1–42 injection (25 pmol, 1 μL) did not increase intracellular Zn^{2+} levels in the dentate gyrus, indicating a Zn-independent mechanism of toxicity (Tamano, Takiguchi, Shimaya, et al., 2019; Tamano, Takiguchi, Tanaka, et al., 2019).

The existing contradictions may have resulted from different methodological approaches to assess Zn-Ab interaction, as well as the animal species used in the experiments (Arena & Rizzarelli, 2019). It has also been proposed that the outcome of Zn-Aβ interaction may be a function of Zn concentrations (Viles, 2012), age and gender (Datki et al., 2020).

4.4 Zinc and (non)amyloidogenic pathways

Zinc was shown to be involved in the crossroad between amyloidogenic and non-amyloidogenic pathways of APP processing (Kim et al., 2018). Zn treatment was shown to increase APP expression and its amyloidogenic APP cleavage with subsequent Aβ deposition both *in vivo* (APP and presenilin 1 transgenic mice) and *in vitro* (SHSY-5Y) (Wang et al., 2010). Exposure to Zn-containing drinking water (10 ppm as ZnCO3) was shown to increase deposition of insoluble Aβ, whereas ZnT3 were characterized by an inverse correlation with soluble Aβ levels (Flinn, Bozzelli, Adlard, & Railey, 2014).

In contrast, Zn administration for 4–10 months at 100 mg/kg body weight/day did not increase Aβ or tau deposition in AβPP and AβPP/tau transgenic mice (Akiyama et al., 2012). Moreover, in a transgenic 3xTg-AD mouse model of AD Zn supplementation for 11–13 months (30 ppm as $ZnSO_4$) significantly reduced Aβ and tau pathology in hippocampus, also significantly increasing BDNF expression and ameliorating memory deficits (Corona et al., 2010).

Although earlier data demonstrate the potential inhibitory effects of Zn^{2+} on α-secretase, in a cell model Zn exposure was shown to reduce Aβ1–40 production through inhibition of γ-secretase activity (Li, Liu, et al., 2018). It is also notable that Zn is capable of increasing APP-C99 dimerization and reducing its cleavage by γ-secretase (Gerber, Wu, Dimitrov,

Osuna, & Fraering, 2017). At the same time, other studies demonstrated the potential role of Zn-metalloproteinases in Aβ and APP non-amyloidogenic cleavage (Gough, Parr-Sturgess, & Parkin, 2011). It has also been proposed that Aβ Zn binding may interfere with Aβ clearance mechanisms (Lanza, Bellia, & Rizzarelli, 2018).

4.5 Zinc and tau

In a transgenic murine model of Alzheimer's disease expressing human gene for tau protein (P301L) Zn supplementation was shown to increase neurofibrillary tangle formation, although the level of free Zn^{2+} decreased due to sequestration by tangles (Craven, Kochen, Hernandez, & Flinn, 2018). Zn^{2+} was shown to increase Tau aggregation with subsequent cytotoxicity and apoptosis in SH-SY5Y neuroblastoma cells (Hu et al., 2017). Zn binding was also shown to increase toxicity of Tau aggregates (Zn^{2+}-tau-R3), resulting in reduced neurite number and length (Li, Du, & Ni, 2019).

It has been also demonstrated that Zn promotes Tau phosphorylation at Ser262 through a mechanism involving GSK3β activation (Kwon et al., 2015). Release of Zn^{2+} in glutamatergic synapses was also shown to induce tau hyperphosphorylation through protein phosphatase 2A (PP2A) down-regulation (Sun et al., 2012) through Src-dependent enzyme phosphorylation (Xiong et al., 2013). Another study demonstrated a key role of COX-2 and its products PGI2 and F2α in tau phosphorylation (Wang, Guan, et al., 2017).

It is also notable that Zn^{2+}-mediated increase in Tau toxicity may occur due to direct binding of metal ion to Tau without inducing its phosphorylation (Huang et al., 2014).

5. Parkinson's disease (PD)

5.1 Zinc status in PD in epidemiological and experimental studies

In a meta-analysis including data from 822 PD patients and 777 healthy controls serum Zn levels were found to be significantly lower as compared to the control values (SMD=−0.779, 95%CI=[−1.323, −0.234], P< 0.001) (Sun et al., 2017). Another meta-analysis revealed similar associations (SMD=− 0.59; 95% CI [−1.06, −0.12]; $P = 0.014$), also demonstrating a tendency to reduced CSF Zn levels (Du, Liu, Zhong, & Wei, 2017). At the same time, higher hair Zn levels were associated with depression, hallucination, illusion, paranoid ideation, and total Scales for Outcomes in Parkinson's disease-Psychiatric Complications (SCOPA-PC) score in Brazilian PD patients (Dos Santos, Bezerra, Rocha, Barreto, & Kohlmeier, 2019). However, Zn intake was not associated with PD risk (Cheng et al., 2015). No significant PD-specific differences in Zn levels in brain regions were revealed (Genoud et al., 2017). Furthermore, patient-derived human olfactory neurosphere cultures with ATP13A2 deficiency were characterized by lower intracellular Zn^{2+} levels, aberrant expression of Zn transporters, and increased susceptibility to Zn^{2+}-induced mitochondrial dysfunction and cytotoxicity (Park, Koentjoro, Veivers, Mackay-Sim, & Sue, 2014).

Intranasal exposure to ZnO nanoparticles resulted in significant accumulation of Zn in olfactory bulb, hippocampus, striatum, and cerebral cortex inducing oxidative stress and neuroinflammation. In a model of PC12 cells differentiated to dopaminergic neurons under NGF stimulation ZnO nanoparticles significantly affected cytoskeletal proteins, induced

mitochondrial dysfunction and oxidative stress, leading to reduced cell viability (Liu, Yang, et al., 2020).

In turn, increased PARK9 expression improves zinc resistance increasing its transport to vesicular compartments, as well as reduces intracellular α-synuclein levels through its externalization in exosomes (Kong et al., 2014). It is also interesting that Zn supplementation to a level where control Drosophila flies demonstrate adverse effects significantly improves lifespan and motor function in parkin mutants Drosophila (Saini & Schaffner, 2010).

5.2 Zinc and α-synuclein

In male Wistar rats Zn exposure resulted in a significant Zn accumulation in substantia nigra, loss of dopaminergic neurons with striatal dopamine decline, as well as elevated α-synuclein expression and aggregation, whereas L-DOPA treatment partially restored these effects and behavioral changes (Kumar et al., 2018). Zn was found to be increased in the regions of α-synuclein aggregation in the olfactory bulb, whereas high free Zn^{2+} levels were noted in Lewy bodies, mitochondria, and lipofuscin, supporting the role of zinc in PD pathogenesis (Gardner et al., 2017).

Zn^{2+} was demonstrated to bind α-synuclein molecule due to the presence of high (Asp121) and lower (His50) affinity sites (Ramis, Ortega-Castro, Vilanova, Adrover, & Frau, 2018). Although certain studies demonstrated a significant increase in α-synuclein fibrillation in presence of high Zn^{2+} (Khodabandeh et al., 2020), it has been revealed that ZnO nanoparticles prevent α-synuclein fibrillation, shifting to lesser toxic flocs formation (Asthana et al., 2020). Increased Zn^{2+} levels were found to be associated with lysosomal dysfunction and α-synuclein accumulation in cases of ATP13A2 (PARK9) mutation characterized by juvenile-onset parkinsonism (Tsunemi & Krainc, 2014).

5.3 Zinc dopaminergic toxicity

Zn-induced alteration of dopaminergic system may be also considered as the potential Zn-dependent mechanism of PD. In an *in vivo* study using intraperitoneal injection of $ZnSO_4$ (20 mg/kg) for 12 weeks, Zn-induced a decrease in striatal dopamine which was associated with NF-κB and Bax activation, whereas treatment with anti-inflammatory compounds ameliorated both behavioral and neurochemical disturbances, corroborating a significant role for neuroinflammation in Zn-induced dopaminergic neurodegeneration (Chauhan, Mittra, Kumar, Patel, & Singh, 2016). In addition, minocycline, an inhibitor of microglia activation, also alleviated Zn-induced alteration of tyrosine hydroxylase (TH), vesicular monoamine transporter-2 (VMAT-2), and dopamine transporter (DAT) expression, as well as loss of TH-positive neurons (Kumar et al., 2016). Such mechanism of Zn dopaminergic neurotoxicity resembles that of paraquat, a neurotoxic pesticide (Mittra, Chauhan, Singh, Patel, & Singh, 2020).

Zn^{2+} influx into nigrostriatal dopaminergic neurons due to AMPA receptor activation was considered as the key mechanism of 6-hydroxydopamine (6-OHDA)-induced PD (Tamano, Nishio, Morioka, & Takeda, 2019). Correspondingly, striatal synaptic Zn^{2+} release may contribute to 6-hydroxydopamine-induced behavioral, locomotor, and memory deficits in

mice, whereas ZnT3-deficient mice characterized by lower synaptic Zn^{2+} release are more resistant to 6-hydroxydopamine-induced disorders (Sikora, Kieffer, Paoletti, & Ouagazzal, 2020). These findings corroborate earlier data from the same laboratory, indicating the association between AMPA-induced Zn^{2+} influx into nigrostriatal dopaminergic neurons and movement disorders in rats (Tamano, Morioka, Nishio, Takeuchi, & Takeda, 2018). Similarly, inhibition of Zn influx or toxicity using Zn chelator or antioxidant prevents paraquat-induced PD in rats (Tamano, Morioka, Nishio, et al., 2019;). Of all redox events, increased NADPH-oxidase activity and reduced GSH pools were shown to play a key role in Zn^{2+}-induced oxidative stress, apoptosis, and dopaminergic neurodegeneration (Kumar et al., 2012). In contrast, a recent study demonstrated that Zn^{2+} may possess protective effects against dopamine neurotoxicity due to modulation of Nrf2 and Bach-1 signaling (Kaufman, Salvador, Liu, & Oteiza, 2020).

It has been also demonstrated that Zn^{2+} exposure both activates and inhibits intrinsic excitability of nigrostriatal dopaminergic neurons through modulation of transient A-type K + (KA) channel (Noh, Chang, Wang, & Chung, 2011). Modulation of Ca^{2+}-channels may be also considered as the mechanism of Zn-induced modulation of dopaminergic system (Noh & Chung, 2019). Binding Zn^{2+} ion to Zn^{2+}-binding site of the human dopamine transporter (DAT) was shown to possess biphasic effect with stimulation at low doses (1 μM) and inhibition at high ones (10 μM) (Li, Mayer, et al., 2017; Li, Zhang, et al., 2017).

The particular mechanisms of Zn toxicity to dopaminergic neurons are still to be elucidated. Currently, it has been revealed that Gadd45b-induced cell death pathway activation and the associated inhibition of JNK survival pathway may be considered as the potential mechanism underlying Zn and DA dopaminergic degeneration, being in agreement with the observed increase in Gadd45b mRNA levels in PD patients (Yang et al., 2016). Another mechanism of Zn^{2+}-induced nigrostriatal dopaminergic degeneration may include inhibition of neuronal NOS activity, whereas the use of NO-donors was capable of reversal of striatal dopamine depletion, tyrosine hydroxylase expression, as well as the resulting behavioral changes (Singh et al., 2017).

Altogether, the most recent findings in the field demonstrate that Zn^{2+} may be involved in pathogenesis of neurodegenerative diseases through modulation of amyloid β and α-synuclein processing. Alteration of Zn homeostasis in neurodegenerative diseases was shown to be organ specific, resulting in reduced systemic Zn^{2+} levels in parallel with its cerebral accumulation and subsequent toxic effects.

6. Diabetes mellitus type 2

6.1 Zinc status and diabetes mellitus type 2

The results of a meta-analysis demonstrated that low Zn status as assessed by serum Zn levels or increased urinary Zn excretion is associated with poor glycemic control in patients with DM2 (da Silva Bandeira et al., 2017). We have also demonstrated that serum Zn levels are inversely associated with glucose and HbA1c levels even independently of diabetes (Skalnaya et al., 2017). Our recent data revealed an association between lower serum Zn levels and insulin resistance (HOMA-IR) in prediabetic women (Skalnaya et al., 2018).

Similarly, serum Zn levels and circulating oxysterol levels were significantly associated with these parameters even after adjustment for the presence of DM1 or DM2 (Samadi et al., 2020). It is also mote worthy that serum Zn levels were significantly lower in diabetic subjects injected with insulin than those not treated with insulin (Jansen et al., 2012). In another meta-analysis duration of DM2 was inversely associated with whole blood Zn levels, albeit being not significantly related to lower Zn intake (Fernández-Cao et al., 2018). However, a recent meta-analysis from the same research group revealed an association between elevated serum/plasma zinc concentration and increased T2DM risk in the general population (Fernández-Cao et al., 2019), being generally in agreement with earlier studies demonstrating a direct correlation between exchangeable Zn pool and fasting insulin and HOMA-IR values (Perez et al., 2018). While considering Zn status and diabetes, it is essential to note a recently estimated decrease in circulating Zinc-α2-glycoprotein in subjects with altered glucose metabolism, although this association may be highly affected by increased body weight (Pearsey et al., 2020).

Due to the role of Zn in insulin synthesis and signaling, as well as the observed inverse association between Zn status and diabetes, multiple studies were performed in order to assess the impact of Zn supplementation on glycemic control and other metabolic parameters in DM2. A systematic review and meta-analysis by Wang et al. (2019) which included data from 1700 participants in 14 countries demonstrated a significant reduction of fasting and 2-h postprandial glucose, fasting insulin and HOMA-IR, HbA1c and CRP levels (Wang et al., 2019). The results of the most recent analysis demonstrated that the effect of Zn on carbohydrate metabolism in DM2 depends on both dose and treatment duration. Briefly, short-term (<12 weeks) interventions reduced glucose and triglyceride levels as well as insulin resistance, whereas long-term treatment (>12 weeks) reduced serum glucose, triglycerides, total and LDL cholesterol. In turn, low-dose zinc supplementation (<25 mg/d) significantly reduced serum glucose, triglycerides, total and LDL cholesterol, and decreased insulin resistance. Significant reduction in insulin resistance and HbA1c was revealed in the case of high-dose zinc supplementation (≥25 mg/d). Therefore, the authors recommend long-term low-dose Zn supplementation for significant improvement of metabolic parameters in DM2 patients (Pompano & Boy, 2021). Significant improvement of lipid profile in diabetic patients in response to Zn supplementation was also demonstrated in another study (Asbaghi et al., 2020). It is also notable that the particular form of Zn supplements (Wang et al., 2019) as well as its coadministration with other nutraceuticals (Jafarnejad, Mahboobi, McFarland, Taghizadeh, & Rahimi, 2019) may have a significant impact on the efficiency of Zn treatment.

In addition to therapeutic potential of Zn treatment in diabetes, preventive effect of Zn supplementation is of particular interest, although the existing data are insufficient. A double-blind randomized placebo-controlled pilot study performed in Bangladesh an involving 55 subjects with prediabetes demonstrated that daily intake of 30 mg for 6 months significantly improved fasting glucose, beta cell function, and insulin resistance as compared to placebo (Islam et al., 2016). At the same time, systematic reviews and meta-analyses of the effect of zinc supplementation in pre-diabetes are lacking (Du et al., 2019). Indications of preventive effect of Zn intake may arise from prospective studies. Specifically, a 5-year prospective study involving 16,160 healthy Japanese adults (40–65 y.o.) revealed an inverse

association between dietary Zn intake and DM2 risk, that was diagnosed in 396 cases within a 5-year period (Eshak, Iso, Maruyama, Muraki, & Tamakoshi, 2018).

Despite the rather clear indications of the beneficial effect of Zn in DM2, the results of epidemiological studies regarding the relationship between both Zn status and Zn supplementation in DM2 are still contradictory (Ruz, Carrasco, Sánchez, Perez, & Rojas, 2016). In contrast, experimental *in vivo* studies aimed at investigation of antidiabetic potential of Zn are less contradictory. In addition to significant improvement of Zn metabolism (Barman, Pradeep, & Srinivasan, 2017; Pathak, Sharma, Kumar, & Dhawan, 2011) and glycemic control (Cooper-Capetini et al., 2017; Wang, Li, Fan, & Liu, 2012) Zn supplementation was shown to prevent or reduce diabetes-associated disorders including osteoporosis (Qi, He, et al., 2020), nephropathy (Barman, Pradeep, & Srinivasan, 2018), cardiomyopathy (Wang, Wang, et al., 2017), lung dysfunction (Sacan et al., 2016), cataract (Barman & Srinivasan, 2019), and others.

Despite certain contradictions, both human and experimental data clearly indicates the interference between Zn status either at baseline or in response to supplementation and glycemic control in DM2. The observed association is mediated by the regulatory role of Zn^{2+} in carbohydrate metabolism that has been significantly highlighted in the recent years.

6.2 Zinc as a factor of β-cell development and functioning

Zinc is essential for β-cell development and functioning due to its clearly demonstrated role in insulin processing and secretion (Li, 2014). Recent studies further characterized the role of Zn^{2+} in β-cell development and regulation. Zn^{2+} levels in cellular environment has a regulatory effect on β-cell functioning. Specifically, chelation and supplementation of Zn^{2+} in the physiological range reduce and increase insulin content and secretion, whereas more profound decreases and increases in Zn^{2+} levels are associated with β-cell apoptosis and necrosis, respectively (Nygaard, Larsen, Knuhtsen, Rungby, & Smidt, 2014). Maturation of insulin-producing cells differentiated from human adipose-derived stem cells is associated with significant changes in intracellular Zn^{2+} levels due to modulation of ZIP4 expression (Ohta et al., 2019). Differentiation of human exfoliated deciduous tooth-derived stem cells into β cell-like stem cells was also associated with up-regulation of ZnT8 expression and Zn^{2+} significantly increases insulin secretion (Kim, Shin, & Pae, 2016). Zinc (ZnO) was also used as an essential factor for promotion of endometrial stem cells differentiation into insulin-producing cells (Hoveizi & Mohammadi, 2019). Secreted Zn^{2+} may also regulate glucose-stimulated insulin secretion by β-cells in an autocrine manner through modulation of KATP/Ca^{2+} channels (Slepchenko, Daniels, Guo, & Li, 2015).

6.3 Zinc and insulin signal transduction

Although the role of Zn^{2+} in the key mechanisms of insulin signal transduction has been clearly demonstrated previously (Maret, 2017b), the most recent studies clarified the insulin mimetic effect of Zn^{2+} and its influence on the mechanisms of insulin resistance (Fig. 3). Wu et al. (2016) demonstrated that in insulin-resistant L6 myotubes Zn^{2+} increases glucose uptake through upregulating Akt phosphorylation, GLUT4 translocation, and GSK3β phosphorylation, as well as inhibiting mTOR and S6K1 expression (Wu et al., 2016). It is

also notable that Zn and insulin possessed synergistic activity in promotion of myogenic cell proliferation through phosphoinositide 3-kinase (PI3K)/Akt and ERK cascade (Ohashi et al., 2015). It is also notable that in human skeletal muscle cells Zn^{2+} activated ERK1/2, Akt, GSK-3β, and p38 signaling, whereas in murine cells activation of PRAS40, ERK1/2, Akt and GSK-3β was observed (Norouzi, Adulcikas, Sohal, & Myers, 2018). Insulin-mimetic effects of Bis-(hinokitiolato)-zinc complex ([Zn(hkt)2]) were also attributed to induction of Akt phosphorylation and inhibition of PTP1B and PTEN activity that were observed without activation of insulin receptor (Naito et al., 2016). A similar effect was observed for bis-(maltolato)-zinc(II) complex in adipose tissue (Naito, Yamamoto, Yoshikawa, & Yasui, 2019). The role of Zn^{2+} in insulin-dependent Akt activation was also supported in Znt7-KO mice (Tepaamorndech et al., 2016). Generally, the most recent data demonstrate that Akt is one of the key target pathways activated by Zn^{2+} and mediating its insulin-mimetic activity (Sun et al., 2018), although the antidiabetic effect involves multiple other pathways (Vardatsikos, Pandey, & Srivastava, 2013).

6.4 Zinc transporters in β-cell functioning and diabetes

In addition to the role of Zn^{2+} ions in pancreatic physiology and pathology, in the last decade significant progress was achieved in understanding the involvement of ZnT (Zn^{2+} influx) and ZIP (Zn^{2+} efflux) transporters in the effects of Zn. Moreover, it has been demonstrated that (patho)physiological effects of Zn^{2+} under certain circumstances is mediated by modulation of zinc transporters.

ZnT8 (SLC30A8) plays a key role in Zn^{2+} uptake by insulin secretory granules in β cells (Davidson, Wenzlau, & O'Brien, 2014). Specifically, an *in vivo* study using Znt8 knockout (Znt8KO) mice demonstrated that ZnT8 is essential for beta-cell zinc influx, glucose-stimulated insulin secretion, insulin processing, and formation of insulin granules (Wijesekara et al., 2010). The predominant role of ZnT8 as compared to ZnT7 in glucose-stimulated insulin secretion (Syring et al., 2016). Moreover, ZnT8 expression is also essential for regulation of adequate hypoglycemia-induced secretion of glucagon in a particular subset of α-cells (Solomou et al., 2015), whereas ZnT8-mediated Zn^{2+} signals from β-cells do not impact glucagon production (Hardy, Serino, Wijesekara, Chimienti, & Wheeler, 2011). Due to numerous functions associated with ZnT8, disturbances of the latter are significantly associated with impaired pancreatic function, playing a distinct role in pathogenesis of DM1 and DM2 (Yi, Huang, & Zhou, 2016).

In pediatric DM1 patients, ZnT8 is considered as a major CD8+ T-cell autoantigen proposed to play a pathogenetic role in DM1 (Éńee et al., 2012). ZnT8 autoantibody levels were found to be associated with diabetes-related antibodies to glutamic acid decarboxylase (GAD), IA2, and islet cell autoantibody in adult patients with DM1 (Rogowicz-Frontczak, Pilacinski, Wyka, Wierusz-Wysocka, & Zozulinska-Ziolkiewicz, 2018), being considered as a tool for DM1 differential diagnosis (Boudiaf et al., 2018). Correspondingly, a positive association between ZnT8 autoantibodies and risk of ketoacidosis was observed (Niechciał et al., 2018). However, ZnT8 antibody levels were shown to decrease during the first year after disease onset (Vaziri-Sani et al., 2010).

At the same time, loss of ZnT8 function in human β cells was shown to result in improved glucose responsiveness and insulin secretion (Dwivedi et al., 2019). Downregulation of ZnT8 in pancreatic β-cells was shown to reduce inflammation-induced cytotoxicity protecting the cells from apoptosis (Merriman & Fu, 2019). Correspondingly, genetic variants of human ZnT8 were found to be differentially associated with DM risk. Hyperreactive Arg-325 variant is linked to increased DM2 susceptibility, whereas loss-of--function mutations as well as Trp-325 variants of ZnT8 were associated with reduced DM2 risk (Merriman, Huang, Rutter, & Fu, 2016). The latter are related to enhanced glucose responsiveness and proinsulin processing with subsequent insulin synthesis (Zhang, Jian, He, & Wu, 2020).

ZnT3 was found to localize in insulin containing granules being functionally antagonistic to ZnT8 (Smidt et al., 2016). It has been demonstrated that siRNA-mediated knock-down of ZnT3 results in a reduction of insulin secretion in INS-1E cells, whereas ZnT8 knock-down is associated with increased intracellular insulin content (Petersen et al., 2011).

ZIP7 and ZIP6 were found to be involved in regulation of insulin excretion through modulation of cytosolic Zn^{2+} levels, whereas the latter may be also responsible for maintaining β cell survival from fatty acid-induced cell apoptosis (Liu et al., 2015). Myers, Nield, Chew, and Myers (2013) demonstrated that Zip7 is implicated into regulation of carbohydrate metabolism in skeletal muscle cells and its deficiency is associated with altered expression of insulin receptor, IRS-2, GluT4, impaired Akt signaling, as well as impaired expression of downstream genes of glucose metabolism (Myers et al., 2013). Moreover, ZIP7 response to glucose levels in skeletal muscles was shown to depend on insulin sensitivity. Specifically, insulin-resistant cells respond to glucose load with downregulation of ZIP7 expression, that is associated with decreased expression of Akt, GluT4, and other genes involved in carbohydrate metabolism (Norouzi et al., 2019). The involvement of ZIP7 in insulin signaling and insulin resistance may be also associated by regulation of endoplasmic reticulum stress (Adulcikas, Sonda, Norouzi, Sohal, & Myers, 2019).

ZnT7 is considered as an essential regulator of insulin secretion (Nunemaker & Benninger, 2016). ZnT7 localized predominantly to Golgi apparatus positively regulates insulin gene transcription, mRNA and protein synthesis through modulation of metal-responsive transcription factor Mtf1, also increasing glucose-induced (Huang, Yan, & Kirschke, 2010). The role of ZnT7 in glucose metabolism is also supported by the observation of increased susceptibility to diet-induced insulin resistance in ZnT7-KO mice due to reduced mRNA expression of Insr, Irs2, and Akt1 in skeletal muscles, whereas ZnT7 overexpression upregulated insulin sensitivity and improved glucose uptake (Huang et al., 2012). It is also interesting that the role of ZnT7 in carbohydrate metabolism may be at least partially mediated by its interference with fatty acid metabolism. Particularly, insulin resistance in ZnT7 knockout mice was found to be associated with increased fatty acid accumulation in skeletal muscles due to upregulation of fatty acid-binding protein 3 and other fatty acid transporters (Huang et al., 2018).

Maxel et al. (2019) demonstrated an essential role of Zip14 in INS-1E beta-cell line, that was shown to increase in response to glucose exposure. Zip14 was shown to be involved in

regulation of protein biosynthesis, oxidative phosphorylation, and insulin secretion (Maxel et al., 2019). Involvement of ZIP14 into pathogenesis of diabetes was found not to be limited only to pancreatic beta-cells. Specifically, in addition to altered insulin production and secretion, ZIP14-KO was associated with increased intestinal barrier permeability, endotoxinemia (Kim et al., 2020), systemic inflammation, and hepatic insulin resistance (Aydemir, Kim, & Cousins, 2017). The latter was shown to be mediated by Zn-dependent regulation of endosomal insulin receptor activity (Aydemir, Troche, Kim, & Cousins, 2016).

6.5 Zinc and hyperglycemia

Zn was shown to be a mediator of the (patho)physiological effects of hyperglycemia, that vary significantly between β-cells and other tissues.

Glucose exposure was shown to increase cytosolic Zn^{2+} levels to a maximum observed at 24 h through increased expression of ZIP6, ZIP7, and ZIP8 and reduced metallothionein expression in order to stimulate insulin processing and secretion, although chronic increase in $[Zn^{2+}]_i$ levels contributes to β-cell toxicity (Bellomo, Meur, & Rutter, 2011). At the same time, the results of another study demonstrated that prolonged stimulation of beta-cells (MIN6) with potassium chloride mimicking hyperglycemia resulted in a nearly threefold reduction in total Zn content, down-regulation of ZIP1, ZIP6, ZIP7 and ZIP14 mRNA expression, as well as altered expression of β-cell markers (Lawson, Maret, & Hogstrand, 2018).

In non-pancreatic tissues, Zn was also involved in mechanisms of glucose toxicity. Specifically, glucose-induced ROS overproduction was shown to induce mitochondrial fission and increased mitochondrial Zn^{2+} that promoted fission through the recruitment of the fission factor Drp-1 ultimately resulting in mitochondrial fragmentation (Abuarab, Munsey, Jiang, Li, & Sivaprasadarao, 2017). It is also noteworthy that hyperglycemia-induced alterations of intracellular Zn^{2+} levels with reduction of cytoplasmic and mitochondrial metal levels and increased endoplasmic reticulum Zn^{2+} content are mediated by opposite regulation of ZIP7 (upregulation) and ZNT7 (downregulation) in cardiomyocytes (Tuncay, Bitirim, Durak, Rutter, & Turan, 2016). Correspondingly, hyperglycemia-induced increase in ZIP7 and ZIP14, and decrease in ZIP8 and ZnT7 expression in insulin resistant cardiomyocytes was found to be inversed by sodium-glucose cotransporter 2 inhibitor (dapagliflozin) followed by improved MMP-2 and MMP-9 protein expression, and reduced oxidative stress (Olgar & Turan, 2019). Generally, the studies from the last decade provided more detail on the involvement of Zn in regulation of carbohydrate metabolism and its disturbance in diabetes mellitus type 2. In addition to further understanding of the role of Zn in β-cell development, insulin production, and insulin signaling, the particular role of Zn transporters was demonstrated. The existing data clearly demonstrate that modulation of Zn homeostasis could be considered as the potential prophylactic or therapeutic tool in management of diabetes mellitus type 2, although more systematic data on its efficiency are required.

7. Obesity

7.1 Zinc status in obesity

The existing data demonstrate a significant decrease in blood (Fan, Zhang, & Bu, 2017), serum (Rios-Lugo, Madrigal-Arellano, Gaytán-Hernández, Hernández-Mendoza, & Romero-Guzmán, 2020) and hair (Sulibursk a, Bogdański, Pupek-Musialik, & Krejpcio, 2011) Zn levels in patients with overweight/obesity. Correspondingly, the results of meta-analysis demonstrated lower serum Zn levels in obese children and adults (Gu, Xiang, Zhang, Sun, & Jiang, 2019). However, certain studies failed to reveal any obesity-related difference in markers of Zn status (García et al., 2012; Jaksic et al., 2019). The latter may be associated with inhomogeneous distribution of Zn in the various biosamples. Particularly, we have demonstrated reduced hair Zn levels in patients with overweight/obesity, whereas no significant group difference in hair contents was observed. In contrast, urinary Zn level was found to be higher in high-BMI group, being potentially indicative of increased Zn excretion in obesity (Tinkov et al., 2020). In turn, weight-loss in overweight/obese subjects was associated with increased plasma Zn levels (Voruganti et al., 2010) and redistribution of Zn between tissues (Freire, Fisberg, & Cozzolino, 2013).

Epidemiological studies also demonstrated an association between impaired Zn status and obesity-associated metabolic disturbances including insulin resistance (García et al., 2013), systemic inflammation and altered lipid profile (Costarelli et al., 2010). Similar associations were observed in patients with metabolic syndrome tightly associated with obesity. Particularly, serum Zn levels significantly correlated with the number of metabolic syndrome components including triglyceride levels (Seo, Song, Han, Lee, & Kim, 2014). Urinary Zn levels were increased in obese subjects characterized by higher cardiovascular risk (Severo, Morais, Beserra, Clímaco Cruz, et al., 2020). Correspondingly, higher Zn excretion was found to be associated with altered metabolic profile in obese subjects (Xu et al., 2020).

Multiple studies evaluated the impact of Zn supplementation on obesity and associated metabolic disturbances. Particularly, Zn supplementation was shown to reduce body weight and body mass index (Payahoo et al., 2013), as well as waist and hip circumference (Khorsandi et al., 2019) in obese subjects. A meta-analysis indicated that Zn supplementation in overweight/obese subjects is associated with a significant reduction in body weight, although the results were highly heterogeneous (Abdollahi et al., 2020). The results of systematic reviews and meta-analyses demonstrated that Zn supplementation in obese subjects is associated with reduced insulin resistance (Cruz, Morais, de Oliveira, Severo, & do Nascimento Marreiro, 2017) and dyslipidemia (Severo et al., 2019). In a placebo-controlled trial Zn supplementation was shown to reduce IL-6 and CRP levels, serving as markers of systemic inflammation in obesity (Kim & Ahn, 2014). In addition, it has been shown that Zn supplementation may reduce circulating leptin levels, although this effect was mainly attributable to long-term interventions (>6 weeks) performed in women (Khorshidi et al., 2019).

In vivo laboratory experiments generally corroborate to results noted in human studies, demonstrating protective effect of Zn on diet-induced obesity and associated metabolic risk. Zinc supplementation (6 mg/kg) starting from the 15th week of dietary intervention

significantly reduced diet-induced increase in body weight, adipose tissue mass, circulating insulin, leptin, and triglyceride levels in high-fat/high-fructose-fed rats (Thoen et al., 2019). Combining *in vivo* (high-fat diet-fed mice) and *in vitro* (HepG2 cells) approaches, Qi, Zhang, et al., 2020 demonstrated that Zn^{2+} supplementation significantly improves diet-induced alterations in lipid and carbohydrate metabolism reducing gluconeogenesis, increasing glycolysis and promoting glucose uptake, as well as decreasing lipid accumulation (Qi, Zhang, et al., 2020). Our previous study also demonstrated a significant decrease in hepatic liver accumulation in Zn supplemented (227 mg/L Zn as ZnSO4 in drinking water) high-fat high-carbohydrate diet-fed rats (Gatiatulina et al., 2019).

In addition to supplementation studies, the protective role of Zn in obesity and metabolic syndrome was revealed in restriction studies. Specifically, Zn deficiency aggravated, whereas Zn supplementation ameliorated diet-induced alteration of glucose homeostasis, insulin resistance, and hypertriglyceridemia, well as cardiac inflammation and hypertrophy (Wang, Luo, et al., 2016). Similar modulatory effect of Zn status was demonstrated on obesity-induced vascular inflammation, oxidative stress, and aortic remodeling (Chen et al., 2016). Prenatal and postnatal Zn deficiency was shown to result in increased adipocyte hypertrophy, as well as elevated triglyceride levels and insulin resistance (Abregú et al., 2019), being in agreement with the observation of Zn-deficiency-induced dysglycemia (Jou, Philipps, & Lönnerdal, 2010).

7.2 Adipose tissue as a target for zinc

In parallel with obesity-associated alteration of Zn content in various tissues (Min & Chung, 2018), a number of studies demonstrated a significant decrease in adipose tissue Zn levels (Tallman & Taylor, 2003; Tinkov et al., 2016). Adipose tissue Zn content was inversely associated with circulating leptin levels, insulin resistance, and systemic inflammation (Tinkov et al., 2016). Moreover, Zn deficiency in high-fat diet mice resulted in its decrease in adipose tissue due to altered expression of Zn transporters, as well as leptin overproduction and exacerbation of adipose tissue macrophage infiltration (Liu et al., 2013). Reduced Zn content in obese adipose tissue may be indicative of its role as the potential target of Zn physiological effects.

7.3 The impact of zinc on adipogenesis

Modulation of Zn levels has a significant impact on adipocyte differentiation. Particularly, ZnO treatment increased 3T3-L1 differentiation with subsequent lipid accumulation through upregulation of PPARγ, FABP4, C/EBPα, and SREBP1 mRNA and protein expression (Pandurangan, Jin, & Kim, 2016). These findings corroborate the results of the pioneer study by Tanaka and coauthors (Tanaka, Takahashi, Matsui, & Yano, 2001). Upregulation of PPARγ and C/EBPα in zinc ascorbate-induced adipogenesis are also associated with increased aP2 and GLUT4 expression, resulting in insulin-responsive adipocytes (Ghosh et al., 2013). Zn citrates were found to induce differentiation of pre-adipocytes into mature adipocytes accompanied by upregulation of PPARγ, adiponectin, GluTs expression (Tsave et al., 2018). It is also notable that Zn potentiated stimulatory effect of insulin treatment on PPARy expression (Tsave et al., 2015). In turn, high dose Zn supplementation significantly increased adipose tissue, adipocyte hypertrophy, and leptin production through modulation

of Akt signaling (Huang et al., 2017). Therefore, Zn^{2+} may be considered as a potent regulator of adipogenesis. At the same time, both Zn deficiency (Pandurangan et al., 2016) or excess (Huang et al., 2017) result in adipose tissue dysfunction. The particular role of zinc transporters and Zn-containing effector molecules in adipose tissue physiology will be discussed below.

7.4 Zinc transporters in adipose tissue and obesity

The interaction between Zn metabolism and obesity may be mediated by alteration of zinc transporters (Noh, Paik, Kim, & Chung, 2014). Particularly, *Psammomys obesus*, being a model of obesity and diabetes, is characterized by multidirectional changes in ZIP6, ZIP8, ZIP9, and ZnT9 expression in visceral and subcutaneous adipose tissue depots (Maxel, Pold, et al., 2015).

ZIP14 is specifically expressed in white adipose tissue playing a significant role in its physiology (Aydemir & Cousins, 2018). It has been demonstrated that Zip14 deficiency is associated with adipocyte hypertrophy and upregulation of proinflammatory cytokine expression due to NF-κB activation, especially under endotoxinemia (Troche, Aydemir, & Cousins, 2016). It has been also demonstrated that patients with obesity are characterized by reduced Zip14 expression in subcutaneous adipose tissue. At the same time, Zip14 expression is up-regulated during adipogenesis, being associated with PPARγ expression (Maxel, Smidt, et al., 2015). In turn, ZIP14 expression in adipose tissue was found to be reduced in obesity, also positively correlating with PPARγ expression (Maxel et al., 2017).

In turn, ZIP13 functioning is associated with inhibition of “brite” adipocyte transformation through modulation of C/EBP-β expression (Fukunaka et al., 2017).

Another transporter, tightly involved in adipogenesis regulation is Znt7 (Tepaamorndech, Kirschke, & Huang, 2014). Znt7 is significantly upregulated during adipogenesis, reaching peak values in fully differentiated 3T3-L1 cells (Huang et al., 2016). At the same time, the results of another study demonstrate that inhibition of adipogenesis due to Znt7 deficiency is not associated with altered PPARγ and C/EBPα expression (Tepaamorndech et al., 2016).

7.5 Zinc-α2-glycoprotein (ZAG)

Zinc-α2-glycoprotein (ZAG) is an adipokine that is inhibited by obesity, high-fat intake, inflammatory response (TNFα), and glucocorticoid and β3-adreno receptor antagonists (Bing, Mracek, Gao, & Trayhurn, 2010). Given the presence of Zn-binding sites in ZAG molecule, as well as the role of Zn^{2+} in its polymerization (Zahid et al., 2016) it is proposed that ZAG may mediate at least a part of Zn effects in adipose tissue (patho)physiology.

The existing data demonstrate a significant decrease in ZAG mRNA expression in subcutaneous and epididymal adipose tissue of ob/ob mice, with TNFα overproduction being considered as the leading mechanism of ZAG downregulation (Mracek et al., 2010). In addition, increased ZAG expression in high-fat fed mice resulted in a significant decrease in adipose tissue mass (Liu et al., 2018), and prevented obesity-associated non-alcoholic fatty liver disease (Xiao et al., 2018). ZAG was also responsible for improvement of glucose uptake and insulin sensitivity in adipocytes (Ceperuelo-Mallafré et al., 2015) and skeletal

muscles (Gao et al., 2018), underlying the earlier mentioned association between ZAG levels and insulin resistance.

ZAG acts as autocrine and paracrine regulator of adipocyte metabolism (Severo, Morais, Beserra, dos Santos, et al., 2020) primarily regulating lipid metabolism by increasing lipolysis and reducing lipogenesis (Pelletier et al., 2013). Particularly, ZAG overexpression in obese mice significantly increased hormone-sensitive lipase and decreased fatty acid synthase mRNA expression (Gong et al., 2010). The influence of ZAG on lipid metabolism may be also mediated by modulation of SREBP-1c (Liao et al., 2016). It is also notable that ZAG-dependent changes in lipid metabolism were shown to affect response to dexamethasone treatment (Zhang, Qiao, et al., 2020). In addition to modulation of lipid metabolism, ZAG may promote browning of white adipose tissue and the corresponding increase in mitochondrial biogenesis and UCP1 expression through PKA and p38 MAPK pathways (Elattar, Dimri, & Satyanarayana, 2018; Fan et al., 2020).

The observed decrease in lipogenic genes is also associated with down-regulation of PPARγ and C/EBPα expression in ZAG-overexpressing 3T3-L1 cells (Zhu et al., 2013). On the one hand, PPARγ is considered as one of the regulators of ZAG production (McDermott, Jadoon, & Cunningham, 2012), whereas ZAG may also possess modulatory effect on PPARγ expression (Wei et al., 2019). It is also notable that the influence of ZAG on adipose tissue metabolism may be also mediated by its stimulatory effect on adiponectin expression (Balaz et al., 2014).

Human data also corroborate the results of laboratory studies, demonstrating a tight association between ZAG metabolism and obesity. It has been demonstrated that ZAG mRNA expression in subcutaneous adipose tissue, as well as its circulating levels, are significantly increased in obese subjects (Liu et al., 2018). Moreover, adipose tissue ZAG content is associated with insulin resistance, and adiponectin expression and circulating levels (Garrido-Sánchez et al., 2012). The most recent study demonstrated that low serum ZAG levels are associated with metabolically unhealthy phenotype in obese subjects and together with adiponectin levels may be successfully used for discrimination of metabolic health abnormalities (Liu, Zhang, et al., 2020). At the same time, a significant decrease in plasma ZAG levels following Roux-En-Y gastric bypass surgery (RYGB), as well as an inverse association between ZAG and reductions in BMI and body fat, may be indicative of the protective effect of ZAG during rapid weight loss (Morse, Astbury, Walczyszyn, Hashim, & Geliebter, 2017).

7.6 Zinc finger proteins in adipogenesis

The influence of Zn on adipocyte differentiation may be mediated by its structural role in zinc finger proteins, being considered as early adipogenic regulators (Wei et al., 2013). Being a rather heterogenous group of proteins, various molecules may possess both stimulatory and inhibitory effect on adipogenesis.

Specifically, it has been demonstrated that Znf638 is induced at early stages of adipocyte differentiation and stimulates adipogenesis through C/EBPα and subsequent PPARγ upregulation (Du, Ma, Meruvu, Hugendubler, & Mueller, 2014). At the same time, Znf638

deficiency inhibits adipogenesis (Meruvu, Hugendubler, & Mueller, 2011). Another protein, Zfp423 may be also considered as adipogenic regulator stimulating PPARγ expression (Gupta et al., 2010). Correspondingly, Zfp423 overexpression accompanies adipocyte differentiation, whereas its epigenetic dysregulation is associated with subcutaneous adipocyte hypertrophy (Longo et al., 2018). Zfp423 inhibition with retinoic acid *in vitro* results not only in reduced white adipogenesis, but also increases brown adipocyte development (Wang, Fu, et al., 2017). It is also notable that biological effects of Zfp423 strongly depend on the functional state of the cell. In particular, at early stages of development Zfp423 deficiency results in altered differentiation and adipose tissue dysfunction, whereas in mature adipocytes it is associated with a shift to brown adipocyte phenotype (Shao et al., 2016). Zfp467 also up-regulated adipogenic differentiation of the precursor cells through increased expression of regulatory PPARγ and C/EBPα with subsequent induction of adiponectin and resistin production (Quach et al., 2011).

In turn, Zfp521 was shown to be a negative regulator of adipogenesis (Chiarella et al., 2018) preventing precursor cells from adipogenic differentiation and maintaining proliferative activity, whereas Zfp521 inhibition results in increased number of adipocytes and its maturation (Gustafson, Nerstedt, & Smith, 2019). Inhibitory effect of Zfp521 on adipogenesis may be at least partially mediated by downregulation of Zfp423 expression (Kang et al., 2012).

A significant role in regulation of adipogenesis was also demonstrated for ZFP217 (Liu et al., 2019), ZFP30 (Chen, Schwalie, et al., 2019) and other zinc finger proteins (Wei et al., 2013).

Although main focus in Zn studies was aimed at β-cells for a long time followed by the role of Zn in insulin signaling, the most recent data demonstrate that Zn may be considered as “adipotropic” metal due to its specific impact on adipose tissue development and functioning. In addition, particular Zn-containing effector molecules in adipose tissue including ZAG and zinc finger proteins, as well as their role in obesity was revealed. Therefore, addressing adipotropic effects of Zn may be considered as a potential treatment of obesity and obesity-associated disorders.

8. Male reproduction

8.1 Zinc, sperm quality, and infertility

The results of meta-analysis of 2600 infertile men and 867 controls demonstrated that infertility is associated with significantly lower seminal plasma Zn levels, whereas Zn supplementation significantly increased semen volume, sperm motility, and improved sperm morphology (Zhao et al., 2016). Correspondingly, a significant correlation between seminal plasma Zn levels and reduced risk of asthenozoospermia was observed in another meta-analysis (Taravati & Tohidi, 2016). Seminal plasma (Kothari & Chaudhari, 2016) as well as hair (Chang, Choi, Kim, & Park, 2011) Zn levels were also found to be associated with free testosterone levels. It is also notable that chronic prostatitis may significantly contribute to reduced seminal plasma Zn levels (Cui et al., 2015).

In infertile patients with varicocele lower seminal Zn level was associated with higher DNA fragmentation index (Nguyen, Trieu, Tran, & Luong, 2019). In turn, *in vitro* treatment with Zn in combination with D-aspartic acid, and coenzyme Q10 reduced lipid peroxidation in sperm of both normozoospermic and asthenozooseprmic subjects, although no effect on sperm DNA fragmentation was observed (Giacone et al., 2017).

Correspondingly, a number of studies addressed the efficiency of Zn supplementation for improvement of semen quality and male fertility. Zn supplementation (220 mg daily) for 3 months resulted in a significant increase in semen volume, sperm motility, and morphology, and was associated with increased high- and low-molecular weight Zn binding ligands (Hadwan, Almashhedy, & Alsalman, 2012). The results of meta-analysis performed by Salas-Huetos et al. (2018) demonstrated that Zn supplementation is capable of increasing total sperm concentrations and sperm motility (Salas-Huetos et al., 2018).

8.2 Zinc in spermatogenesis and sperm functioning

The observed associations between altered Zn status and male infertility are mediated by the critical role of Zn in spermatogenesis (Foresta et al., 2014). Short-term low-dose exposure to ZnO nanoparticles also promoted spermatogenesis through stimulation of cell self-renewal and differentiation of spermatogonia (Javadi et al., 2020). In turn, Zn deficiency was shown to result in oxidative stress, inflammatory response, and increased proapoptotic signaling (Bax, caspase-3) in germ cells, whereas antiapoptotic signals were reduced (Bcl-2) (Omu et al., 2015). Zn deficiency was associated with reduced Zip6 and Zip10 expression and altered seminiferous tubule structure with abnormal germinal epithelium irrespectively of systemic Zn and testosterone levels (Croxford, McCormick, & Kelleher, 2011). Leydig cell atrophy may also indirectly contribute to Zn deficiency-induced alterations in spermatogenesis (Kumari, Nair, & Bedwal, 2011).

Further studies also demonstrated that activation of proapoptotic and proinflammatory pathways induced by CCl4 treatment in testicular cells was aggravated by Zn deficiency (Chen, Yang, Wang, Yang, & Guo, 2019). Modulation of apoptosis, inflammation, and oxidative stress was also attributable to the protective effect of Zn against diabetes-induced testicular damage (Maremanda, Khan, & Jena, 2016). Zn^{2+}also improved DNA methylation, chromatin integrity, testicular structure, and increased spermatogonial stem cell number in a model of testicular toxicity induced by bleomycin etoposide and cis-platin treatment (Khadivi, Razavi, & Hashemi, 2020).

Along with spermatogenesis Zn^{2+} regulates other aspects of sperm physiology (Fallah, Mohammad-Hasani, & Colagar, 2018). It has been demonstrated that Zn^{2+} stimulates sperm capacitation and acrosome reaction by epidermal growth factor receptor activation and G-protein coupled receptor (Michailov, Ickowicz, & Breitbart, 2014). Conversely, sperm capacitation was associated with Zn^{2+} redistribution (Kerns, Zigo, Drobnis, Sutovsky, & Sutovsky, 2018). Signaling pathways of Zn^{2+}-induced capacitation are also responsible for hyperactivated sperm motility (Allouche-Fitoussi, Bakhshi, & Breitbart, 2018).

9. Female reproduction

9.1 Zinc and pregnancy, its complications, and outcome

Recent data demonstrate that pregnant women are characterized by lower serum Zn levels as compared to non-pregnant ones (Iqbal, Ali, Rust, Kundi, & Ekmekcioglu, 2020), being indicative of both increased Zn requirements and higher risk of Zn deficiency. A systematic review and meta-analysis demonstrated that cord blood Zn levels was significantly lower in pregnancies with complications as compared to physiological pregnancy (Akdas & Yazihan, 2020). Particularly, the risk of preeclampsia (Ma, Shen, & Zhang, 2015) and eclampsia (Zhu et al., 2016) is significantly associated with Zn deficiency. Correspondingly, the risk of pregnancy-induced hypertension also correlates with low Zn status (He, Lang, Li, Liu, & Yao, 2016). Although no association between Zn intake and circulating levels and GDM was observed (Wilson, Grieger, Bianco-Miotto, & Roberts, 2016), in women with gestational diabetes mellitus material Zn levels were inversely associated with birth weight (Luo et al., 2020). Zn status also has a significant impact on pregnancy outcome. Particularly, maternal Zn deficiency was shown to increase the risk of preterm birth by a factor of more than two (OR= 2.41) (Wang, Hu, et al., 2016), also being a significant risk factor for fetal growth restriction (Wang et al., 2015). In addition, lower serum Zn levels were also observed in women with miscarriage (Omeljaniuk et al., 2015). Correspondingly, increased maternal Zn level is associated with lower risk of stillbirth (Özgan Çelikel, Doğan, & Aksoy, 2018).

In view of a tight relationship between Zn status and pregnancy, the efficiency of Zn supplementation for improvement of pregnancy outcome was studied. A systematic review and meta-analysis involving 7637 women and indexed in Cochrane Database demonstrated that Zn supplementation reduced preterm birth by 14% (Ota et al., 2015).

9.2 Zinc and female infertility

Zinc is known to play a significant role in female reproductive system functioning and reproductive disorders (Nasiadek, Stragierowicz, Klimczak, & Kilanowicz, 2020). Grieger et al. (2019) demonstrated that women with lower plasma Zn levels are characterized by significantly longer time to pregnancy (Grieger et al., 2019). Our previous studies also revealed lower hair Zn content in women who underwent in vitro fertilization-induced pregnancy as compared to those with spontaneous pregnancy (Skalny et al., 2018). Certain studies unraveled the association between Zn status and causes of female infertility. Despite being rather heterogeneous, the existing data demonstrate that women with polycystic ovarian syndrome are characterized by inefficiently lower circulating Zn levels (Abedini, Ghaedi, Hadi, Mohammadi, & Amani, 2019). Similarly, Zn deficiency was observed in endometriosis (Lai et al., 2017), although patients with endometriosis who had IVF-induced pregnancy had higher follicular Zn levels as compared to cases with tubal infertility (Singh, Chattopadhyay, Chakravarty, & Chaudhury, 2013).

9.3 Zinc in oocyte, placenta, and fetal development

Physiological role of Zn^{2+} was demonstrated at all steps of fetal development starting from preconceptional oocyte development, its fertilization, trophoblast and placenta development, and fetal organogenesis.

Zn accumulation is essential during oocyte meiosis and may possess regulatory effect on cell cycle by modulation of cytostatic factor activity through EMI2 component (Bernhardt, Kong, Kim, O'Halloran, & Woodruff, 2012). Correspondingly, Zn deficiency results in meiotic block in oocytes altering its maturation and blastocyst formation (Jeon et al., 2015). In another study, maternal Zn deficiency before conception was shown to decrease histone and DNA methylation, lower fertilization rate and impaired blastocyst formation (Tian & Diaz, 2013). Recent study demonstrated that Zn supplementation was also capable of endoplasmic reticulum stress reduction in oocytes, thus promoting normal maturation and embryogenesis (Ridlo, Kim, Taweechaipaisankul, Kim, & Lee, 2020). Formation of Zn spark containing millions of Zn^{2+} ions due to exocytosis of Zn-containing vesicles is also known to be an essential mechanism of embryo formation and avoiding polyspermy (Duncan et al., 2016).

Zn is also involved in regulating of trophoblast invasion and migration through modulation of matrix metalloproteinase-2/9, thus contributing to placental development and ameliorating fetal growth restriction (Zong, Wei, Gou, Huang, & Lv, 2017). Correspondingly, Zn deficiency is associated with impaired placental morphogenesis through modulation of placental labyrinth microstructure ultimately resulting in lower blood flow and altered nutrition of the fetus (Wilson et al., 2017). These findings corroborate earlier indications of smaller fetal placenta formation and decreased key placental transcripts expression ultimately leading to higher incidence of neural tube defects in embryo (Tian, Anthony, Neuberger, & Diaz, 2014). Zn deficiency may be also responsible for increased NF-κB expression in placenta in cases of fetal growth restriction (Wang et al., 2015). In turn, Zn treatment was shown to reduce inflammatory response in decidual endothelial cells exposed to proinflammatory TNF-α (Balduit et al., 2020). Correspondingly, Zn supplementation was shown to prevent lipopolysaccharide-induced fetal growth restriction through its anti-inflammatory activity (Chen et al., 2012).

Maintenance of adequate Zn supply is essential for fetal organogenesis including development of cerebral cortex (Hasna, Bohic, Lemoine, Blugeon, & Bouron, 2019) and myocardium (Lin & Li, 2018). Correspondingly, maternal Zn deficiency and the concomitant decrease in placental metallothionein-1 and ZnT-1 mRNA expression are associated with heart malformations (Liu et al., 2014). Placental and fetal ZIP8 deficiency was shown to reduce Zn transport and adversely affect organogenesis resulting in liver, spleen, kidney, and lung hypoplasia (Gálvez-Peralta et al., 2012). Taken together, the existing data clearly demonstrate the role of zinc deficiency in fetal growth restriction and malformations, as well as complications in preterm neonates (Terrin et al., 2015).

10. Zinc and urgent challenges: Covid-19 pandemic

In December 2019, the worldwide community faced a massive outbreak of COVID-19 infection caused by SARS-CoV-2 coronavirus. During less than two years, more than 163 million people worldwide were infected by COVID-19 with more than 3.3 million patients deceased https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (World Health Organization, 2021). COVID-19 predominantly affects respiratory system causing viral pneumonia that is associated with systemic inflammation, endothelial dysfunction (Varga et

al., 2020), and immune dysregulation. The latter is characterized by reduced T helper, T suppressor, and Treg cell counts in parallel with leukocytosis (Qin et al., 2020).

Zinc was proposed as a useful adjuvant for COVID-19 therapy due to its systemic anti-inflammatory, antioxidant, immunoregulatory activity, as well as its role in respiratory protection (Skalny, Rink, et al., 2020). Indirect data supporting the potential usefulness of Zn in management of COVID-19 pneumonia included indications of negative association between Zn status and pneumonia (Barnett, Hamer, & Meydani, 2010), as well as certain viral diseases (Read, Obeid, Ahlenstiel, & Ahlenstiel, 2019). However, evidence supporting this hypothesis was published only recently.

In a study involving 249 COVID-19 patients a significant inverse correlation between serum Zn levels and disease severity was demonstrated, with the highest mortality and highest severity in patients with serum Zn< 50 μg/dl. In an *in vitro* study using Vero E6 cells the authors also revealed higher viral expansion in SARS-CoV-2-infected cells (Vogel et al., 2020). We have also demonstrated a 8% lower serum Zn levels in COVID-19 patients as compared to healthy controls (Skalny et al., 2021). In an Indian study patients with Zn deficiency were characterized by longer hospital stay and higher frequency of complications, acute respiratory distress syndrome, and higher mortality as compared to Zn adequate patients. In an *in vitro* study the authors also demonstrated that Zn deficiency promotes interaction between angiotensin-converting enzyme 2 (ACE2) and SARS-CoV-2 spike protein (Jothimani et al., 2020).

In addition to the role of zinc in immunity in general, and antiviral immunity in particular, the interest in Zn as the potential treatment agent in COVID-19 was supported by results from an *in vitro* study by Te Velthuis et al. (2010). Specifically, the authors have demonstrated that Zn^{2+} inhibits RNA-dependent RNA polymerase (RdRp) in SARS-coronavirus, resulting in reduced replication of viral particles (Te Velthuis et al., 2010). However, direct data on the efficiency of Zn compounds in COVID-19 treatment are still insufficient. Carlucci et al. (2020) demonstrated that inclusion of ZnSO4 into the protocol of COVID-19 treatment with hydroxychloroquine and azithromycin significantly reduced the need in ventilation, admission to the intensive care unit, as well as decreased mortality in COVID-19 patients, although no significant impact of Zn treatment on the length of hospitalization, ventilation, or hospital stay was observed (Carlucci et al., 2020). A number of trials on the efficacy of Zn in COVID-19 treatment protocols have been registered, although systematic data are not available to date (Doboszewska, Wlaź, Nowak, & Młyniec, 2020).

Therefore, Zn supplementation may be recommended for improvement of antiviral resistance in deficient subjects (Wessels, Rolles, & Rink, 2020). It is proposed that Zn supplementation may prevent excessive inflammatory response and cytokine storm in COVID-19 (Alexander et al., 2020). However, it is still unclear whether Zn compounds may be included in treatment protocols.

11. Conclusion

Recent findings significantly expanded the understanding of the role of Zn in neurodevelopmental and neurodegenerative disorders, diabetes and obesity, male and female infertility, and support the use of Zn in management of COVID-19. However, recent advances in Zn research biology and medicine are not limited to these diseases, and supporting the importance of Zn in human health. These findings are of extreme importance especially in view of still persisting high risk of Zn deficiency even in developed countries. Further laboratory studies in this field should focus on the particular mechanisms of the role of altered Zn homeostasis in disease pathogenesis. In turn, human studies should be designed in order to obtain high-quality systematic data on therapeutic and prophylactic efficiency of Zn to provide evidence-based support for the use of Zn in the management of various diseases.

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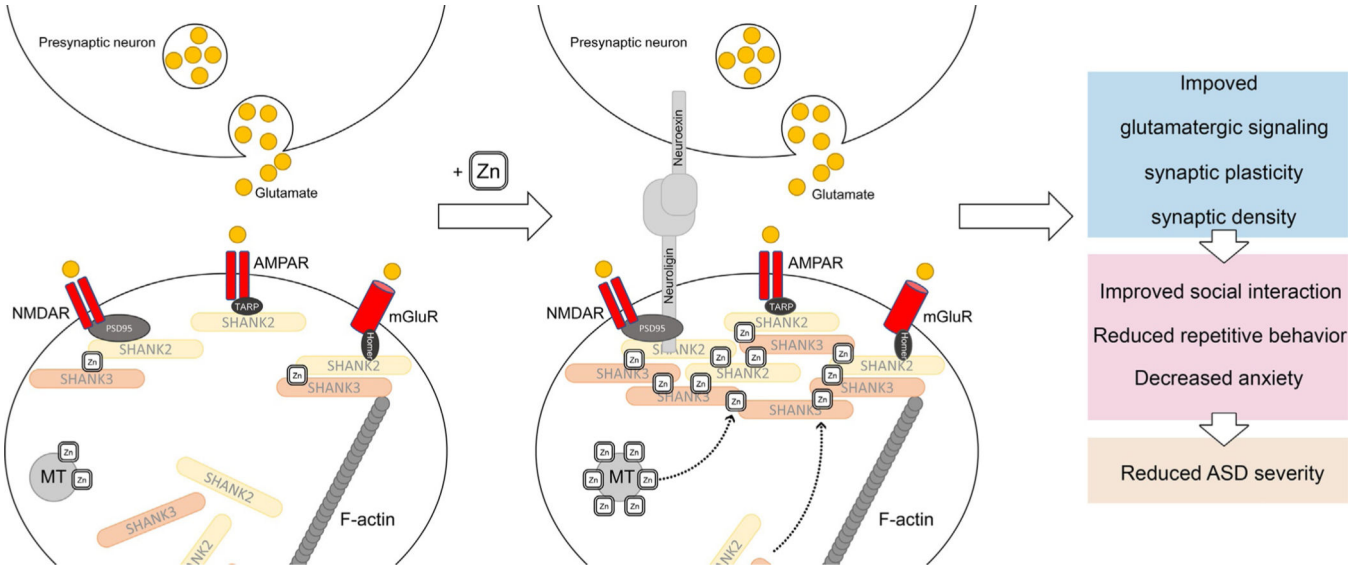

Fig. 1.

Involvement of ProSAP/Shank scaffold Zn^{2+}-induced modulation of synaptic (dys)function in ASD. Zn^{2+} supplementation was shown to increase SHANK2 recruitment to synapses, modulate postsynaptic NMDAR currents (Fourie et al., 2018), increase Shank gene expression, and improve synaptic density (Hagmeyer, Mangus, Boeckers, & Grabrucker, 2015), altogether resulting in improved social interaction and reduced autism-like repetitive and anxiety behaviors (Fourie et al., 2018; Lee et al., 2015). Furthermore, Zn deficiency is associated with altered synapse plasticity, formation, and maturation (Grabrucker, 2014; Grabrucker et al., 2014).

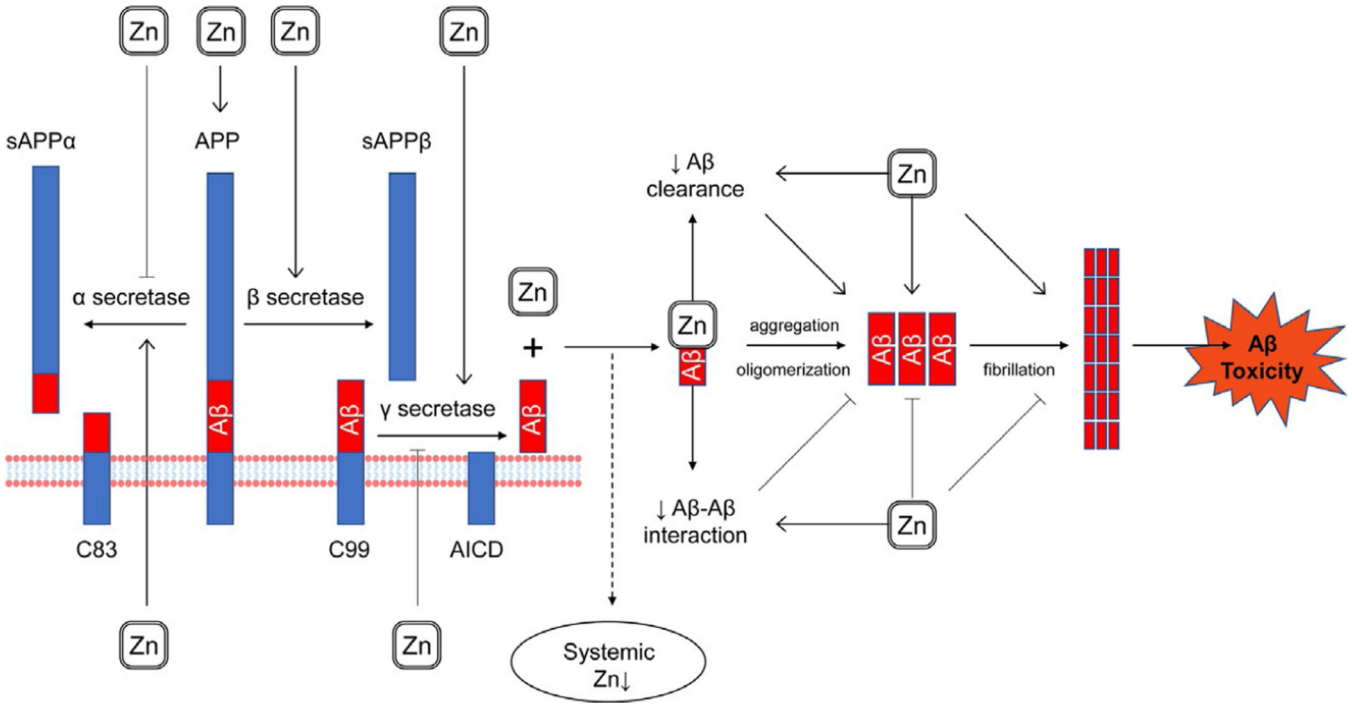

Fig. 2.

The impact of Zn^{2+} on amyloid production and processing. Zn^{2+} is capable of direct interaction with amyloid β, although data on this interaction have yet to be fully delineated. On one hand, Zn^{2+}-Aβ binding induced protein oligomerization (Istrate et al., 2016) and subsequent aggregation (Khatua, Mondal, & Bandyopadhyay, 2019), whereas its prevention was shown to reduce Aβ toxicity (Takeda & Tamano, 2015). On another hand, certain studies reported that Zn^{2+} may decrease Aβ-Aβ interactions (Hane, Hayes, Lee, & Leonenko, 2016) and reduced fibril elongation (Abelein, Gräslund, & Danielsson, 2015). In turn, direct interaction between Zn2 + and Aβ results in plaque Zn sequestration ultimately leading to a decrease in systemic Zn levels (Baum et al., 2010). In addition to direct interaction with Aβ, Zn^{2+} was also shown to modulate amyloidogenic pathways (Kim, Lim, & Kim, 2018), although the data are highly contradictory. Particularly, certain studies demonstrated antiamyloidogenic effects of Zn^{2+} through inhibition of γ-secretase (Li, Liu, Xu, Li, & Xu, 2018), whereas others revealed activation of amyloidogenic pathway through inhibition of α-secretase and a concomitant activation of β- and γ-secretase (Wang et al., 2010).

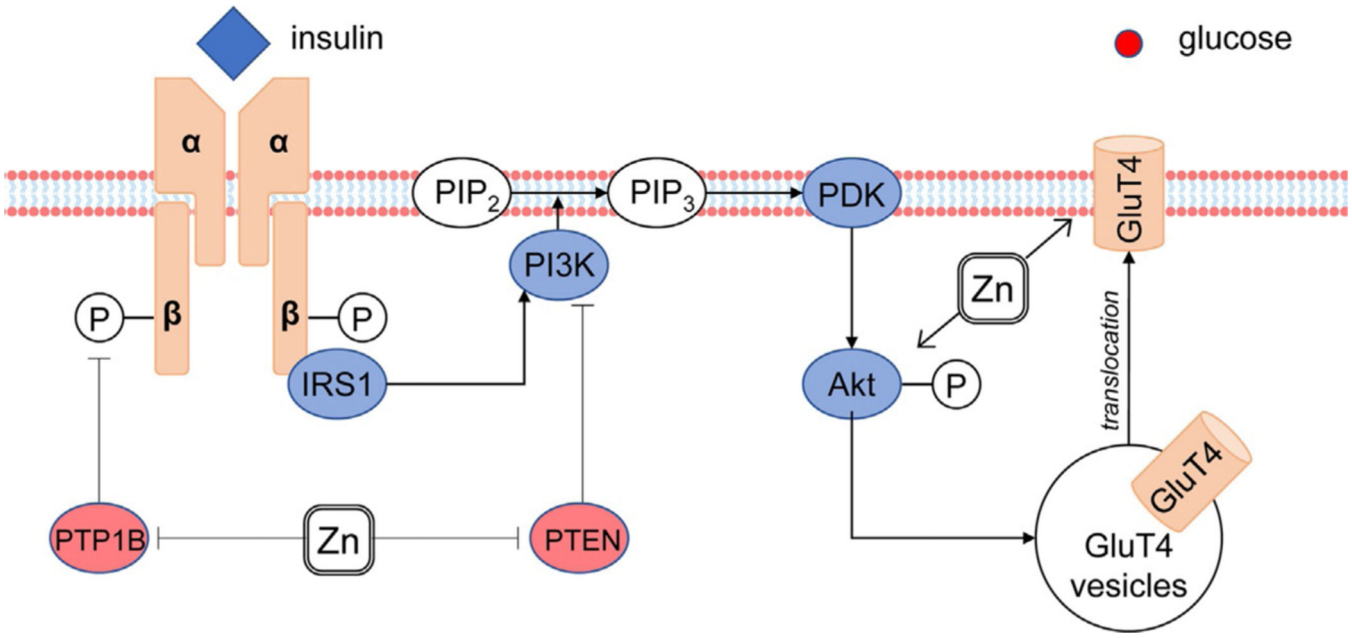

Fig. 3.

Involvement of Zn^{2+} in insulin signal transduction. Zn^{2+} increases phosphorylation of insulin receptor through inhibition of PTP1B, as well as up-regulates phosphoinositide 3-kinase (PI3K)/Akt due to PTEN down-regulation. These effects mediate stimulatory effects of Zn^{2+} on GluT4 translocation and glucose uptake. It is also notable that Akt phosphorylation and inhibition of PTP1B and PTEN activity that were observed without activation of insulin receptor (Naito, Yoshikawa, Masuda, & Yasui, 2016).