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The Role of Zinc Dynamics in Growth Hormone Secretion

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Key Words
Growth hormone · Secretory pathway · Zinc · Zinc deficiency · Growth impairment

Abstract
Human growth hormone (GH) causes a variety of physiological and metabolic effects in humans and plays a pivotal role in postnatal growth. In somatotroph cells of the anterior pituitary, GH is stored in concentrated forms in secretory granules to be rapidly released upon GH-releasing hormone stimulation. During the process of secretory granule biogenesis, self-association of GH occurs in the compartments of the early secretory pathway (endoplasmic reticulum and Golgi complex). Since this process is greatly facilitated by the presence of zinc ions, it is of importance to understand the potential role of zinc transporters that participate in the fine-tuning of zinc homeostasis and dynamics, particularly in the early secretory pathway. Thus, the role of zinc transporters in supplying the secretory pathway with the sufficient amount of zinc required for the biogenesis of GH-containing secretory granules is essential for normal secretion. This report, illustrated by a clinical case report on transient neonatal zinc deficiency, focuses on the role of zinc in GH storage in the secretory granules and highlights the role of specific zinc transporters in the early secretory pathway.

Introduction

The process of normal somatic growth requires the integrated function of many hormonal, metabolic and other growth factors involved in the hypothalamo-pituitary growth axis. Human growth hormone (GH) plays a particularly important role in human physiology and its pivotal role in postnatal linear growth is undisputed. In addition, GH controls a variety of other physiological and metabolic processes such as bone mineralization, glucose and lipid metabolism, protein synthesis and stimulation of the immune system, and is in turn influenced by important external factors such as stress, sleep, exercise and food intake [1–4].

The *GH1* gene is mainly expressed as a major 22-kDa isoform in somatotroph cells of the anterior pituitary gland. After being translated, GH protein passes throughout the regulated secretory pathway where it gets packed and stored in concentrated forms in secretory granules [5, 6]. Two key central regulatory factors are known to modulate the pulsatile secretion of GH, stimulatory GH-releasing hormone (GHRH) and inhibitory somatostatin [7]. The feedback of GH on GHRH and somatostatin is supplemented with central and peripheral regulators to ensure that the release of GH meets physiological demands. The biological actions of GH are mediated through activation of the GH receptor on the surface of

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the target cells. The binding of GH to the GH receptor triggers the Jak/Stat signalling cascade which results in transactivation of a series of GH-responsive genes, leading to the observed biological effects of GH [8].

Zinc (Zn^{2+}) is considered as the second most abundant 'trace' metal in the human body. It is required for numerous cellular mechanisms like DNA synthesis, protein synthesis, cell growth and division [9], as well as for many physiological processes like immune function [10] and reproduction [11, 12]. Hence, cellular Zn^{2+} homeostasis and dynamics are tightly regulated and maintained by various zinc transporters responsible for transporting these high-charge density ions across cellular membranes and various intracellular organelles [13, 14]. Over 2 decades ago, a high concentration of Zn^{2+} was reported to be localized mostly in the Golgi complex and GH-containing secretory granules of rat anterior pituitary cells [15], suggesting an important role of Zn^{2+} in the regulated secretory pathway of GH. During the process of secretory granule biogenesis, self-association (aggregation) of a hormone destined for secretion facilitates its storage in granules in fairly high amounts, and in the case of GH it occurs in the presence of Zn^{2+} [16]. In this report, we describe a clinical case of an infant with impaired growth, which might be caused, at least partially, by a transient Zn^{2+} deficiency. Further, we highlight the role of Zn^{2+} and specific zinc transporters in the secretory pathway of GH.

Clinical Case Report: Stunting Growth Caused by Zn^{2+} Deficiency in a Breast-Fed Infant due to Low Zn^{2+} Levels in Breast Milk

Zn^{2+} is an essential mineral, and infants are particularly vulnerable to Zn^{2+} deficiency as they require large amounts of Zn^{2+} for their normal growth and development. The rapid growth experienced by term infants, while they are still breast-fed, underscores the suitability and importance of breast milk during the first months of life. Unlike iron and copper, Zn^{2+} in breast milk occurs at a much higher concentration, especially in the first 3 months [17]. Transient neonatal zinc deficiency (TNZD, OMIM #608118) is a well-described disorder [18–20] characterized by a low level of Zn^{2+} found in the serum of exclusively breast-fed infants which occurs due to the defective secretion of Zn^{2+} in the mother's milk. Only recently, mutations in the *SLC30A2* gene (encoding for the zinc transporter ZnT2) have been associated with TNZD [21, 22], providing an explanation of why some otherwise healthy and normally nursing mothers may present with low Zn^{2+} levels in breast milk which leads to various abnormalities in the baby, including growth arrest. It is noteworthy that TNZD is clinically almost indistinguishable from acrodermatitis enteropathica (OMIM #201100), which is characterized by aberrant mucosal Zn^{2+} uptake in the small intestine. Mutations in the *SLC39A4* gene (encoding for the zinc transporter Zip4) have been associated with this disorder [23].

Here we describe the clinical case of an infant, born after 37 weeks of gestation with a birth weight of 2,550 g (25th percentile) and birth length of 47 cm (40th percentile) [24]. This otherwise healthy, exclusively breast-fed infant presented at the age of 6 months with a 3-week history of increasing skin problems, abdominal cramps and diarrhoea with no obvious malnutrition. The skin lesions involving the face in a peri-oral distribution (nasal, oral, auricular; fig. 1a), back (fig. 1b) and perineum appeared like acrodermatitis enteropathica, while the analysis of serum revealed a very low Zn^{2+} level (table 1) and decreased level of alkaline phosphatase. The serum Zn^{2+} level in the mother measured normal while Zn^{2+} concentration in the mother's breast milk was 0.12 mg/kg, which was significantly lower than the normative values (table 1). Hence, all the clinical parameters were in line with the diagnosis of TNZD. In addition, analysing the length and weight of the infant indicated obvious failure to thrive and stunting, starting at the age of 3 months and progressing further until the age of 5 months. At that age the length had dropped below the 3rd percentile on the growth curve (fig. 2). As the basic finding was Zn^{2+} deficiency, no GH stimulation test was performed, thus serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) levels (–2.3 and –2.9 SDS, respectively) were considered as indirect measurements of impaired GH secretion. Importantly, an oral Zn^{2+} supplementation therapy was initiated (administered orally as zinc sulphate heptahydrate) at a dose of 4 mg/kg/day while the child was breast-fed and until Zn^{2+} levels reached the normal range and thereafter was reduced to 2 mg/kg/day. Zn^{2+} supplementation therapy led to the disappearance of all clinical symptoms within the following few weeks (fig. 1c, d) and resulted in complete catch-up-growth of the child within 4 months (fig. 2), as well as in normalization of IGF-1 and IGFBP-3 levels (table 1). Therefore, a sufficient Zn^{2+} serum concentration in this infant seems also to be of crucial importance for GH secretion and, thus, normal growth and development. Based on this clinical description, we focus on the impact of Zn^{2+} – zinc transporters necessary for normal and sufficient GH secretion.

Such a Long Way Just to Get Secreted: From *GH1* to GH-Containing Secretory Granules

In many eukaryotic cells, secretory proteins are transported through the constitutive secretory pathway immediately after being synthesized, and their secretion by exocytosis does not require specific stimulus. One of the main hallmarks of endocrine and neuroendocrine cells is that they have an additional specialized pathway, called the regulated secretory pathway, in which proteins are 'stored' in concentrated forms in membrane-enclosed core vesicles with dense cores, also called secretory granules. Upon specific stimulation these vesicles fuse with the plasma membrane causing the dense cores to be released and dissolved, resulting in increased amounts of hormone to be released into the bloodstream.

The long and complex process of GH from the gene to secretory granule begins in the nucleus where the gene en-

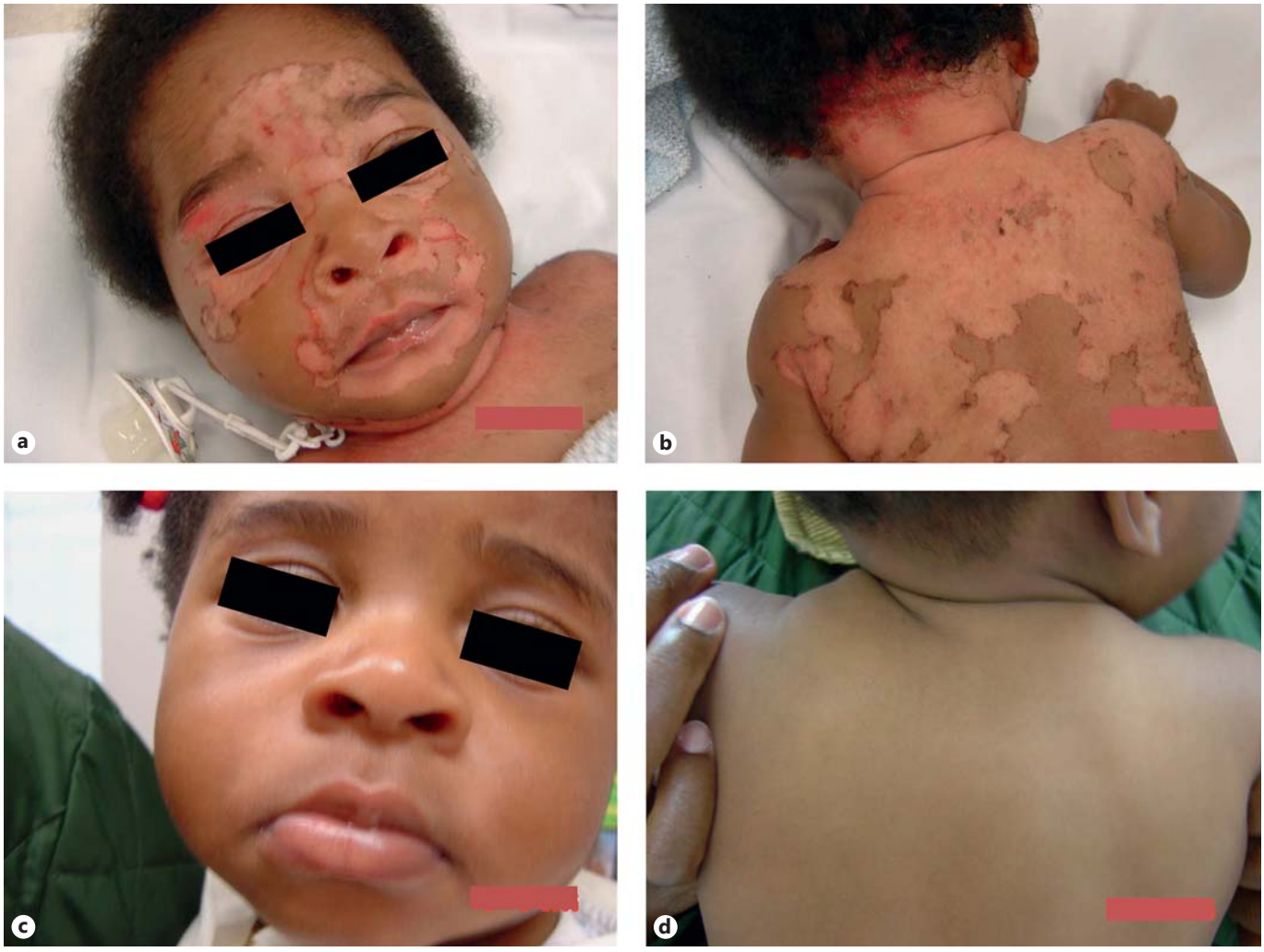

Fig. 1. Skin lesions in a peri-oral region and on the back of the patient before (**a**, **b**) and after (**c**, **d**) the Zn^{2+} supplementation therapy.

Table 1. Laboratory data of the child and mother

	Child			Mother
	before Zn^{2+} supplementation therapy	after 1 month on Zn^{2+} supplementation therapy	normative values	
Zn^{2+} in serum, μmol/l	2.3	14.6	9–21	12.2 (11–18)
Alkaline phosphatase, IU/l	73	465	96–336	88 (36–108)
IGF-1, ng/ml	10 (–2.3 SDS)	62 (0 SDS)	18–146	
IGFBP-3, mg/l	0.89 (–2.9 SDS)	2.95 (+0.5 SDS)	1.19–3.81	
Zn^{2+} in breast milk, mg/kg				0.12 (0.2–0.76)

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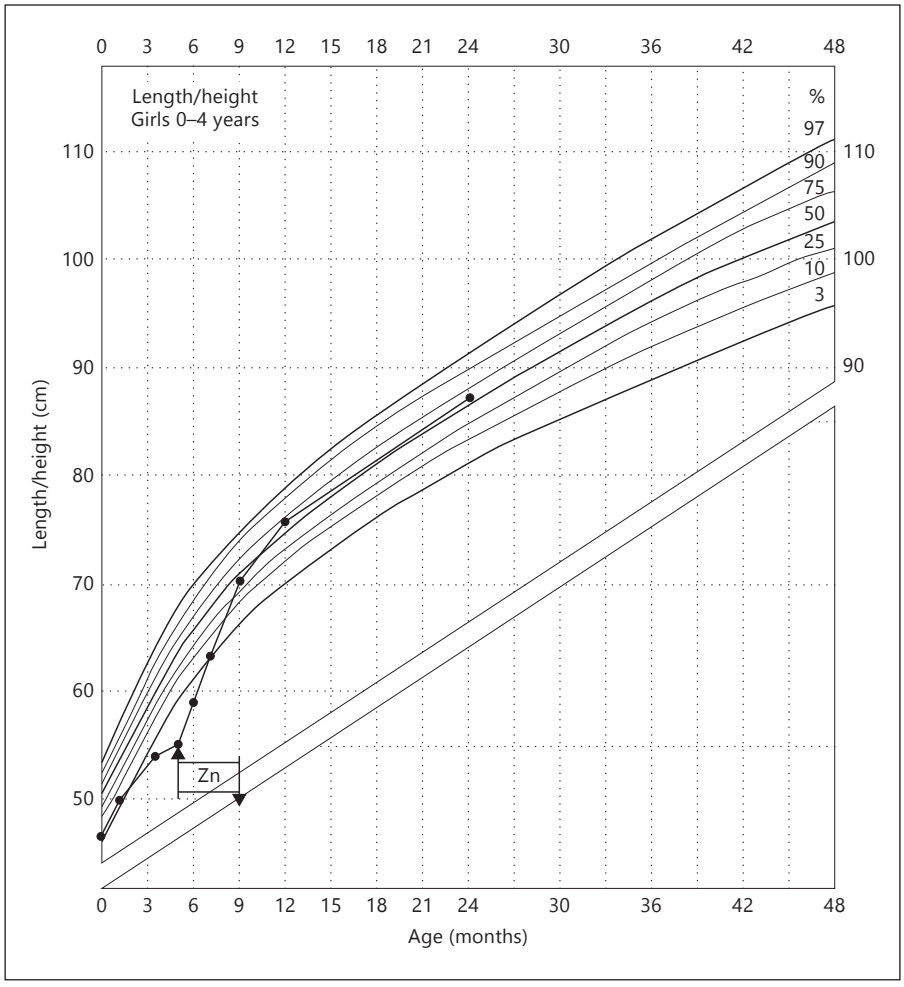

Fig. 2. Growth chart of the patient. The solid circles indicate the height measurements. Percentiles are shown on the extreme right. The arrows pointing up and down indicate the beginning and the end of the Zn^{2+} supplementation therapy.

coding GH *(GH1)*, located on the long arm of chromosome 17 (17q22–24), is expressed. Expression is regulated by the highly polymorphic proximal promoter and a locus control region 15–32 kb upstream of the gene conferring the pituitary-specific, high-level expression of GH [25]. The correct splicing of *GH1* gives rise to a transcript that contains all 5 exons spliced together to encode the full-length 22-kDa peptide – the major biologically active form of GH which represents approximately 75% of circulating GH [26]. Alternative splicing of *GH1* results in the generation of a small percentage of GH-splicing products (isoforms): a 20-kDa isoform that lacks amino acids 32–46 (5–10% of GH transcripts) [27] and a less abundant 17.5-kDa variant that results from complete skipping of exon 3 and lacks amino acids 32–71 (1–5% of GH transcripts) [28].

In the somatotroph cells of the anterior pituitary, GH is primarily produced as a larger precursor (217 amino acids) on the rough endoplasmic reticulum (ER), which is then transported into the luminal space of ER via a mechanism that involves the recognition of the signal peptide (amino acids 1–26). Following enzymatic cleavage of the signal peptide, a single GH polypeptide chain of 191 amino acid residues is yielded and then properly folded by ER-resident chaperons [29] in a globular, monomeric protein stabilized by two disulphide bridges with a molecular mass of 22 kDa, representing the major biologically active form found later in circulation.

From the ER, GH is subsequently transported to the second intracellular compartment of the regulated secretory pathway, the Golgi complex. Transport of most proteins targeted for secretion through the Golgi complex follows the model called cisternal maturation [30–32], which starts with the arrival of COPII vesicles carrying soluble proteins from the ER lumen at the intermediate compartment where they fuse to form a new Golgi cisterna. Once formed, the cisterna moves up through the Golgi stacks,

starting from *cis*-, progressing further to medial- and to *trans*-Golgi side, undergoing at the same time the process of maturation. During this process, many proteins destined for secretion localized in the lumen undergo a series of enzymatic modifications that include phosphorylation, sulfation and glycosylation in the case of glycoproteins. As the newer cisternae form behind it, the older ones ahead that ended the maturation process are eventually disassembled [33]. Furthermore, the lumen of the *trans*-Golgi layer is a particular place within the secretory pathway where aggregation of some hormones like GH and prolactin (PRL) occurs; this is considered one of the crucial steps in the formation of secretory granules. The last two-to-three *trans*-Golgi layers, known as the *trans*-Golgi network, serve as one of the few 'sorting stations' present within the secretory pathway required for different secretory proteins to be sorted into distinct tubular carriers, which are targeted to different final intracellular destinations such as plasma membrane, lysosomes, early, late and recycling endosomes and secretory granules [33]. Once a hormone aggregate is formed, its 'content' is recognized by specific membrane proteins required for transport and release of secretory granules, which localize in the membrane around the aggregate. At this stage, immature secretory granules containing GH are formed that still contain an excess of membranes, inappropriate membrane proteins and other soluble proteins. A number of maturation steps are required to progressively convert immature secretory granules into their mature form. The whole process includes acidification of immature secretory granules to activate enzymes for the processing of the regulated secretory pathway proteins, removal of constitutive secretory proteins and lysosomal enzymes packed into immature secretory granules, loss of clathrin coat and other coat proteins and condensation of their protein constituents, thus increasing secretory granule dense cores. Once formed, mature secretory granules containing hormone are ready to be secreted in a regulated manner upon a specific stimulus [34], which in the case of GH is the GHRH produced in the arcuate nucleus of the hypothalamus.

The Biogenesis of GH Secretory Granules Begins with Zn^{2+}-Mediated GH Aggregation at Acidic pH in the *trans*-Golgi Lumen

The complex process of secretory granule biogenesis begins with an aggregation of proteins (hormones) destined for secretion to form dense cores of granules composed of large insoluble aggregates. Upon appropriate stimulation, aggregates are released into the bloodstream, leading to a burst of hormones on a time scale much faster than could be achieved from increased synthesis.

Protein aggregation takes place in the lumen of the *trans*-Golgi layer where specific environmental factors like pH and higher concentrations of divalent ions like zinc seem to play an important role in inducing this process. In fact, measurement of the steady-state pH throughout different cellular compartments of the secretory pathway in live AtT-20 cells revealed that pH gradually decreases from neutral 7.2 measured in the ER through mildly acidic 6 in the Golgi and to acidic pH of 5.5 measured in mature secretory granules [35]. These data are in line with the generally accepted model for aggregation of secretory granule proteins to be induced by the acidic pH in the *trans*-Golgi compartment. However, only aggregation of human PRL transiently expressed in AtT-20 cells was completely prevented by agents neutralizing intracellular acidic compartments, as opposed to only partially prevented aggregation of human GH, suggesting that aggregation of GH might be less dependent on acidic pH than that of PRL [36].

Apart from specific pH requirements, aggregation of GH apparently requires high amounts of divalent cations like Zn^{2+}. The first clues pointing towards this direction came over 2 decades ago, when a high concentration of Zn^{2+} was reported to be localized mostly in GH-containing secretory granules and to a lesser extent in the Golgi complex of rat anterior pituitary cells [15], confirming the presence of Zn^{2+} in the regulated secretory pathway of GH.

A step further towards unravelling the role of Zn^{2+} in the storage of GH in secretory granules came with the study reporting that two Zn^{2+} ions associate with each GH dimer in a cooperative fashion through binding at high-affinity residues in GH (His18, His21 and Glu174) [37]. Replacement of these residues with alanine caused reductions of dimeric GH formation as demonstrated by size exclusion chromatography and sedimentation equilibrium analysis. In addition, the data presented also demonstrate that Zn^{2+} binding to GH would enhance stability of the stored form, and that the Zn^{2+}-GH complex was more resistant to denaturation compared to monomeric GH. These data suggested that Zn^{2+}-GH dimers may be the main storage form in the secretory granules [37].

The potential contribution of high-affinity Zn^{2+}-binding residues in GH to the pathogenetic mechanisms involved in dominantly transmitted isolated GH deficiency type II was further studied by Iliev et al. [38]. The production and extracellular secretion of *wt*-hGH transiently

transfected in GH_4C_1 cells (rat pituitary tumour cells) was compared to that of GH mutants in which the amino acids that bind Zn^{2+} with high affinity were mutated to alanine in various combinations (Zn^{2+}-binding GH mutants). Co-expression of any of these GH mutants (which display reduced Zn^{2+} binding to various extents) with *wt*-hGH had no significant effect on constitutive GH secretion (i.e. without stimulation) and intracellular production. Interestingly, each of the Zn^{2+}-binding GH mutants (single, double or triple mutants) singly expressed displayed about 50% lower extracellular secretion and intracellular production compared to the *wt*-hGH, suggesting a possible role of these residues in GH stability. In addition, in vitro data reported in this study do not suggest involvement of Zn^{2+}-binding residues in GH in the dominant negative mechanism of isolated GH deficiency type II.

The formation of GH aggregates can be studied in cells by using pulse-chase method in combination with detection of protein aggregates based on their insolubility in Lubrol (non-ionic detergent) [39]. Aggregation of rat GH and PRL endogenously produced in GH_4C_1 cells revealed that GH was found to be soluble in Lubrol immediately after synthesis, while 30 min later roughly 40–50% of newly synthesized hormone acquired the form of aggregate (Lubrol, insoluble form) with the same time course and to about the same maximum extent as PRL [39]. Moreover, after transient expression in AtT-20 cells, over 40% of newly synthesized hGH aggregated 30 min after synthesis (following in the same manner), with the same kinetics as that of the rGH in GH_4C_1 cells analysed in the same study.

GH and PRL are two hormones that are structurally related. Therefore, it is of no surprise that they display many similarities in the process of aggregation, as reported in the study mentioned above. However, alanine mutation introduced at His27 in hPRL (topologically corresponding to His18 in hGH) resulted in the H27A-PRL mutant reported not to bind Zn^{2+} [40]. Interestingly, even without the high-affinity Zn^{2+} binding site, H27A-PRL is still able to aggregate in the presence of Zn^{2+} with parameters similar to the aggregation of *wt*-PRL [36]. Hence, these data suggest that PRL and GH do not behave similarly in the presence of Zn^{2+}, and that PRL does not form dimers under the same conditions as GH, indicating that the dimer is unlikely to be the storage form of PRL in secretory granules. Zn^{2+} binding to human PRL and GH can occur through histidine residues (the high-affinity binding sites) [37, 40] or through glutamate, aspartate and glutamine residues (the low-affinity binding sites) [41]. Acidic pH in the *trans*-Golgi lumen where the process of aggregation occurs leads to protonation of His residues preventing their binding to Zn^{2+}. Therefore, it is more likely that Zn^{2+} binding to glutamate and aspartate residues (low-affinity binding) of PRL facilitates the formation of PRL oligomers as the storage form in dense cores of secretory granules.

Finally, as mentioned earlier, Zn^{2+} binding to GH through high-affinity binding sites is proven to be necessary for the formation of GH dimers, but whether this is the final storage form of GH in secretory granules still remains to be elucidated. Alternatively, additional intramolecular cross-linking might occur through low-affinity Zn^{2+} binding with amino acids other than histidine (as described above for PRL), thus enhancing GH aggregation and storage in secretory granules.

Zinc Transporters Mediate Zn^{2+} Dynamics in the Early Secretory Pathway and May Play an Important Role in the Formation of GH-Containing Secretory Granules

Out of all proteins synthesized in eukaryotic cells approximately one third are targeted to the secretory pathway [42] and the first compartment encountered along their road towards secretion is the ER. Together with the Golgi complex, ER comprises the early secretory pathway, which plays the key role in regulating the folding, assembly and transport of newly synthesized proteins, as well as modification and trafficking during the secretory process. There are estimates that between 3 and 10% of all proteins in mammalian genomes bind Zn^{2+} [43] and many zinc-dependent proteins pass through the secretory pathway on their way to other compartments within the cell (e.g. vacuole, lysosomes) or prior to their secretion. Due to its high charge density, Zn^{2+} requires transporters to pass across the cellular membranes and in and out of each of the organelles participating in the regulated secretory pathway (ER, Golgi complex and secretory granules). More than 20 zinc transporters identified and characterized up to date, classified into two families, ZnT and Zip transporters encoded by the solute carrier family 30 *(SLC30A)* and 39 *(SLC39A)* genes, reflect the complexity and importance of maintaining cellular Zn^{2+} homeostasis and dynamics. The role of ZnTs is to reduce intracellular Zn^{2+} by transporting it from the cytoplasm into various intracellular organelles and by moving Zn^{2+} into extracellular space. Zips increase intracellular Zn^{2+} by transporting it in the opposite direction. Thus, the coor-

dinated action of both is essential for the maintenance of Zn^{2+} homeostasis in the cytoplasm and accumulating evidence suggests that this is also true for the secretory pathway.

Even though nearly half of the characterized zinc transporters of both families are localized in the early and regulated secretory pathway, for the actual purpose we will focus only on ZnT5, ZnT6 and ZnT7 implicated in the entry of Zn^{2+} into the early secretory pathway. Thus, they might play a role in transporting Zn^{2+} required for GH storage in secretory granules.

The first predictions about their localization in the ER and Golgi complex, the subcellular compartments of the early secretory pathway, came from the analysis of sequence homology to other ZnT transporters and their homologues [44–46]. In addition, their ability to transport Zn^{2+} into the lumen of the secretory pathway assessed by zinc transport assay using radioactively labelled Zn^{2+} and by zinc-staining analysis using fluorescent zinc probes confirmed these predictions, but also suggested that their transport activities are not robust [45, 46]. Moreover, Suzuki et al. [47] reported that ZnT5–7 overexpression does not provide significant resistance to a high concentration of Zn^{2+}, while combined disruption of the genes for *ZnT5–7* in DT40 cells (chicken B lymphocyte-derived cell line) had no significant impact on the total cellular Zn^{2+} compared to that of wild-type cells. Thus, the main role of ZnT5–7 is more likely to load Zn^{2+} to zinc-requiring enzymes biosynthesized in the early secretory pathway. In addition, a combination of ZnT5–7 gene disruption/re-expression experiments performed in DT40 cells revealed involvement of the ZnT5–7 in Zn^{2+}-dependent activation of tissue-non-specific alkaline phosphatase (TNAP) [48, 49]. Several studies suggest that activation of TNAP in the early secretory pathway requires the formation of ZnT5/ZnT6 heterodimers or, in the case of the ZnT7, homo-oligomers as demonstrated by combinational re-expression experiments and co-immunoprecipitation studies [47, 48]. Ohana et al. [50] went a step further and measured directly Zn^{2+} transport mediated by ZnT5/ZnT6 heterodimer, showing that ZnT5 is an essential component for Zn^{2+} transport while ZnT6 is catalytically non-functional. In addition, the authors demonstrated for the first time that Zn^{2+} transport mediated by ZnT5 is catalysed by H^+/Zn^{2+} exchange and that the core of the Zn^{2+} transport site (composed of two His and two Asp residues) is essential for the transport.

Generation of *ZnT5*-null mice, as the result of crossing between heterozygous mice according to mendelian expectations, provided some in vivo data about the phenotype caused by the complete deletion of only 1 ZnT transporter, ZnT5 [51]. *ZnT5*-null mice displayed abnormal bone development, loss of weight and lethal, male-specific, cardiac arrhythmia. Interestingly, these mice presented with significantly impaired growth compared to the wild-type animals and with a high degree of osteopenia due to systemic decrease in bone density as a result of the reduced activity of osteoblasts [51].

Table 2. Relative expression data of zinc transporters in GFP-sorted somatotrope cells from GH-eGFP transgenic mouse

Zinc transporter	Relative expression	Gene bank	Significance (p value)
SLC30A1	1.72357	NM_009579	0.76
SLC30A3	2.13821	U76007	0.65
SLC30A4	7.08943	NM_011774	0.18
SLC30A5	28.88617	NM_022885	0.03
SLC30A6	4.13821	AF233346	0.34
SLC30A7	9.60162	AF233322	0.12
SLC30A9	9.59349	BB117951	0.12

Robinson IC (pers. commun.). $p < 0.05$ is considered significant.

Finally, Robinson and colleagues [52, 53] isolated GH-producing cells from GH-eGFP transgenic mice using the FACS technique [52, 54] and analysed specific gene expression patterns using a microarray technique. Relative expression data of all zinc transporters assessed (table 2) revealed the expression of ZnT5 to be the strongest in somatotrophs. Hence, these data suggest high involvement of ZnT5 in the processes of GH storage and secretion.

As far as Zip transporters and their role in the early secretory pathway is concerned, Zip7, Zip9 and Zip13 have been reported to localize in ER and Golgi complex and to regulate Zn^{2+} content in the lumen of these organelles, playing modulatory roles in the activity of zinc-requiring enzymes like TNAP [55–57]. Moreover, Hojyo et al. [58] generated the *SLC39A14*-KO mouse and reported that these mice, lacking Zip14, exhibit growth retardation, dwarfism and significant reduction in length of the long bones compared to control mice. However, the proposed underlying mechanism includes disrupted G-protein-coupled receptor signalling in the growth plate, pituitary gland and liver. In addition, the analysis of mRNA expression levels of SLC39A family members confirmed the presence of Zip1, 6, 7, 13 and 14 in the primary pituitary cells from normal mice [58]. Taking these factors together, this study provides a new insight into the role of Zn^{2+}, and particularly Zip14, in normal body growth.

Conclusions

The complexity and importance of cellular Zn^{2+} homeostasis and dynamics is reflected by the large number of ZnT and Zip transporters found in virtually every cell compartment. The localization and function of various zinc transporters known to mediate the fine-tuning of Zn^{2+} transport in and out of the ER, Golgi complex and secretory granules – the organelles participating in the regulated secretory pathway – has been well documented.

The process of GH aggregation (self-association), which is considered a prerequisite for the proper storage of GH in secretory granules, takes place in the *trans*-Golgi lumen under specific conditions (acidic pH, high amount of Zn^{2+}). Therefore, a proper function of zinc transporters involved in the early secretory pathway of GH and their role in supplying a sufficient amount of Zn^{2+} required for the biogenesis of GH-containing secretory granules might be of crucial importance for normal GH secretion. Impaired growth of the patient with TNZD presented in this report combined with in vivo data from mice lacking specific zinc transporters are in line with this hypothesis, suggesting at the same time that the role of Zn^{2+} and zinc transporters in the process of linear growth might be greater than previously anticipated.

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Disclosure Statement

The authors have nothing to disclose.

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