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Non-Alcoholic Fatty Liver Disease, Diabetes Mellitus, and Zinc/Zinc Transporters: Is there a Connection?

Kurt Grüngreiff

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Abstract

Immune response and metabolic regulation are closely connected with each other in such a way that dysfunction could lead to a variety of metabolic diseases such as obesity, diabetes mellitus (Dm), lipid metabolism disorders, and fatty liver disorders. Combined with uncritical "sugar-based" overeating and malnutrition, these multisystem metabolic diseases expand into a global epidemic. There are correlations between a fatty liver disease and diabetic metabolism state. A fatty liver leads to insulin resistance and thus to the development of a type 2 Dm; insulin resistance in turn augments the fatty liver. Zinc is a trace element of fundamental importance for a variety of biological processes. The liver is the main organ of the zinc metabolism. Metallothionein and zinc transporters are the key regulators of cellular zinc homeostasis. Molecular studies support the assumption of a correlation between zinc and Dm. Zinc is essential for the synthesis, secretion, and storage of insulin. ZnT8 is a significant autoantigen for type 1 Dm. Genetic polymorphisms in the ZnT8 gene are associated with an increased risk of developing type 2 Dm. Cellular zinc restriction induces the release of stress, particularly in the endoplasmic reticulum (ER). ER stress alone or coupled with cellular stress, as well as chronic inflammation, are central to the development of insulin resistance and type 2 Dm. The present insights into the context of a non-alcoholic fatty liver disease (NAFLD) and a type 2 Dm indicate that zinc and zinc transporters at the cellular level in various forms and in interactions with other mediators both in the regulation of physiological processes and in the formation of pathological processes, such as the cellular and ER stress, as well as chronic inflammation, and the development of metabolic disorders are involved.

Keywords: NAFLD, HCC, insulin resistance, diabetes mellitus, zinc, zinc transporter

1. Main text

Non-alcoholic fatty liver diseases (NAFLD) comprise a broad spectrum of liver diseases that go from non-alcoholic fatty liver (NAFL) to non-alcoholic fatty liver hepatitis (NASH), secondary fatty liver to fatty liver cirrhosis [1–4]. NAFLD represent 11–46% of all chronic liver diseases in the world [1]. NAFLD-induced liver changes look similar to those of alcoholic liver damage [4]. The accumulation of triglycerides and free fatty acids in the hepatocytes and an increased lipogenesis are typical features of an NAFLD. NAFLD is in part also causally associated with other diseases (e.g., metabolic multisystemic diseases such as obesity, type 2 diabetes mellitus (Dm), dyslipidemia, and hypertension [5, 6]. These diseases show a strongly increasing prevalence in particular in the Western and Asian industrialized states [4]. Due to the central role of the liver in the glucose metabolism, fatty acids and amino acids, there is a close interaction between the fatty liver and development of a diabetic metabolic state. On the one hand, the fatty liver will lead to insulin resistance and development of type 2 Dm; on the other hand, insulin resistance compounds the fatty liver [1, 7, 8]. Insulin resistance results in a reduction of glucose intake of the liver and other organs at concurrently increased hepatic glucose production. For this reason, modulation of the hepatic glucose metabolism is a target for antidiabetic treatment [9]. It is not clear yet whether the fatty liver is a cause or consequence of insulin resistance [8]. To differentiate NAFLD from alcoholic fatty liver disease or a mixed form, a daily alcohol limit of 10 g/day in women and 20 g/day in men is assumed. NASH, which can occur in up to 30% of the patients with NAFLD, is characterized by the presence of a mixed-cell infiltration in the hepatic lobules and a cell swelling of the hepatocytes (ballooning). NASH has a multifactorial genesis where genetic as well as environmental factors (e.g., excessive fat accumulation, mitochondrial dysfunction, influence of endotoxins and proinflammatory cytokines) contribute to chronic inflammation of the hepatocytes [1, 5, 6]. NASH as such is deemed a risk factor for the development of cirrhosis and hepatocellular carcinoma (HCC) [1, 4, 10]. Liver biopsy with subsequent histopathological evaluation is the diagnostic gold standard for differentiation between NASH and NAFLD [2, 6, 11]. At this time, NASH is the second most frequent underlying liver disease in the USA in patients to receive a liver transplant for HCC [12]. In a large, population-based study, Younoussi et al. [11] examined the prevalence and incidence of HCC in 2004–2009. Chronic hepatitis C-infection, at 54.9%, was the most frequent cause, and NAFLD was the third most frequent one at 14.1%. The authors explain the annual increase of the HCC incidence around the world with increased HCC screening, as well as with the increase of NAFLD [4, 11]. It is forecast that NAFLD will be the main cause of HCC development in approximately 20 years, after successful eradication of chronic hepatitis C infection, reduction of hepatitis B infection, and concurrent global increase of overnutrition [11, 13]. In particular, type 2 Dm is considered an independent risk factor of HCC [14]. Although liver cirrhosis is a precancerous condition and more than 90% of liver carcinomas develop based on cirrhosis, HCC can, similar to hepatitis B, develop without cirrhotic changes to the liver in NASH as well [15–17].

Zinc is an essential trace element that can be found in all tissues and that is of fundamental relevance for many biological processes, including the division, growth, and differentiation

of cells [18–20]. Regulation of zinc homeostasis involves many proteins such as metallothioneins, zinc transporters, and specific permeable channels [21, 22]. Metallothioneins are important for the resorption and storage of zinc.

There are two major protein families that mammalian zinc transporters belong to [23, 24]. The first group of transporters are ZIP (Zrt/-like proteins), which are responsible for transporting zinc into the cytosol from either extracellular space or from intracellular compartments. There are 14 ZIP transporters, designated as solute family SLC39A1-A14 [23, 24]. The second group of 10 transporters are ZnT (zinc transporters), which designated as SLC30A1-A10 [23, 24]. They generally transport zinc out the cytosol into extracellular space or intracellular organelles such as zincosomes. Zincosomes are vesicles that can sequester high levels of zinc [25].

The liver is essential for zinc homeostasis, with zinc deficits leading to the impairment of many hepatic functions. On the other hand, liver diseases are often associated with zinc deficits [26, 27]. The scope of zinc deficit is not determined as much by the genesis (alcohol, viruses, etc.), but rather by the severity of liver damage, fibrosis or cirrhosis, with or without metabolic and/or portal decompensation, or the presence of a HCC [28]. Although a connection between zinc and the development of Dm has been discussed for years, only molecular studies of the last few years have supported this hypothesis [29]. Zinc increases the insulin effect in peripheral tissues and is indispensable for synthesis, secretion, and storage of insulin in the pancreatic ß-cells. It stabilizes the insulin structure, protects against insulin degradation, and is secreted together with insulin, proinsulin, and C-peptide in the early phase of glucose-stimulated insulin secretion; it has an insulin mimetic effect [30]. Type 2 Dm is usually associated with decreased plasma or serum zinc concentrations, whereas type 1 Dm plasma or serum zinc mostly elevates [30]. This is interpreted that at the beginning of type 1 Dm, a destruction of ß-cells takes places, and with decreased zinc concentration later, when the hyperzincuria outweighs the zinc release from ß-cells [30]. **Table 1** shows the causes of zinc deficiency in liver cirrhosis and diabetes mellitus.

Liver cirrhosis [28]	Diabetes mellitus [30]
Inadequate intake	Inadequate intake
Changes in protein and amino	Polyuria, hyperzincuria
acid metabolism	Osmotic diuresis
Diminished hepatic extraction	Increased intestinal secretion
Portosystemic shunts	Decreased intestinal absorption
Alcohol-induced impaired absorption	
Cytokines, IL-1, IL-6	Inflammation, cytokines, IL-1, IL-6
Endotoxins	Acidosis
Catabolism	

Table 1. Causes of zinc deficiency in liver cirrhosis and diabetes mellitus.

Current studies on the function of zinc transporters show that genetic variations of ZIP or ZnT genes, as well as changes to the expression and activity of the zinc transporters, are involved in the pathogenesis of various diseases [31–33]. Pancreatic ß-cells express various zinc transporters (e.g., ZnT3, ZnT5, ZnT8), which are required to ensure zinc homeostasis [29, 34, 35]. Examinations by Yi et al. [32] show that reduced expression of ZnT8 impairs biosynthesis and release of insulin and ß-cell functions. For example, hypoglycemia releases glucagon from pancreatic a-cells as regulated by the activity of ZnT8 [36]. Impaired ß-cell function leads to an absolute or relative deficit of insulin, which subsequently causes type 1 or type 2 Dm. The functional relevance of the ZnT8-function for glucose regulation is supported by association of the auto-antibodies against ZnT8 (ZnT8A) with diabetes; these auto-antibodies have an increased prevalence (in type 1: 60%, type 2: 6–24%) as compared to healthy persons (8%; [33]). Genetic polymorphisms in the SLC30A81 ZnT8-gene are associated with an increased risk of developing Dm type 2 [29, 37–40]. Genetic variants of the ZnT8 protein (e.g., rs13266634) lead to different hepatic insulin "clearance" rates that regulate the peripheral insulin concentration [41]. Individuals with the above risk allele have an impaired insulin metabolization and storage. This is also associated with reduced effectiveness of zinc substitution [33]. Reduced function of ZnT8 and the resulting reduced zinc content in islet cells are a genetic predisposition of such persons for an impaired glucose regulation and type 2 Dm [40, 42]. Predictive examinations of these gene versions that are sensible for clinical relevance in the meaning of diagnostic risk stratification (e.g., at positive family history for Dm, metabolic syndrome, NAFLD) will require further studies [43]. Modulation of ZnT8 activities also provides a new potential therapeutic point of attack for Dm and NAFLD [38]. In addition to ZnT8, the "influx transporter" ZIP14 plays a functionally relevant role in hepatic zinc regulation [24, 44]. According to the examinations by Aydemir et al. [9], ZIP14-mediated zinc transport is involved in regulation of the insulin receptor activity and maintenance of the glucose homeostasis in the hepatocyte. They also observed that there was an increase of ZIP14 and an increase of controlled zinc transport during glucose absorption on the cell surface. In the course of this, zinc is relocated to various locations in the hepatocyte through sequential translocations, from the membrane surface to the earlier and late endosomes. The authors conclude from this that ZIP14 may have a relevance analogue to that of ZnT8 regarding the diagnosis and treatment of type 2 Dm and NAFLD. Current findings by Kim et al. [45] showed the relevance of zinc trafficking and the functional ZIP14 activity for adaptation to endoplasmic reticulum (ER) stress connected to metabolic diseases. According to Zhang [46], zinc restriction in the cells triggers ER stress, which highlights the relevance of zinc for maintaining a normal ER function. There are epidemiological, clinical, and experimental indications that cellular stress (impaired biological processes in the cell) and excessive inflammation are causatively connected to various metabolic conditions, for example, obesity, type 1 and 2 Dm and arteriosclerosis [47–49]. Öczan et al. [50] found that ER stress plays a central role in peripheral insulin resistance and type 2 Dm on a molecular, cellular, and organismal level. The conditions triggering ER include glucose and food withdrawal, viral infections, lipids, increased synthesis of secretory proteins as well as mutated or incorrectly designed proteins [50].

In an excellent review for expression of ZIP 9 transporters in ß-cells of the pancreas, Lawson et al. [51] showed how complex, overlapping, and interlocking zinc transporters work. They

identified ZIP6, ZIP7, ZIP9, ZIP13, and ZIP14 in humans and rodents and ZIP1 in rodents as potentially biologically relevant for the zinc effects in the ß-cells of the pancreas.

Inflammation is the first reaction of the immune system to infection or other damage to cells and tissues to protect the human or animal organism. Prolonged or chronic inflammations are harmful and release inflammatory substrates such as pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha), free radicals, hormones and other small molecules, leading to impairment and damage of the physiological cellular processes [47]. Zinc and zinc transporters are involved in the development of ER stress and impairment of the protein synthesis, the unfold protein response (UPR; 45). UPR could be triggered in yeasts and in some mammals by zinc restriction UPR [45, 52, 53]. In the liver, impaired apoptosis leads to dysregulation of the lipid metabolism, causing hepatic steatosis [54]. Kim et al. [45] were able to show that the ZIP14-mediated zinc transport is critical for the prevention of prolonged apoptotic cell death and steatosis during ER stress, that is, for hepatocellular adaptation to ER stress.

Hashimoto et al. [55] found in patients with chronic hepatitis C that zinc deficiency promotes the insulin resistance by exacerbating iron overload in the liver and induces hepatic steatosis by facilitating lipid peroxidation.

Both type 2 Dm and NAFLD are consequences of chronic inflammation and cellular and ER stress. Although the processes that occur during this have not been fully determined yet, it seems highly likely that zinc and zinc transporters play an essential role in the pathogenesis of such diseases.

Zinc supplementation has been investigated as a potential adjunct therapy in the management of Dm; however, the outcomes of such interventions are conflicting [56, 57]. Capdor et al. [57] found a modest reduction in glucose concentration and tendency for a decrease in HbA1c following zinc supplementation and suggested that zinc may contribute to the management of hyperglycemia in individuals with chronic metabolic disease. Ruz et al. [58] remarked that studies available to date on zinc supplementation in type 2 Dm suggest that zinc supplementation is only effective in patients with initially reduced zinc concentrations.

Pia et al. [59] studied the protective effects of zinc supplementation on diabetic liver injury in a rat model of type 2 Dm. They found that zinc supplementation improved liver conditions in type 2 Dm rat models through multiple pathways, in which GRP78 linked ER stress and LC3-II-linked autophagy are ameliorated to some degree. The results of a systematic review by Barbosa de Carvalho et al. [60] about the role of zinc in patients with type 2 Dm confirming the role of zinc in controlling circulating glucose concentration through maintenance of insulin homeostasis. Based on these positive findings, the authors concluded that adequate dietetic ingestion and/or zinc supplementation are essential in the control of type 2 Dm. Lastly, Islam et al. [61] reported in a double-blind randomized placebo controlled pilot study an improving of glucose handling in pre-diabetes by zinc supplementation.

According to the long-term experiences with zinc supplementation in patients with chronic liver diseases, in particular in case of decompensated liver cirrhosis, administration of zinc leads to an increase and often normalization of the zinc levels, with the duration depending

on the scope of zinc deficit in the serum [28]. Zinc supplementation improved in patients with liver cirrhosis and hepatic encephalopathy with and without Dm neurologic symptoms and signs of malnutrition [62–64]. Zinc administration increased glucose disposal entirely due to noninsulin-mediated glucose uptake without any systematic effect on insulin secretion and sensitivity [65]. Ruz et al. [58] recommended to further determine the role of zinc in type 2 Dm and therapeutic effectiveness of supplementation by long-term studies under observation of factors such as stage of disease, comorbidities, that is, also NAFLD, duration and type of medication (zinc preparation), and, finally, also examining the genetic variations in SLC30A8 as well due to the heterogeneity and complexity with multiple influences on the disease (**Figure 1**).
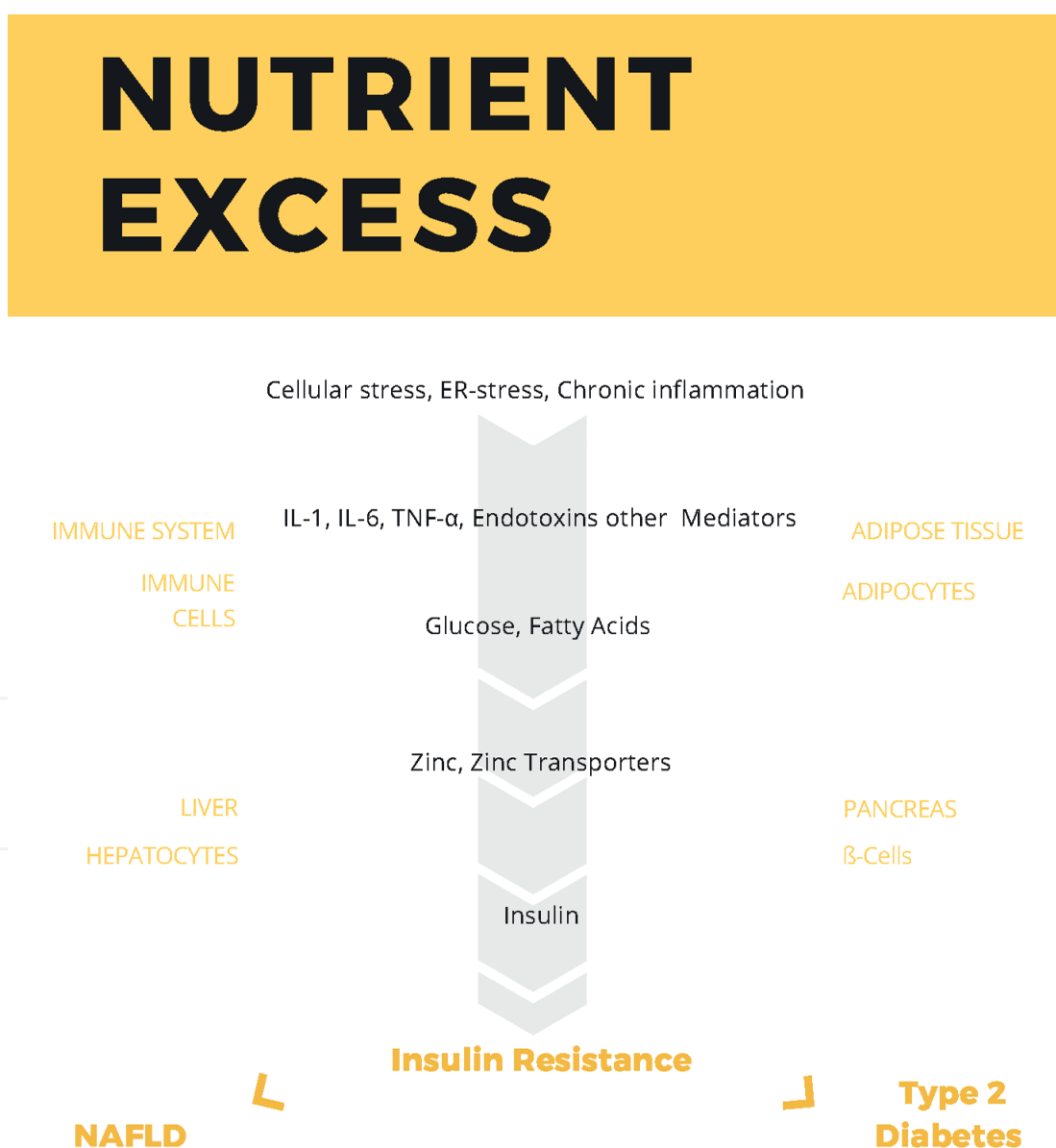
Figure 1. Schematic illustration of the organs, cells, substrates and main mediators involved in the development of insulin resistance linking NAFLD and type 2 Dm.

2. Concluding remarks

The data and findings that are available to date, and certainly not comprehensive, on the interrelation of fatty liver disease and type 2 diabetes mellitus show that zinc and zinc transporters on a cellular level are involved in the regulation of physiological processes as well as the development of pathological processes such as cellular stress, ER stress and not least chronic inflammation in diverse manners and interactions with other mediators, and therefore also in the development of such metabolic diseases.

Due to high complexity of the diseases, there are no simple solutions, that is, normalization of one "pathway" is not enough to recover functional homeostasis (controlling the diseases, health) of the integrated processes. Sole zinc substitution is surely ineffective in most cases, but may promise success in combination with other substrates.

Acknowledgements

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