Review Article

EMERGING ROLE OF ZINC TRANSPORTER-8 AUTOANTIBODIES (ZnT8A) IN TYPE 1 DIABETES MELLITUS- A REVIEW

ABSTRACT:

Zinc is an important micronutrient for the storage, structural stabilization, secretion and insulin action having highest concentration in pancreas. The transport of zinc occurs through the transporter ZnT8 to the insulin secretory vesicles. ZnT8 is recently recognized as a new autoantigen in Type 1 Diabetes Mellitus (T1DM). Studies revealed that 50-60% individuals with T1DM showed positive autoantibodies against ZnT8 (ZnT8A). Moreover, ZnT8 autoantibodies (ZnT8A) exhibit humoral auto reactivity which is not displayed by any of the other islet autoantigen like glutamine decarboxylase(GAD), insulin or tyrosine phosphate-related molecules(IA-2). ZnT8A has been already associated with Type 2 Diabetes Mellitus. Immunity against ZnT8 is dependent on clinical characteristics, which may provide evidence to recognize the importance of this transporter in the pathogenesis of T1DM.

Information regarding this article was retrieved through PubMed, Google Scholar and other search engines available in the University by using the keywords zinc, ZnT, ZnT8, SLC30A8 and Type 1 Diabetes Mellitus. Information was gathered through original researches, reviews and epidemiological studies published up to August 2019.The aim of this review is to summarize the emerging role of ZnT8A in diagnosis and genetic basis of Type 1 Diabetes Mellitus.

KEYWORDS: Type 1 Diabetes Mellitus, ZnT8, ZnT8A, Zinc transporter, SLC30A8.

INTRODUCTION:

The progress of Type 1 Diabetes Mellitus (TIDM) and the role of ZnT8A has been under consideration for the homeostasis of zinc for decades. Researchers observed that zinc supplementation has shown favorable effects in the prevention of T1DM [1]. It was actually not deliberated as the classical organ-specific disease as it is now recognized to be [2]. Type 1 Diabetes Mellitus (T1DM) is a multifactorial autoimmune disease that targets destruction of insulin secreting pancreatic β cells [3][4]. It is a chronic progressive disease mostly diagnosed in children and adolescents but can develop in adults at any age [5].

Genetic makeup and environmental causes are known to contribute in the different clinical characteristics and incidence rates of T1DM among populations supported by the fact that T1DM clusters in families. A number of environmental agents including dietary factors (consumption of cow's milk and formula milk,

exposure of gluten, vitamin D deficiency) and viral agents (causing lymphopenia) may play a potential role in the autoimmunity of β-cell [2] [6]. Coxsackievirus B, rubella, enterovirus, cytomegalovirus, rhinovirus, mumps and adenovirus have been implicated in inducing certain cases of the disease [7][8]. The specific etiology of T1DM remains unclear but is considered as cell-mediated disease that occurs from immune dysfunction with consequent loss of tolerance to β cell antigens and destructive lymphocytic infiltration of the islets. As a result of which insulin deficiency occurs leading to the impaired glucose homeostasis and ultimately hyperglycemia with symptoms [3].

The population of diabetics is anticipated to increase from 425 million to 629 million from 2017 to 2045 [9]. A Finnish study showed that 22% of the children diagnosed with T1DM have a positive family history [10]. A monozygotic twin of an individual with T1D is more prone to develop diabetes than a dizygotic twin; additionally, there is no difference in the appearance of autoimmunity against β cell between siblings and dizygotic twins [11]. The risk of T1DM development increases with multiple first-degree relatives [12].

The hallmark of T1DM is the antigen-specific T cells but identification of the occurrence of pathogenic T cells in vivo is challenging. Multiple autoantigens for islet are commonly employed as the standard diagnostic and predictive marker in T1DM development [1]. To clarify the etiology in idiopathic T1DM, a number of researches are being done on new pancreatic antigens, such as zinc transporter 8 (ZnT8), islet amyloid polypeptide, chromogranin A and pancreatic duodenal homeobox factor-1. These antigens may help in the development of new treatment options [13] [14]. The earlier established autoantibodies against insulin, glutamic acid decarboxylase (GAD) and tyrosine phosphatase-like islet antigen 2 (IA2) are standard for the diagnosis of T1DM, zinc transporter 8 autoantibody (ZnT8A) is lately identified as another major biomarker for T1D diagnosis through bioinformatics, expanding the panel of T1D diagnostic autoantibodies [15]. In this review paper, we aim to summarize the emerging role of ZnT8A in T1DM.

Review Method

This review work was done by extensive study of the literature on the emerging role of ZnT8A in T1DM. Information regarding this article was retrieved through PubMed, Google Scholar and other search engines available in the University by using the keywords zinc, ZnT, ZnT8, SLC30A8 and Type 1 Diabetes Mellitus. Information was gathered through original researches, reviews and epidemiological studies published up to August 2019.

RESULT AND DISCUSSION

Zinc is an essential micronutrient for all the biological processes. Its homeostasis is regulated by the transporters and zinc transporter-8 (ZnT8) plays a vital role in the secretion of insulin. ZnT8 is currently known as an autoantigen in T1DM development and ZnT8A has already been associated with Type 2 Diabetes Mellitus. Therefore, we recapitulated the role of zinc, its transporter and ZnT8A in the development of Type 1 Diabetes Mellitus.

Zinc transporters:

Zinc transporters in mammals come from two major families, ZIP (SLC39) family and ZnT (SLC30) family. The family members of ZIP promote the influx of zinc from the intracellular compartments and from the outside of the cells into the cytosol while the members of the family of ZnT allow the transport of zinc from the cytosol to the outside the cell or into the lumen of intracellular organelles [20]. To regulate the cellular zinc homeostasis, both ZnT and ZIP groups of transporters work in coordinated manner but in an opposite direction [21].

Zip:

There are 14 ZIP transporters encoded by the human genome and have now been identified at all phylogenetic levels. The transporters are designated as ZIP1 to ZIP14 and are encode by the genes SLC39A1 to SLC39A14 respectively [22]. ZIP transporters are expected to have 8 transmembrane domains (TMD) and comparable expected topologies. This topology has been established for yeast.

The presence of histidine-rich region in most of the members of this family is between the TMD III and IV as a long loop region that is proposed to be zinc-binding domain. Most members of the ZIP family share an analogous proposed topology with both C and N terminals extra-cytoplasmic [20]. The principal function of Zip transporter is that it helps in the influx of zinc from the lumen of intracellular compartments and from the extracellular space into the cytosol [23].

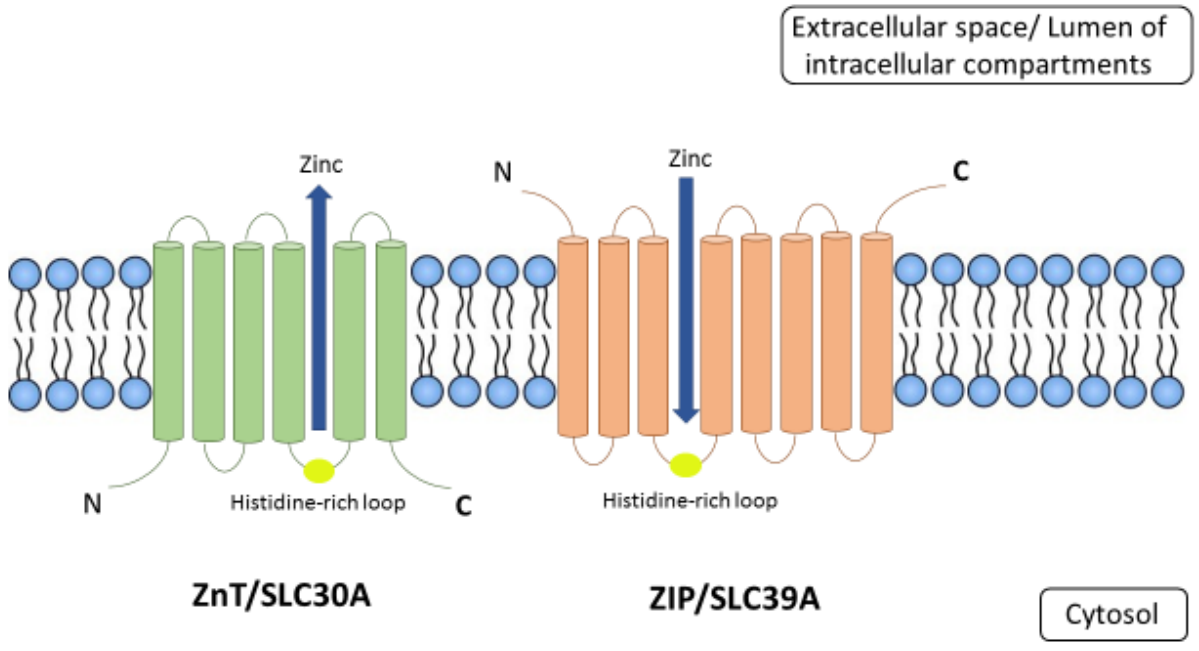
ZnT:

In mammals, the SLC30 family encodes for 10 members as Zinc transporters (ZnTs). The transporters are designated as ZnT1 to ZnT10 and are encoded by the genes SLC30A1 to SLC30A10 respectively. This family belongs to the zinc transporters that facilitate the transport of zinc from the cytosol to the outside of the cell or into the lumen of intracellular organelles. Most transporters of this family are expected to have six transmembrane domains (TMD), except for ZnT-5 which contains an additional TMD and are suggested to have cytoplasmic N and C termini. Like the ZIP family, it also contains a long histidine-rich loop between TMD IV AND V that acts as a zinc-binding domain [20] [24] [25].

There is a large C- terminal Domain (CTD) on ZnTs with a copper chaperone-like architecture, in spite of nonexistent sequence homology. The significance of this protein has been related to diabetes as the researchers have found an association of ZnT8 variants with the risk of diabetes. Particularly, the W325R variants affects the thermostability increasing diabetes risk. Likewise, ZnT8 is recently recognized as a

Figure 1: Homeostasis of zinc is maintained by two groups of transporters ZnT (SLC30A gene family) with six transmembrane domains and ZIP (SLC39A gene family) zinc transporters with eight transmembrane domains.

the recognition of antigen linked [26].



ZnT8 in Insulin Processing and Secretion:

Pancreas has the highest concentration of zinc ions and the concentration of free zinc ions is highest in the secretory vesicles. They are essential for the structural stabilization, secretion, storage and insulin action [1] [16]. Insulin hormone plays a vital role in the homeostasis of glucose as it is the only hormone that lowers the concentration of blood glucose. Because of this reason insulin deficiency causes severe metabolic disorders like T1DM and uncompensated Type 2 Diabetes Mellitus (T2DM). Electrical activity plays a critical role in the secretion of insulin. The β cells that secrete insulin are present in the pancreatic islet of Langerhans. Insulin secretion occurs as a result of elevated intracellular Ca^{2+} by the extracellular influx of Ca^{2+} via Ca-channels (voltage dependent) [17].

Insulin is a polypeptide that is secreted from the pancreatic beta cells [3]. The synthesis of preproinsulin is initiated in the cytosol. The newly synthesized preproinsulin is then guided to the ER for translocation by its signal peptide [18]. Pre proinsulin is converted to proinsulin by the cleavage of signal sequence.

The assembly of two zinc ions and calcium ions occurs in the proinsulin forming a hexameric proinsulin in the Golgi apparatus [1]. In B-chain (His B10) at 10^{th} amino acid, histidine coordinates with the two central zinc ions [3]. Prohormone convertase (PC1/3, PC2) and exoprotease carboxypeptidase E are the proteolytic enzymes that cause the excision of the C-peptide forming insulin hexamer [1].

Zinc is also required for its transport into the insulin secretory granules and cytoplasm by zinc transporters. In the pancreatic *β*-cells of rat model of insulinoma, zinc was recognized as a K_{ATP} channel activator. It activates hyperpolarization of membrane potential and decreases the voltage-dependent Ca^{2+} current. Once there is elevation of glucose in the cells, elevation of intracellular ATP occurs. ATP elevation inhibits the activity of K_{ATP} channel, activating the electrical activity by increase in intracellular Ca^{2+} leading to the release of insulin [17]. In the β-cells, there is co-secretion of zinc with it into the extracellular space of islet during the exocytosis of insulin. At high pH of blood, zinc is then released from the insulin and these ions provide negative feedback to the α-cells for glucagon release during glucose deprivation by closing the α-cell K_{ATP} channel [1]. During the exocytosis of insulin, frequent exposure of ZnT8 antigen occurs on glucose stimulated insulin secretion. Hence, it is supposed that ZnT8 exposure can exacerbate or trigger the production of autoantibodies against ZnT8 antigens in genetically susceptible individuals [19].

SLC30A8 Gene (ZnT8 Protein) Polymorphism:

After thousands of genetic studies for more than forty years, HLA region on the human genome remains the risk determinant for Type 1 Diabetes [27]. It shows association of disease susceptibility with multiple genetic loci encoding Major histocompatibility complex class II glycoproteins [21]. According to a recent genetic study, more than 60 risk loci showed association with the development of T1DM [28]. Some other genetic studies documented that 2 types of genes are involved in Type 1 DM: HLA genes and non-HLA genes. The HLA gene includes HLADR3, DQB1(also denoted as DR3-DQ2), DR4, DQB1(also denoted as DR4-DQ8) and the non-HLA genes include Insulin gene(INS), Protein tyrosine phosphatase, non-receptor type 22 (PTPN22), Cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and Solute carrier family 30 A8 (SLC30A8) [2].

Two unique SLC30 genes were identified, SLC30A8 and SLC30A10 that extend the SLC30 family to 10 members from genomic databank [29]. The SLC30A8 gene is located on 8^{th} Chromosome on q arm at position 24.11 and it encodes for ZnT8 auto-antigen that is made of 369 amino acids [30]. ZnT8 is a six transmembrane protein that facilitates the efflux of Zn^{+2} from the cell and stores it intracellularly [21].

Autoantibodies against ZnT8 are produced and detected before the disease onset. Single Nucleotide Polymorphism (SNP) rs13266634 C/T is known to be responsible for the altered immune response to ZnT8. In the presence of β cell dysfunction and impaired autoimmunity, this SNP displays a susceptible role in the development of T1DM [19]. SLC30A8 genotypes were strongly associated with ZnT8 autoantibodies in T1DM. In a cohort on the offspring of Diabetic parent, children who were ZnT8 positive in their follow-up had at least 1C allele out of which 82% were homozygous (CC genotype) [31].

An Asian study showed that stratification of T1DM risk can be done by SLC30A8 in ZnT8A-positive children [32]. Another one reported a significant association of R325W C allele with an increased risk in the development of GDM and the postpartum T1DM [33]. Therefore, it is proposed that individuals carrying C- allele are at increased risk for developing Type 1 Diabetes Mellitus.

Autoimmunity Against ZnT8:

The role of essential trace element zinc in autoimmunity for regulation of biological processes has been known for many years along with enzyme regulation at cellular level. Zinc homeostasis is critical for the influence of innate and adaptive immunity by modifying the host defense and immune response [34] [35]. Researchers observed that zinc has a protective function for β-cells of pancreas from cytokine-induced destruction in Type 1 Diabetes Mellitus and the deficiency induces lymphopenia, thymic atrophy, natural killer cell activity, suppression of cytolytic T-cells and delayed hypersensitivity reactions [1].

Literature suggested that the initiation of the autoreactive cascade is by the immunologic response to antigen. There is a binding of antigen to the antigen presenting cells (APCs) by a groove in major histocompatibility complex(MHC) class II molecules. In T1DM, APCs are then presented to antigen receptors on helper T cells or autoreactive CD4 inducers which in turn stimulates immune facilitated injury to the β cell of pancreas. Furthermore, B7 protein on APC binds to CD28 and Lymphocyte functional antigen-3 (LFA-3) enhancing the T-cell activation by costimulatory pathway. Some other molecules also contribute in the immune response such as interleukin-2 binding to its receptor (IL-2R). The balance of both the regulatory (Treg) and effector (Teff) T lymphocytes are crucial for conserving body cells [36] [2].

There is an association of ZnT8 with β-cell survival [37]. Zinc transporter 8 down regulation usually promotes cell survival of beta-cells [38]. Zinc content is increased in β-cells by the overexpression of ZnT8 that protects them from zinc depletion induced cell death [37]. However, some researchers suggested that the overexpression of ZnT8 makes the cells susceptible to IL-1 β induced apoptosis and ZnT8 expression is regulated by IL-1 β [39]. It is proposed that ZnT8 might play an active role in regulating the cell survivals by expressing at a subcellular level that is supported by the fact that at position 325(aa325) the amino acid substitution encodes for a polymorphism [1].

ZnT8 in Three Sub-Types of Type 1 Diabetes:

It is eminent that there are at least three subtypes of type 1 diabetes in Japan, acute-onset, slow onset, and fulminant type 1 diabetes [1]. Type 1 Diabetes Mellitus (T1DM) is usually developed in childhood but a greater proportion is diagnosed in their adulthood exhibiting different manifestations [40]. About 90% of the patients demonstrated acute-onset form in both childhood and adolescent-onset type 1 diabetes while the rest of the patients showed slow-onset form. In childhood, fulminant T1DM is scarce [1]. On the other hand, 2/3rd of the patients showed slow-onset form and nearly 20% presented with ketoacidosis or ketosis were classified as fulminant type 1 diabetes. It was suggested in a study that ZnT8 is identified as a major autoantigen in T1DM [41].

In Caucasian patients of T1 Diabetes Mellitus, it was previously reported that 60-80% of them were positive for the ZnT8 autoantibodies (ZnT8A). In Japanese population, it was also observed that 58% and 20% patients were positive for ZnT8A with acute-onset and slow-onset T1DM respectively.

ZnT8A was positive in 58% T1DM patients with acute-onset and in 20% with slow- onset T1DM [40]. In comparison, the sera obtained from fulminant T1DM were non-reactive to ZnT8 construct demonstrating that ZnT8 cannot be used as a diagnostic marker in fulminant type 1 diabetes [1]. ZnT8A can be used in the diagnosis of acute and slow onset diabetes but not in fulminant T1DM.

ZnT8 as a Diagnostic Tool:

Clinical disease (T1DM) is typically preceded by humoral auto-reactivity and takes months or years, and the progression to clinical manifestations is marked by intramolecular and intermolecular epitope spreading [6].

It has been suggested to utilize measurements of combination markers for the diagnosis of Type 1 (autoimmune) diabetes. Monitoring of GAD65, IA-A2, insulin autoantibodies in combination with ZnT8 autoantibodies in diabetic subjects allowed confirmation of autoimmunity in more than 96% of the cases [3]. ZnT8 share some common features with insulin, GAD, IA-2 which are as follows:

1. Constituents of the secretory pathway
2. Membrane proteins
3. Tissue specific gene expression
4. Evidence of alternative splicing

Almost 10% of the new T1DM patients are negative for any GADA, ICA, IA-A2 or IAA and addition of ZnT8 autoantibody variants can improve the diagnostic sensitivity in adults [4]. In another study, several patients with presumed diagnosis of T1D lack GAD65A and IA2A autoantibodies, establishing the autoimmune basis sometimes becomes difficult [6]. In a Turkish study, all the well-defined pancreatic antigens (ICA, GAD, Insulin and IA-2) are positive for 80% of new onset T1D patients and almost 13% of cases were ZnT8 positive all of which were negative for GADA, IA-2A and IA [36]. The three variants of the autoantibodies are ZnT8RA, ZnT8WA or ZnT8QA and a study result showed that the three ZnT8WQA improved the 2% of diagnostic sensitivity in patients of T1DM. by improving it from 93-95% [4]. Some studies stated that ZnT8 plays a decisive role in the diagnosis of T1DM and it is the only autoantibody present in some patients.

ZnT8 is prevalent in Type 1 Diabetics in different populations and is more frequently seen in children than in adults (Table 1). Therefore, there is a need to improve the diagnostic criteria and add ZnT8 as a standard autoantibody for the diagnosis of T1DM.

Table 1: Studies showing prevalence of 3 Autoantibodies (GADA, IA-2A and ZnT8A) and ZnT8A alone in the patients of Type 1 Diabetes Mellitus (T1DM).

Studies	Country	Patients showing positivity of 3 Autoantibodies			Only ZnT8A
		GADA	IA-2A	ZnT8A	
Yang et al. [42]	China 539	53.4%	25.8%	24.1%	5.4%
Gomes et al. [6]	Latin America 629	68.3%	64.8%	68.7%	24.1%
Niechcial et al. [43]	Poland Children=218 Adults=149	69.7% 75.4%	80.7% 44.0%	81.1% 34.8%	2.9% 5.0%

Boudiaf et al. [44]	Algeria 160	53.125%	32.5%	46.25%	8.75%
Rogowicz et al. [5]	Poland 35 years< =66 35 years> =53	35 years< 81.8% 35years> 77.3%	35 years< 51.5% 35 years> 34%	35 years< 45.4% 35 years> 34%	—
Garnier et al. [45]	France Children=119 Adults=109	68% 60%	41% 25%	61% 34%	7% 9%

Antibodies formed against ZnT8 (ZnT8A) are regarded as an independent autoimmunity demonstrator in T1DM diagnosis [36]. “Prediabetes” individuals who are ZnT8 autoantibody positive and positive for any one autoantibody of T1D are at increased risk for development of the T1D than those who are positive for any two autoantibodies excluding ZnT8. Therefore, monitoring all these systemic autoantibodies is the valid biomarker for identification of prodromal phase of T1DM as their appearance precedes years or even decades before onset [3].

NEW GENES IDENTIFICATION THROUGH DIFFERENT PATHWAYS:

There was a hypothesis that Toll-like receptors are involved in the initial phase of diabetes and found that TLR-induced IL-1β and IL-6 were frequently involved in children. The variations in innate immunity pathways are detectable in genetically susceptible individuals [Alkanani et al. 2016]. Previously, PPI (Protein Protein Interaction) was used for the network analysis for finding candidate genes in diseases [Gao et al. 2009]. Weighted Gene Co-Expression Analysis(WGCNA) is used in a study to find the association with the disease and was found that IL-1 was significantly increased in newly diagnosed T1DM patients. Some other genes that showed some relevance by this approach are IL-1β, FAS, CXCL8 etc [Medina et al. 2016].

Enriched pathways among different diseases were observed and links between T1D and IL-2- mediated signaling genes has been found. Prioritization of IL-2-mediated signaling genes showed 7 non-MHC candidate disease loci with strong evidences. Four of them are validated by other studies and 3 (*RAF1*, *MAPK14* and *FYN* are assumed to be novel loci in T1D for future studies [Carbonetto et al. 2013]. Understanding of Type 1 diabetes was done by another study based on conventional GWAS, gene expression, PPI and STRING data. They concluded that 8 (*IFNGR1*, *CD83, IL17RD*, *IL27RA*, *TRAF3IP2*, *PLCG2*, *CXCR7 and MYO1B*) regulated genes in the network sheltered SNPs associated with T1DM [Jensen et al. 2009]. New insight to the pathways and genes behind T1DM pathogenesis may offer the plan to develop innovative treatment strategies [51].

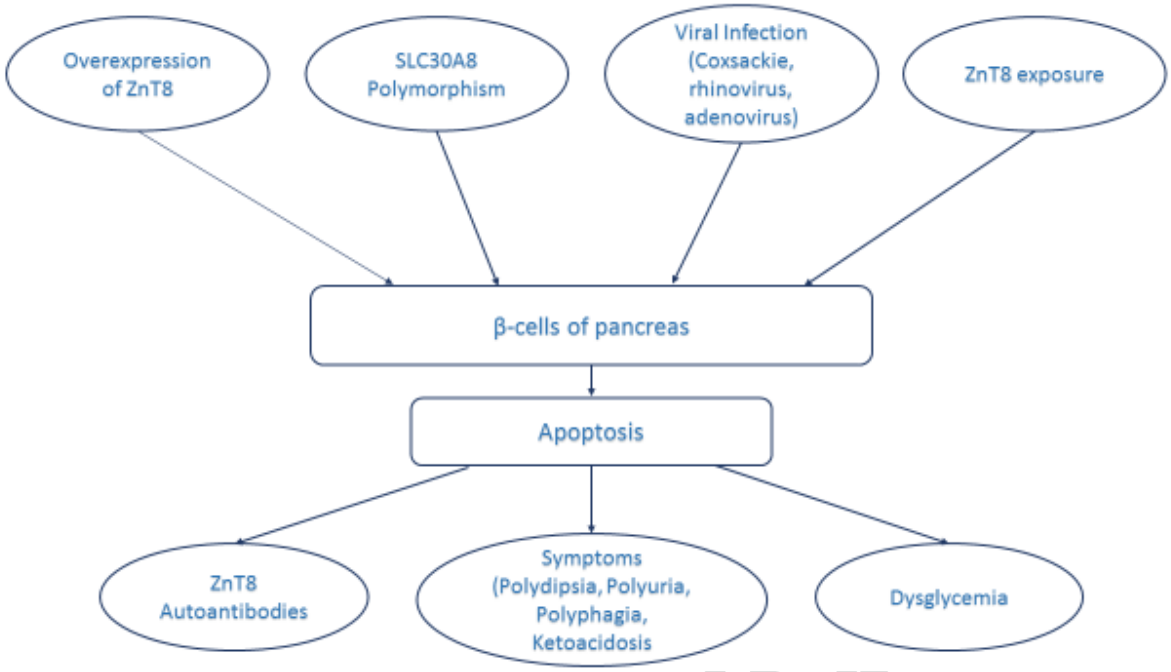


Figure 2: Proposed mechanism of development of Type 1 Diabetes Mellitus

CONCLUSION:

ZnT8 is recently identified as a major target of autoantibodies in Type 1 Diabetes Mellitus patients. ZnT8A is the only antibody in some of the individuals with negative autoantibody profile for T1DM and recurrent exposure of ZnT8 can trigger the formation of ZnT8A in genetically susceptible individuals supports that ZnT8 measurement should be more widespread for a better and earlier diagnosis. The individuals carrying C- allele are at increased risk for developing Type 1 Diabetes Mellitus. Further studies are required on antigenic determinants of ZnT8 to make the autoantibody measurement an expedient tool for early diagnosis of T1DM. Better understanding of the new pathways and genes involved in the pathogenesis of T1DM may help to advance inventive strategies.

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