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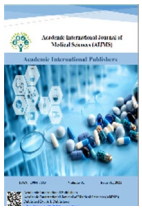

Document heading

A Possible Diagnostic Value of Zinc Transporter-8 Autoantibody for Pediatrics Type 1 Diabetic Ketoacidosis; A Systematic Review

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Abstract

Background: Type 1 diabetes mellitus (T1D) is a health concern all around the world. One of the most dramatic features of this disease is pediatric incidence. The most important metabolic clinical feature of T1D is ketosis and ketoacidosis. The exact role of autoantibodies in T1D pathogenesis is not completely clear yet. However, the diagnostic use for these autoantibodies is established. Zinc Transporter-8 Autoantibody (ZnT8A) is assumed to be the most specific antibody for islet beta cells. The current study aims to evaluate all relevant documents with possible risk and diagnostic value of ZnT8A for pediatrics T1D ketoacidosis (DKA) by a systematic review approach.

Materials and methods: Most popular electronic databases such as PubMed, Scopus, Science Direct, and Google Scholar were used for searches the following keywords pediatrics, children, diabetic ketoacidosis, type 1 diabetes mellitus, zinc transporter-8 autoantibodies without year or any other limitations. All relevant original studies that mention ZnT8A and Ketosis or DKA in the pediatric population were evaluated and in case of being matched with the criteria extracted.

Results: Primary search results led to 7233 queries. By considering the study inclusion criteria and bias assessment, six studies were included. Majority of included studies suggested ZnT8A as a risk factor for DKA in T1D pediatrics.

Conclusion: The current study tried to provide an overview on the conducted studies in possible risk and diagnostic value of ZnT8A for pediatrics DKA. The majority of included studies suggest the ZnT8A as a risk factor with diagnostic association to DKA, while there are some conflicting documents. We tried

to highlight the importance of this research theme for future studies to maintain a more precise conclusion with clinical relevance.

Introduction

Type 1 diabetes (T1D) is a health concern all around the world. T1D is an endocrine and autoimmune disorder. T1D incidence is primarily in childhood or adulthood, but it can be presented at any time in life. During the disease, part of the pancreatic exocrine cells known as beta cells will be disrupted. This will lead to a permanent replacement of the beta cell product, insulin. The reduced levels of insulin are represented by a high blood glucose level. This increased glucose in the blood is the main feature of the disease. The glucose is increased in blood because it cannot enter cells, which makes cells use other sources of energy, leading to ketogenesis and further development of diabetic ketoacidosis (DKA). One of the most dramatic features of this disease is the pediatric incidence of DKA. The most important metabolic clinical feature of T1D is ketosis and ketoacidosis. Other long-term macro and microvascular disorders are also critical and life-threatening [1, 2].

The genetic basis of T1D is complicated. There is a variety of genetic factors that are essential in T1D development. These genetic factors include HLA alleles and non-HLA genes that can be combined to assess T1D as a type 1 diabetes genetic risk score (T1DGRS) [3].

One of the pathogenesis and diagnostic features of T1D is autoantibodies. These autoantibodies indicate the autoimmune nature of this disease. The exact role of autoantibodies in T1D pathogenesis is not completely clear yet. However, the diagnostic use of these autoantibodies is established. There are five autoantibodies known to be associated with T1D. These include islet cell cytoplasmic autoantibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase autoantibodies (GADA), insulinoma-associated-2 autoantibodies (IA-2A), and zinc transporter-8 autoantibodies (ZnT8A) [4]. The use of these autoantibodies in combination will increase the sensitivity of disease diagnosis by more than 90%. Using GADA, IA-2A, and IAA represents 94% sensitivity, while adding ZnT8A will increase the sensitivity to 96% [5].

ZnT8 (Slc30A8) was introduced as a T1D marker and is found in 60-80% of these patients. Furthermore, ZnT8A can be detected in 26% of people with T1D without other autoantibodies [6]. Some polymorphisms in the SLC30A8 gene have also been associated with T1D [7]. ZnT8A is assumed to be the most specific antibody for islet beta cells [8]. Since DKA is a life-threatening consequence of T1D in pediatric patients, detection of DKA risk in this population will be lifesaving. There is evidence that ZnT8A has diagnostic value for DKA [9]. In this regard, the current study aims to evaluate all relevant documents with possible risk and diagnostic value of ZnT8A for pediatric T1D ketoacidosis (DKA) by a systematic review approach.

Materials and methods

Search strategy

For the current systematic review, we performed the search in databases including PubMed, Scopus, ScienceDirect, and CrossRef using keywords pediatrics, children, diabetic ketoacidosis, type 1 diabetes mellitus, zinc transporter-8 autoantibodies, ZnT8A, Diabetes Mellitus, and autoantibody without any

particular time range. CrossRef was used for the search in conference papers or any other gray literature. More information about the search strategy and exact queries for search is provided in Supplementary Data 1.

Inclusion criteria

The study was designed based on the PRISMA guidelines [10]. The inclusion criteria were original research publications in English that assessed DKA or ketosis and ZnT8A in the pediatric population. The exclusion criteria included a minimum score in eligibility, review articles, meta-analysis, and evaluations of DKA or ketosis and ZnT8A in adults.

Bias assessment

The risk of bias for the non-randomized controlled trials and observational studies was assessed by the Newcastle-Ottawa Scale (NOS) checklist [11].

Data extraction

The EndNote software (EndNote 20, Thomson Reuters) was used for listing and screening documents. All studies were screened and extracted by two independent authors, and a third expert author strategy was used for conflicts. All original research publications that assessed DKA or ketosis and ZnT8A in pediatric populations with T1D were considered for bias assessment and data extraction. Some features such as author name, year, country, study setting, total included population, laboratory method for ZnT8A assay, and DKA population were extracted.

Results

Search results and bias assessment

Primary search results led to 7233 queries. By considering the study inclusion criteria and bias assessment, six studies were included. More features about the study protocol, search strategy and screening process based on the PRISMA guideline are provided in ***Figure 1***. The risk of bias assessment checklists is provided in ***Supplement Data 2***.

ZnT8A in pediatrics with DKA

All of the six included studies were extracted, and the features of these studies are demonstrated in Table 1. The majority of included studies suggested ZnT8A as a risk factor for DKA in T1D pediatrics. These studies mentioned the importance of ZnT8A as a marker with diagnostic value [9], a marker for patients who are more likely to have ketoacidosis [12], and more acute diabetes onset [13]. Meanwhile, two studies could not find any particular relevance for DKA and ZnT8A positive serology in the T1D pediatric population [14, 15]. The sample size of all studies with positive ZnT8A and DKA is larger than studies with no associated results. All included studies were in cohort settings except one, which was case control [16].

Table 1. All of the six included studies were features for DKA or ketosis and ZnT8A in pediatric population

Author	Year	Country	population	Method for ZnT8A assay	DKA		Non-DKA population		Final conclusion	Ref
					Number	ZnT8A positive rate	Number	ZnT8A positive rate		
Zhang	2022	China	80	ELISA	60	51%	20	25%	diagnostic value for DKA	(Zhang et al., 2022)
Juusola	2016	Finland	723	Radio binding	-	23%	-	15%	more aggressive disease more likely to have ketoacidosis	(Juusola et al., 2016)
Salonen	2013	Finland	2115	Radio binding	-	16%	-	20%	older age ZnT8A prevalence decreased in DR3/DR4 heterozygotes	(Salonen et al., 2013)
Niechciał	2018	Poland	218**	ELISA	78%	78	61%	289	more acute diabetes onset	(Niechciał et al., 2018)
Elmaoğulları	2018	Turkey	84	ELISA	58% *				No association with presence or degree of ketoacidosis	(Elmaoğulları et al., 2018)
Rochmah	2020	Indonesia	30	ELISA	22	86%	8	87.50%	No association with presence or degree of ketoacidosis	(Rochmah et al., 2020)
* Total with and without DKA, ** 218 child and 149 adults										

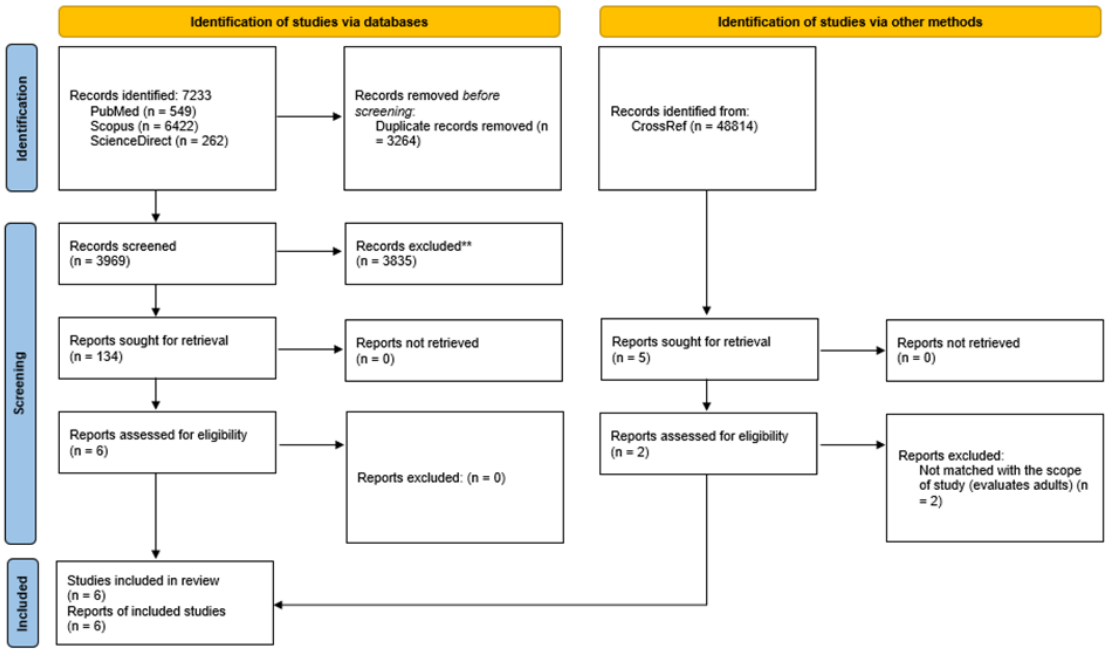

Figure 1. the study search strategy and results based on the PRISMA fellow diagram.

Discussion

The Zinc transporter 8 (ZnT8) is a pancreas-specific zinc transporter encoded by the SLC30A8 gene at chromosome 8q14.11. The product of SLC30A8 is established as a target for the immune system to generate autoantibodies in T1D. ZnT8 is a critical element for zinc accumulation and insulin secretion [2, 6, 19]. The ZnT8A is only present when the β-cells are entirely damaged. It seems to be the most specific autoantibody in T1D [19]. The ZnT8A appears to be a valuable marker for T1D diagnosis [11]. Furthermore, associations between diabetes mellitus type 2 and SLC30A8 highlight the role of ZnT8 as a regulatory factor for islet beta cells [18]. The ZnT8 is also considered a key element in T1D pathogenesis. It's established that T cell responses in T1D against ZnT8 and the association of the HLA DR3 allele and ZnT8A [3].

As mentioned previously, the majority of included studies suggested ZnT8A as a risk factor for DKA in T1D pediatrics. Meanwhile, two studies could not find any particular relevance for DKA and ZnT8A positive serology in the T1D pediatrics population [5, 16]. Elmaoğulları et al. [5] could not find any association with the presence or degree of ketoacidosis in 84 evaluated T1D patients. Also, the same result was obtained by Rochmah and colleagues [16] in the evaluation of 30 T1D pediatric patients. In contrast to these two [5, 16], four other studies [11, 15, 19, 30] represented a statistically significant association between ZnT8A positive status and elevated risk of DKA in the pediatric population. A study by Niechciał et al. [15] highlights the importance of ZnT8A positive status as an independent risk factor for ketosis. However, the number of positive tests for different antibodies was associated with the severity of DKA. Also, the study concluded that ZnT8A and IA-2A are more frequent in pediatrics, while GADA is more frequent in adult T1D cases.

Juusola et al. [11] report that ZnT8A positive children are majorly older, with a median range of 8.85 years. Also, ZnT8A positive children represent more risk for DKA and higher insulin doses. Juusola et al. also established the association of HLA DR3 and ZnT8A status. Pediatric patients with the HLA DR3 allele represent less frequency for ZnT8A.

The ZnT8A is estimated to be positive in 65% of T1D patients worldwide [24]. A higher titer of ZnT8A is associated with multiple autoantibody positive results and specifically with an IA-2A positive result in evaluated patients [7]. The importance of using such antibodies in the pediatric population could be screening potential for T1D that will lead to earlier diagnosis and fewer complications [26]. It has been suggested that antibody screening in high-risk pediatrics for T1D once in 10 years can effectively detect T1D and reduce future DKA development [8]. These kinds of screening can even be helpful for secondary prevention trials [4]. Antibodies profile in T1D had a prognostic feature in patients; for instance, IA-2A and ZnT8A are markers for the rapidly progressing prediabetic stage [17].

The ZnT8 C-terminal represents two epitope regions. The first epitope depends on the presence of Arginine (ZnT8R) or Tryptophan (ZnT8W) in amino acid residue 325. The ZnT8R is more frequent in Europeans and African-Americans, while the ZnT8W is more commonly reported in Asia [28, 27]. In the majority of cases, antibodies against both of these isotopes are detectable in patients at the time of diagnosis, and the titer decreases over the years [22]. The presence of ZnT8A seems to be associated with the ethnicity of the evaluated population [25]. As reported by Yang et al., ZnT8A and IA-2A are less prevalent in the Chinese population than in Caucasians [29].

It needs to be noted that ZnT8A might not be the only autoantibody assumed to be associated with DKA. There is a report of IA-2A association with a higher risk of DKA [21]. The ZnT8A is related to other immune system genes too. A positive result for ZnT8A could also be associated with rs1143627 and rs1143643 in the IL1B gene [14]. Furthermore, in this current study, we aim to evaluate all relevant documents with possible risk and diagnostic value of ZnT8A for pediatric T1D ketoacidosis (DKA) by a systematic review approach. It needs to be considered that there are some limitations in this study. The most critical limitation is the limited number of primary studies in this field. Our study highlights this lack of primary evidence for future original research studies to achieve a more precise conclusion. Another significant limitation is the absence of meta-analysis due to a limited number of primary studies. In this regard, we highly suggest this topic for future, more comprehensive and updated systematic reviews and meta-analyses to establish the clinical value of ZnT8A for DKA in the pediatric population.

Conclusion

The current study tried to provide an overview of the conducted studies on possible risk and diagnostic value of ZnT8A for pediatrics DKA. The majority of included studies suggests the ZnT8A as a risk factor with diagnostic association to DKA, while there are some conflicting documents. We tried to highlight the importance of this research theme for future studies to maintain a more precise conclusion with clinical relevance.

Conflict of interest

There is no conflict of interest in our current study.

Authors participation

IA concept, design, data extraction and manuscript preparation, AJ manuscript preparation, data extraction and screening.

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