Are Perinatal Events Risk Factors for Childhood Thyroid Autoimmunity?

Berglind Jonsdottir Markus Lundgren Sara Wallengren Åke Lernmark
Ida Jönsson Helena Elding Larsson for the DiPiS Study Group

Department of Clinical Sciences, Malmö, Lund University, Skåne University Hospital, Malmö, Sweden

Keywords

Childhood thyroid autoimmunity · Thyroid peroxidase autoantibodies · Thyroglobulin autoantibodies · *HLA-DQ* genotypes · Perinatal and hereditary risk factors

Abstract

Background: Environmental and genetic factors possibly trigger thyroid autoimmunity. Studies on perinatal risk factors for childhood thyroid autoimmunity are sparse. **Objectives:** The aim was to investigate if perinatal factors, family history of autoimmune diseases, and *HLA-DQ* genotypes contribute to thyroid autoimmunity in the Diabetes Prediction in Skåne (DiPiS) study. **Methods:** Samples from 1,874 ten-year-old children were analyzed for autoantibodies to thyroid peroxidase (TPOAb), thyroglobulin (TGAb), and *HLA-DQ* genotypes. Information on perinatal events and family history of autoimmunity was gathered prospectively in questionnaires. **Results:** Thyroid autoimmunity was found in 6.9% of the children (TPOAb 4.4%, TGAb 5.8%, both autoantibodies 3.3%) and was overrepresented in girls. Prematurity was positively related to TGAb (OR: 2.4, $p = 0.003$, $p_c = 0.021$). Autoimmune diseases in the family increased the risk of thyroid autoimmunity: TPOAb (OR: 2.2, $p = 0.012$), any autoantibody (OR: 1.7, $p = 0.04$), and both autoantibodies (OR: 2.2,

$p = 0.024$). A first-degree relative (FDR) with thyroid disease increased the risk for TPOAb (OR: 2.4, $p = 0.03$) and both autoantibodies (OR: 2.6, $p = 0.03$), a FDR or sibling with celiac disease increased the risk for both autoantibodies (OR: 3.7, $p = 0.03$, and OR: 4.8, $p = 0.003$), a FDR or sibling with diabetes increased the risk for thyroid autoantibody (OR: 3.0, $p = 0.01$, and OR: 5.4, $p = 0.032$), and a father with rheumatic disease increased the risk for TPOAb (OR: 15.2, $p = 0.017$), TGAb (OR: 11.3, $p = 0.029$), any autoantibody (OR: 9.6, $p = 0.038$), and both autoantibodies (OR: 20, $p = 0.01$). **Conclusions:** Thyroid autoimmunity was found in 6.9% of the 10-year-old children who were being followed for their risk of type 1 diabetes. No relation to perinatal factors was found, with the exception of a possible association between prematurity and TGAb. Family history of autoimmune diseases increased the risk of thyroid autoimmunity.

© 2017 European Thyroid Association
Published by S. Karger AG, Basel

Introduction

Thyroid autoimmunity is characterized by lymphocytic infiltration of the thyroid gland and is caused by loss of immune tolerance to thyroid antigens and production of autoantibodies to thyroid peroxidase (TPOAb), thyro-

Fig. 1. Flow chart of the DiPiS study from cord samples to analysis of thyroid autoimmunity at 10 years of age with information on type 1 diabetes diagnosis before 10 years of age.

globulin (TGAb), and the TSH receptor [1]. Thyroid autoimmunity may cause cellular damage and result in autoimmune thyroid disease (AITD), with two opposing clinical phenotypes: autoimmune hypothyroidism and Graves' hyperthyroidism. Autoimmune hypothyroidism, characterized by the presence of TPOAb, TGAb, or both, in combination with suppressed thyroid function, is by far more common than Graves' hyperthyroidism [2]. Childhood autoimmune hypothyroidism is more common in girls, with peak incidence in early or mid-puberty [3]. Early diagnosis and treatment of the disease are important, as thyroid function is essential for normal growth, puberty, metabolism, well-being, and cognitive development. As the symptoms of AITD can be nonspecific or lacking, or the child may have an enlarged thyroid gland with still normal function [4], children with other associated diseases such as celiac disease, Turner syndrome, and trisomy 21 as well as children with type 1 diabetes are recommended regular screening [5–9].

It is well known that AITD cumulates in families, confirming that genetic predisposition is important [10]. However, as in other autoimmune diseases, yet undefined nongenetic factors are of importance, as found in studies in populations with a similar genetic background but different socioeconomic circumstances [11] and discussed in Wiersinga [12]. Perinatal factors or events during infancy are of special interest, since this period is important for the development of immunological self-tolerance.

Prospective studies on perinatal events and development of thyroid autoimmunity are lacking. The aim of the current study was to investigate the importance of (1) perinatal events, such as maternal age, infections, smoking, alcohol consumption, and stressful events during pregnancy as well as the child's gestational age and size at birth, (2) autoimmune diseases within the family, and (3) *HLA-DQ* genotypes for thyroid autoimmunity at 10 years of age in children followed in the Diabetes Prediction in Skåne (DiPiS) study.

Fig. 2. Flow chart of the distribution of thyroid autoantibodies and questionnaire data in the study population.

Methods

Population

The children in this cohort participate in the DiPiS study, a prospective population-based study in the southern part of Sweden, with the aim to determine the predictive value of genetic risk combined with islet autoantibodies and identify possible environmental factors of importance for type 1 diabetes. Cord blood samples were obtained from 35,688 children from September 2000 to August 2004, and analyzed for type 1 diabetes risk HLA genotypes (Fig. 1). When the child was 2 months of age, the parents filled out questionnaires about events during pregnancy, delivery, and the first 2 months of life, such as stressful life events (online suppl. material, see www.karger.com/doi/10.1159/000479964), infections, as well as alcohol and smoking habits [13]. Data on diabetes in the family, the child's gestational age, birth weight, and length were recorded. From 2 years of age, children with an increased risk of developing type 1 diabetes, based primarily on HLA genotype, were offered annual follow-up. An additional questionnaire at that time added information on other autoimmune diseases in the family.

Study Group

As shown in Figure 1, 23,670 children replied to the questionnaires; of those, 3,868 accepted an invitation to continued participation at 2 years of age. In 2015, 2,073 blood samples were available from 10-year-old DiPiS children. Of those, 28 chose not to

participate in thyroid autoimmunity testing and 150 samples were not possible to analyze. The remaining 1,874 samples were analyzed for TPOAb and TGAb (Fig. 2). Prospectively collected questionnaire data were correlated to thyroid autoantibodies. Children developing type 1 diabetes before 10 years of age were excluded, since no data on thyroid autoimmunity was available in those (Fig. 1).

TPOAb and TGAb

TPOAb and TGAb were determined in plasma samples using radioimmunoassay kits (art. No. RS-TP/100 and RS-TG/100; RSR Limited, Cardiff, UK).

Levels of TPOAb and TGAb (in U/mL) were derived from the standard curve provided by the supplier. For TPOAb spline point to point curve and for TGAb cubic spline were used. The cutoffs for positive values were >0.30 U/mL for TPOAb and >1.0 U/mL for TGAb, defined using QQ plot analysis (GraphPad Prism 6.03).

HLA Genotyping

HLA-DQ genotyping was done on dried blood spots on filters as described [14]. HLA haplotypes were denoted as *HLA-DQA*03:01-B1*03:02* (DQ8) or *HLA-DQA*05:01-B1*02:01* (DQ2) and divided into 4 risk groups: DQ 8/8 or 8/X, DQ 2/2 or DQ2/X, DQ 2/8, or DQ X/X (X is neither DQ8 nor DQ2).

Statistical Analysis

Statistical analyses were performed using SPSS statistical software (version 22.0; SPSS, Chicago, IL, USA). Differences in proportions between groups were tested using the χ^2 test or the Fisher exact test when appropriate. OR with 95% CI were calculated. A *p* value <0.05 was considered significant. Values for perinatal factors were corrected for multiple comparisons by Bonferroni (*p*). Since the positive findings were sparse, no multivariate analysis was performed.

Results

TPOAb and TGAb in Relation to Gender

A total of 6.9% (130/1,874) of the 10-year-old children were positive for either TPOAb (83/1,874, 4.4%), TGAb (109/1,874, 5.8%), or both (61/1,874, 3.3%) (Fig. 2).

Among the 1,874 tested children, 49.7% (931/1,874) were girls. Girls were overrepresented among the TPOAb-positive children (62/83, 74.7%) (OR: 3.13, 95% CI: 1.90–5.18, *p* < 0.001), among the TGAb-positive children (78/109, 71.6%) (OR: 2.55, 95% CI: 1.70–3.83, *p* < 0.001), and amongst those positive for both TPOAb and TGAb (47/62, 75.8%) (OR: 3.30, 95% CI: 1.83–5.92, *p* < 0.001). The female to male ratios were 2.95:1 for TPOAb-positive children, 2.5:1 for TGAb-positive children, and 3.1:1 for those positive for both.

TPOAb and TGAb in Relation to Perinatal Events

When investigating perinatal factors, no correlation was found between maternal age, infections during preg-

Table 1. Association between thyroid autoantibodies and perinatal factors

Thyroid autoantibody	Perinatal factors					
	positive	negative	OR	95% CI	<i>p</i> value	<i>p_c</i>
Prematurity (<i>n</i> = 115)						
TPOAb+	9	68	1.9	0.9–4.0	ns	
TPOAb–	106	1,546				
TGAb+	14	88	2.4	1.3–4.4	0.003	0.021
TGAb–	101	1,526				
Any thyroid Ab+	14	107	2.0	1.1–3.5	0.024	0.17
Any thyroid Ab–	101	1,507				
Both thyroid Ab+	9	49	2.7	1.3–5.7	0.006	0.04
Both thyroid Ab–	106	1,565				
Smoking during pregnancy (<i>n</i> = 126)						
TPOAb+	7	72	1.3	0.6–2.9	ns	
TPOAb–	119	1,585				
TGAb+	10	92	1.4	0.7–2.9	ns	
TGAb–	116	1,565				
Any thyroid Ab+	14	109	1.8	1.0–3.2	0.053	
Any thyroid Ab–	112	1,548				
Both thyroid Ab+	3	55	0.7	0.2–2.3	ns	
Both thyroid Ab–	123	1,602				
Alcohol (<i>n</i> = 379)						
TPOAb+	16	64	0.9	0.5–1.6	ns	
TPOAb–	363	134				
TGAb+	22	81	1.0	0.6–1.6	ns	
TGAb–	357	1,323				
Any thyroid Ab+	28	96	1.1	0.7–1.7	ns	
Any thyroid Ab–	351	1,308				
Both thyroid Ab+	10	9	0.8	0.4–1.5	ns	
Both thyroid Ab–	369	1,355				
Maternal infection (<i>n</i> = 577)						
TPOAb+	27	52	1.1	0.7–1.7	ns	
TPOAb–	550	1,142				
TGAb+	34	67	1.1	0.7–1.6	ns	
TGAb–	543	1,127				
Any thyroid Ab+	42	80	1.1	0.7–1.6	ns	
Any thyroid Ab–	535	1,114				
Both thyroid Ab+	19	39	1.0	0.6–1.8	ns	
Both thyroid Ab–	558	1,155				
Ab, autoantibody; ns, not significant.						

nancy, smoking or use of alcohol during pregnancy, birth weight, or season of birth and development of thyroid autoimmunity at 10 years of age (Table 1). Neither did reported serious life events (*n* = 79 reported events) affect the risk of thyroid autoimmunity. However, being born before 37 weeks of gestation increased the risk for the child to develop TGAb (OR: 2.4, 95% CI: 1.3–4.4, *p* = 0.003, *p_c* = 0.021), any thyroid autoantibody (OR: 2.0, 95% CI: 1.1–3.5, *p* = 0.024, *p_c* = 0.17), or both thyroid au-

toantibodies (OR: 2.7, CI: 1.3–5.7, *p* = 0.006, *p_c* = 0.04), while the specific risk for TPOAb was not significantly affected (OR: 1.9, 95% CI: 0.9–4.0) (Table 1).

TPOAb and TGAb in Relation to Heredity

Data on autoimmune diseases in the family were available in 1,461 of 1,874 children. Thyroid disease was reported in 77 first-degree relatives (FDR) (68 mothers, 9 fathers, 0 siblings) and 210 grandparents. A correlation

between having a father with thyroid disease and TPOAb (OR: 6.5, 95% CI: 1.3–32, $p = 0.05$, Fisher exact test) as well as both thyroid autoantibodies (OR: 8.5, 95% CI: 1.7–42, $p = 0.03$, Fisher exact test) was found. A likewise association was found between thyroid disease in FDR and TPOAb (OR: 2.37, 95% CI: 1.0–5.4, $p = 0.03$) as well as both autoantibodies (OR: 2.6, 95% CI: 1.1–6.4, $p = 0.03$) (Table 2).

In 69 participants, at least 1 relative was reported to have celiac disease (11 mothers, 5 fathers, 22 siblings, 33 grandparents). A positive relation was found between having a sibling (OR: 4.8, 95% CI: 1.4–16.7, $p = 0.003$, Fisher exact test) or any FDR (OR: 3.7, 95% CI: 1.3–10.9, $p = 0.03$, Fisher exact test) with celiac disease and thyroid autoantibodies (Table 2).

A total of 94 children had 1 or more relatives with insulin-treated diabetes (12 mothers, 12 fathers, 11 siblings, 61 grandparents). Children having a sibling (OR: 5.4, 95% CI: 1.4–20.7, $p = 0.032$, Fisher exact test) or any FDR (OR: 3.0, 95% CI: 1.2–7.5, $p = 0.01$) with insulin-treated diabetes had an increased risk of developing any thyroid autoantibody (Table 2).

Rheumatic disease was reported in 30 FDR (25 mothers, 5 fathers, 0 siblings) and 201 grandparents. Two of the 5 children to fathers with rheumatic disease were positive for both autoantibodies, and an increased risk of developing TPOAb (OR: 15.2, 95% CI: 2.5–93, $p = 0.017$), TGAb (OR: 11.3, 95% CI: 1.9–69, $p = 0.029$), any thyroid autoantibody (OR: 9.6, 95% CI: 1.6–57.9, $p = 0.038$), and both autoantibodies (OR: 20, 95% CI: 3.3–122.4, $p = 0.01$) was found if the father reported rheumatic disease (Fisher exact test) (Table 2).

A total of 177 children reported one or more FDR with any autoimmune disease (thyroid disease, insulin-treated diabetes, celiac disease, Addison disease, B₁₂ deficiency, or rheumatic disease). Having a FDR with an autoimmune disease increased the risk for TPOAb (OR: 2.2, 95% CI: 1.2–4.0, $p = 0.012$), any autoantibody (OR: 1.7, 95% CI: 1.0–3.0, $p = 0.04$), and both autoantibodies (OR: 2.2, 95% CI: 1.1–4.3, $p = 0.024$) (Table 2). Since only few reported B₁₂ deficiency, myasthenia gravis, and Addison disease, analyses were therefore not performed for these diseases separately.

TPOAb and TGAb in Relation to HLA-DQ Genotypes

None of the DQ2/8, DQ2/2, DQ2/X, DQ8/8, DQ8/X, or DQ X/X genotypes were associated with TPOAb, TGAb, alone, or in combination (data not shown).

Discussion

In this study, we analyzed the effect of perinatal factors on the risk of thyroid autoimmunity in a large, prospectively followed cohort of 1,874 children participating in the DiPiS study, finding no consistent association between any of the studied factors and thyroid autoimmunity at 10 years of age. Of the factors investigated, only prematurity was found to be associated with TGAb, any thyroid autoantibody, or both of the thyroid autoantibodies, but not specifically with TPOAb.

Additionally, we investigated if autoimmune diseases within the family affected the risk of thyroid autoimmunity, finding an increased risk in children with a FDR or a father with thyroid disease, a FDR or sibling with celiac disease or diabetes, a father with rheumatic disease, or a FDR with any autoimmune disease.

To our knowledge, prematurity has not been found to be a risk factor for TGAb in earlier studies, although a large nationwide study in Sweden found that prematurity increased the risk for levothyroxine or liothyronine prescription in young adulthood [15]. However, TGAb have not been found to be pathogenic [16] or predictive for later thyroid disease [8, 17] in previous studies. Therefore, the interpretation of our positive association between prematurity and TGAb is uncertain.

We did not find any association between birth size, season of birth, or infections during pregnancy and thyroid autoimmunity. Previous studies on the influence of birth size on thyroid autoimmunity and disease in adults are conflicting [15, 18–20], as is the effect of season of birth [21, 22]. One study on maternal gestational infections found that mothers to children with AITD were more likely to be enterovirus IgM-positive at partum [23].

To our knowledge, there are no previous data on maternal smoking or alcohol habits during pregnancy and the offspring's risk of thyroid autoimmunity, while various studies have found smoking to increase risk for Graves' disease and decrease the risk of hypothyroidism [24, 25]. In our study, no effect of alcohol or smoking during pregnancy on the risk for the child to develop thyroid autoimmunity could be found.

Stress has been reported to provoke Graves' disease [26], while no relation has been found for hypothyroidism. Studies of stress during pregnancy in relation to thyroid autoimmunity in the child are lacking. In the current study, which gathered information on stress prospectively, no relation was found.

The children participating in the DiPiS study were invited based on medium- to high-risk HLA-DQ genotypes

Table 2. Association between thyroid autoantibodies and family history of autoimmune diseases ($n = 1,461$)

Thyroid autoantibody	Thyroid disease					Celiac disease				
	positive	negative	OR	CI	<i>p</i> value	positive	negative	OR	CI	<i>p</i> value
Mother						Mother				
TPOAb+	5	58	1.8	0.7–4.7	ns	0	63	N/A		
TPOAb–	63	1,335				11	1,387			
TGAb+	6	77	1.65	0.7–3.9	ns	0	83	N/A		
TGAb–	62	1,316				11	1,367			
Any thyroid Ab+	7	90	1.67	0.7–3.7	ns					
Any thyroid Ab–	61	1,303								
Both thyroid Ab+	4	45	1.87	0.6–5.4	ns					
Both thyroid Ab–	64	1,348								
Father						Father				
TPOAb+	2	61	6.5	1.3–32	0.05	1	62	5.6	0.6–51	
TPOAb–	7	1,391				4	1,394			
TGAb+	2	81	4.8	1.0–23.7	0.09	0	83	N/A		
TGAb–	7	1,371				5	1,373			
Any thyroid Ab+	2	95	4.1	0.8–19.9	ns					
Any thyroid Ab–	7	1,357								
Both thyroid Ab+	2	47	8.5	1.7–42	0.03					
Both thyroid Ab–	7	1,405								
FDR						Sibling				
TPOAb+	7	56	2.37	1.0–5.4	0.03	3	60	3.6	1.0–12.6	0.07
TPOAb–	70	1,328				19	1,379			
TGAb+	8	75	2.02	0.9–4.4	ns	3	80	2.7	0.8–9.3	ns
TGAb–	69	1,309				19	1,359			
Any thyroid Ab+	9	88	1.9	0.9–4.0	ns	3	94	2.3	0.7–7.8	ns
Any thyroid Ab–	68	1,296				19	1,345			
Both thyroid Ab+	6	43	2.6	1.1–6.4	0.03	3	46	4.8	1.4–16.7	0.034
Both thyroid Ab–	71	1,341				19	1,393			
Grandparents						FDR				
TPOAb+	8	202	0.8	0.4–1.8	ns	4	59	1.0	1.0–8.2	0.07
TPOAb–	55	1,196				33	1,398			
TGAb+	8	202	0.6	0.2–1.3	ns	3	80	1.5	0.4–4.9	ns
TGAb–	75	1,176				34	1,344			
Any thyroid Ab+	10	200	0.7	0.3–1.3	ns	4	93	1.7	0.6–5.0	ns
Any thyroid Ab–	87	1,164				33	1,331			
Both thyroid Ab+	6	204	0.8	0.35–2.0	ns	4	45	3.7	1.3–10.9	0.033
Both thyroid Ab–	43	1,208				33	1,379			

for type 1 diabetes [14], although some children with neutral-risk alleles were included in the study. Studies on HLA alleles in AITD have been less conclusive than in type 1 diabetes, particularly regarding hypothyroidism. Although it is well known that AITD and type 1 diabetes cumulate in families, the *HLA-DQ* alleles do not appear to be the same in the two diseases. The fact that we could not confirm the previously reported association between *HLA-DQ2* and thyroid autoimmunity [27, 28] may in part be due to the population that was selected for type 1

diabetes risk, which is a limitation of the study. In a type 1 diabetes population, we and others previously found that the genotype *HLA-DQ 5.1* was protective for both thyroid autoimmunity [29, 30] and later thyroxine treatment [8]. Since *HLA-DQ* genotypes were not full-typed in the DiPiS study, we could not confirm this finding [31].

AITD are often found in families with autoimmune diseases. In this study, we confirmed that having a sibling or FDR with diabetes or a father or FDR with thyroid disease increases the risk for thyroid autoimmunity. Since the cas-

Table 2 (continued)

	Rheumatic disease					Insulin-treated diabetes				
	positive	negative	OR	CI	<i>p</i> value	positive	negative	OR	CI	<i>p</i> value
Mother						Mother				
TPOAb+	2	61	1.9	0.5–8.5	ns	1	62	2	0.3–16	ns
TPOAb–	23	1,375				11	1,387			
TGAb+	2	81	1.5	0.3–6.3	ns	1	82	1.5	0.2–11.9	ns
TGAb–	23	1,355				11	1,367			
Any thyroid Ab+	2	95	1.2	0.3–5.3	ns	2	95	2.9	0.9–13.2	ns
Any thyroid Ab–	23	1,341				10	1,354			
Both thyroid Ab+	2	47	2.5	0.6–11.2	ns	0	49	N/A		
Both thyroid Ab–	23	1,389				12	1,400			
Father						Father				
TPOAb+	2	61	15.2	2.5–93	0.017	1	62	2	0.3–16	ns
TPOAb–	3	1,395				11	1,387			
TGAb+	2	81	11.3	1.9–69	0.029	1	82	1.5	0.2–11.9	ns
TGAb–	3	1,375				11	1,382			
Any thyroid Ab+	2	95	9.6	1.6–57.9	0.038	1	96	1.3	0.2–10	ns
Any thyroid Ab–	3	1,361				11	1,352			
Both thyroid Ab+	2	47	20	3.3–122.4	0.010	1	48	2.7	0.3–21	ns
Both thyroid Ab–	3	1,409				11	1,401			
FDR						Sibling				
TPOAb+	3	60	2.6	0.8–9.0	ns	2	61	5.1	1.0–24	0.078
TPOAb–	26	1,372				9	1,389			
TGAb+	3	80	1.95	0.6–6.6	ns	2	81	3.8	0.8–17	ns
TGAb–	26	1,352				9	1,369			
Any thyroid Ab+	3	94	1.6	0.5–5.5	ns	3	94	5.4	1.4–20.7	0.032
Any thyroid Ab–	26	1,338				8	1,356			
Both thyroid Ab+	3	46	3.5	1.0–11.9	0.07	1	48	2.9	0.4–23.3	ns
Both thyroid Ab–	26	1,386				10	1,402			
Grandparents						FDR				
TPOAb+	11	52	1.3	0.7–2.6	ns	3	60	2.1	0.6–7.1	ns
TPOAb–	190	1,208				32	1,366			
TGAb+	16	67	1.5	0.9–2.7	ns	4	79	2.2	0.8–1461	ns
TGAb–	185	1,193				31	1,347			
Any thyroid Ab+	17	80	1.4	0.8–2.4	ns	6	91	3.0	1.2–7.5	0.01
Any thyroid Ab–	184	1,180				29	1,335			
Both thyroid Ab+	10	39	1.6	0.8–3.3	ns	2	47	1.8	0.1–7.6	ns
Both thyroid Ab–	191	1,221				33	1,379			
Any autoimmune disease ¹										
	positive	negative	OR	CI	<i>p</i> value	positive	negative	OR	CI	<i>p</i> value
FDR						Grandparents				
TPOAb+	14	49	2.2	1.2–4.0	0.012	1	62			
TPOAb–	163	1,235				60	1,338			
TGAb+	15	68	1.7	0.9–3.0	ns	3	80	0.8	0.2–2.8	ns
TGAb–	162	1,216				58	1,320			
Any thyroid Ab+	18	79	1.7	1.0–3.0	0.04	4	93	1.0	0.4–2.8	ns
Any thyroid Ab–	159	1,205				57	1,307			
Both thyroid Ab+	11	38	2.2	1.1–4.3	0.024	0	49			
Both thyroid Ab–	166	1,246				61	1,351			

Ab, autoantibody; ns, not significant; N/A, not applicable. ¹ Thyroid disease, insulin-treated diabetes, celiac disease, rheumatic disease, Addison disease, B₁₂ deficiency.

es were few, statistical analyses were difficult. Moreover, hereditary information was not updated after the child turned 2 years old, which may result in underestimation of FDR with autoimmune diseases. Although the numbers are low, it is interesting that fathers with thyroid or rheumatic disease are more likely than mothers to have children with thyroid autoimmunity, as it is well known that fathers with type 1 diabetes are more likely to transfer diabetes to their offspring than mothers [32]. Worth mentioning is a positive relation between TPOAb and celiac disease in a sibling, since thyroid autoimmunity is more common in children with celiac disease compared to healthy children [33] and FDR of patients with celiac disease have more other autoimmune diseases, like AITD [34].

A major limitation of our study is that children diagnosed with type 1 diabetes within the DiPiS study before the age of 10 years are not included, due to lack of information on their thyroid autoimmunity status. Thereby various cases and lack of information on hereditary autoimmunity are probably missing.

The strength of this study is the large cohort of children followed prospectively from birth with information on genetic and prenatal factors and hereditary disease. Since the children are followed prospectively until 15 years of age, we will be able to do further testing at a higher age, probably with increasing frequency of thyroid autoimmunity.

In summary, thyroid autoimmunity in 10-year-old children was generally not related to perinatal factors, other than a possible association between prematurity and TGAb. The children positive for thyroid autoimmunity were more likely to have FDR with autoimmune disease, fathers with thyroid or rheumatic disease, or siblings with celiac disease.

Acknowledgements

We thank all the children participating in the DiPiS study and their families.

Statement of Ethics

The study was approved by the regional ethics review board in Lund.

Disclosure Statement

The authors have nothing to disclose.

Funding Sources

Our research is supported in part by the Swedish Research Council (grant No. 14064 to Åke Lernmark), Swedish Childhood Diabetes Foundation, Swedish Diabetes Association, Nordisk Insulin Fund, SUS funds, Lion Club International, district 101-S, The Royal Physiographic Society, the Kristianstad Central Hospital Research and Development fund, the Swedish Diabetes Foundation, and the Skåne County Council Foundation for Research and Development.

Author Contributions

B.J. designed the study, collected, analyzed, and interpreted data and wrote and revised the manuscript. I.J. and S.W. analyzed data and revised the manuscript. M.L. collected data and revised the manuscript. Å.L. designed the study and revised the manuscript. H.E.L. designed the study, interpreted data, and revised the manuscript.

Appendix

Members of the DiPiS Study Group

C. Andersson, R. Bennet, I. Jönsson, M. Ask, J. Bremer, C. Brundin, C. Cilio, C. Hansson, G. Hansson, S. Ivarsson, B. Jonsdotir, Å Lernmark, B. Lindberg, B. Lernmark, M. Lundgren, J. Melin, A. Ramelius, I. Wigheden, U.-M. Carlsson, A. Svård (Department of Clinical Sciences, Malmö, Lund University, Lund, Sweden); A. Carlsson (Department of Clinical Sciences, Lund University, Lund, Sweden); E. Cedervall (Department of Paediatrics, Ängelholm Hospital, Ängelholm, Sweden); B. Jönsson (Department of Paediatrics, Ystad Hospital, Ystad, Sweden); K. Larsson (Department of Paediatrics, Kristianstad Central Hospital, Kristianstad, Sweden); and J. Neiderud (Department of Paediatrics, Helsingborg Hospital, Helsingborg, Sweden).

References

- 1 Sinclair D: Analytical aspects of thyroid antibodies estimation. *Autoimmunity* 2008;41: 46–54.
- 2 Abraham-Nordling M, Bystrom K, Topping O, Lantz M, Berg G, Calissendorff J, Nystrom HF, Jansson S, Jorreskog G, Karlsson FA, Nystrom E, Ohrling H, Orn T, Hallengren B, Wallin G: Incidence of hyperthyroidism in Sweden. *Eur J Endocrinol* 2011;165:899–905.
- 3 Hunter I, Greene SA, MacDonald TM, Morris AD: Prevalence and aetiology of hypothyroidism in the young. *Arch Dis Child* 2000;83: 207–210.
- 4 Wasniewska M, Corrias A, Salerno M, Mussa A, Capalbo D, Messina MF, Aversa T, Bombaci S, De Luca F, Valenzise M: Thyroid function patterns at Hashimoto's thyroiditis presentation in childhood and adolescence are mainly conditioned by patients' age. *Horm Res Paediatr* 2012;78:232–236.

- 5 Oderda G, Rapa A, Zavallone A, Strigini L, Bona G: Thyroid autoimmunity in childhood celiac disease. *J Pediatr Gastroenterol Nutr* 2002;35:704–705.
- 6 Germain EL, Plotnick LP: Age-related anti-thyroid antibodies and thyroid abnormalities in Turner syndrome. *Acta Paediatr Scand* 1986;75:750–755.
- 7 Regueras L, Prieto P, Munoz-Calvo MT, Pozo J, Arguinzoniz L, Argente J: Endocrinological abnormalities in 1, 105 children and adolescents with Down syndrome (in Spanish). *Medicina Clin (Barc)* 2011;136:376–381.
- 8 Jonsdottir B, Larsson C, Carlsson A, Forsander G, Ivarsson SA, Lernmark A, Ludvigsson J, Marcus C, Samuelsson U, Ortvist E, Elding Larsson H; Better Diabetes Diagnosis Study Group: Thyroid and islet autoantibodies predict autoimmune thyroid disease already at type 1 diabetes diagnosis. *J Clin Endocrinol Metab* 2017;102:1277–1285.
- 9 Aversa T, Lombardo F, Valenzise M, Messina MF, Sferlazzas C, Salzano G, De Luca F, Wasniewska M: Peculiarities of autoimmune thyroid diseases in children with Turner or Down syndrome: an overview. *Ital J Pediatr* 2015;41:39.
- 10 Hansen PS, Brix TH, Iachine I, Kyvik KO, Hegedus L: The relative importance of genetic and environmental effects for the early stages of thyroid autoimmunity: a study of healthy Danish twins. *Eur J Endocrinol* 2006;154:29–38.
- 11 Kondrashova A, Viskari H, Haapala AM, Seiskari T, Kulmala P, Ilonen J, Knip M, Hyoty H: Serological evidence of thyroid autoimmunity among schoolchildren in two different socioeconomic environments. *J Clin Endocrinol Metab* 2008;93:729–734.
- 12 Wiersinga WM: Clinical relevance of environmental factors in the pathogenesis of autoimmune thyroid disease. *Endocrinol Metab (Seoul)* 2016;31:213–222.
- 13 Lernmark B, Elding-Larsson H, Hansson G, Lindberg B, Lynch K, Sjoblad S: Parent responses to participation in genetic screening for diabetes risk. *Pediatr Diabetes* 2004;5:174–181.
- 14 Larsson HE, Lynch K, Lernmark B, Nilsson A, Hansson G, Almgren P, Lernmark A, Ivarsson SA: Diabetes-associated HLA genotypes affect birthweight in the general population. *Diabetologia* 2005;48:1484–1491.
- 15 Crump C, Winkleby MA, Sundquist J, Sundquist K: Preterm birth and risk of medically treated hypothyroidism in young adulthood. *Clin Endocrinol (Oxf)* 2011;75:255–260.
- 16 McLachlan SM, Rapoport B: Why measure thyroglobulin autoantibodies rather than thyroid peroxidase autoantibodies? *Thyroid* 2004;14:510–520.
- 17 Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P, Braverman LE: Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *J Clin Endocrinol Metab* 2002;87:3221–3226.
- 18 Brix TH, Hansen PS, Rudbeck AB, Hansen JB, Skytthe A, Kyvik KO, Hegedus L: Low birth weight is not associated with thyroid autoimmunity: a population-based twin study. *J Clin Endocrinol Metab* 2006;91:3499–3502.
- 19 Brix TH, Kyvik KO, Hegedus L: Low birth weight is not associated with clinically overt thyroid disease: a population based twin case-control study. *Clin Endocrinol (Oxf)* 2000;53:171–176.
- 20 Phillips DI, Osmond C, Baird J, Huckle A, Rees-Smith B: Is birthweight associated with thyroid autoimmunity? A study in twins. *Thyroid* 2002;12:377–380.
- 21 Hamilton A, Newby PR, Carr-Smith JD, Disanto G, Allahabadia A, Armitage M, Brix TH, Chatterjee K, Connell JM, Hegedus L, Hunt PJ, Lazarus JH, Pearce SH, Robinson BG, Taylor JC, Vaidya B, Wass JA, Wiersinga WM, Weetman AP, Ramagopalan SV, Franklyn JA, Gough SC, Simmonds MJ: Impact of month of birth on the development of autoimmune thyroid disease in the United Kingdom and Europe. *J Clin Endocrinol Metab* 2014;99:E1459–E1465.
- 22 Krassas GE, Tziomalos K, Pontikides N, Lewy H, Laron Z: Seasonality of month of birth of patients with Graves' and Hashimoto's diseases differ from that in the general population. *Eur J Endocrinol* 2007;156:631–636.
- 23 Svensson J, Lindberg B, Jonsson B, Ericsson UB, Olofsson P, Hyoty H, Ivarsson SA: Intra-uterine exposure to maternal enterovirus infection as a risk factor for development of autoimmune thyroiditis during childhood and adolescence. *Thyroid* 2004;14:367–370.
- 24 Wiersinga WM: Smoking and thyroid. *Clin Endocrinol (Oxf)* 2013;79:145–151.
- 25 Carle A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, Jorgensen T, Laurberg P: Moderate alcohol consumption may protect against overt autoimmune hypothyroidism: a population-based case-control study. *Eur J Endocrinol* 2012;167:483–490.
- 26 Vita R, Lapa D, Trimarchi F, Benvenga S: Stress triggers the onset and the recurrences of hyperthyroidism in patients with Graves' disease. *Endocrine* 2015;48:254–263.
- 27 Levin L, Ban Y, Concepcion E, Davies TF, Greenberg DA, Tomer Y: Analysis of HLA genes in families with autoimmune diabetes and thyroiditis. *Hum Immunol* 2004;65:640–647.
- 28 Zeitlin AA, Heward JM, Newby PR, Carr-Smith JD, Franklyn JA, Gough SC, Simmonds MJ: Analysis of HLA class II genes in Hashimoto's thyroiditis reveals differences compared to Graves' disease. *Genes Immun* 2008;9:358–363.
- 29 Jonsdottir B, Andersson C, Carlsson A, Delli A, Forsander G, Ludvigsson J, Marcus C, Samuelsson U, Ortvist E, Lernmark A, Ivarsson SA, Larsson HE; Better Diabetes Diagnosis Study Group: Thyroid autoimmunity in relation to islet autoantibodies and HLA-DQ genotype in newly diagnosed type 1 diabetes in children and adolescents. *Diabetologia* 2013;56:1735–1742.
- 30 Sumnik Z, Drevinek P, Snajderova M, Kolouskova S, Sedlakova P, Pechova M, Vavrinec J, Cinek O: HLA-DQ polymorphisms modify the risk of thyroid autoimmunity in children with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2003;16:851–858.
- 31 Jacobson EM, Tomer Y: The CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 gene quintet and its contribution to thyroid autoimmunity: back to the future. *J Autoimmun* 2007;28:85–98.
- 32 Harjutsalo V, Reunanen A, Tuomilehto J: Differential transmission of type 1 diabetes from diabetic fathers and mothers to their offspring. *Diabetes* 2006;55:1517–1524.
- 33 van der Pals M, Ivarsson A, Norstrom F, Hogberg L, Svensson J, Carlsson A: Prevalence of thyroid autoimmunity in children with celiac disease compared to healthy 12-year olds. *Autoimmune Dis* 2014;2014:417356.
- 34 Emilsson L, Wijmenga C, Murray JA, Ludvigsson JF: Autoimmune disease in first-degree relatives and spouses of individuals with celiac disease. *Clin Gastroenterol Hepatol* 2015;13:1271–1277.e1272.