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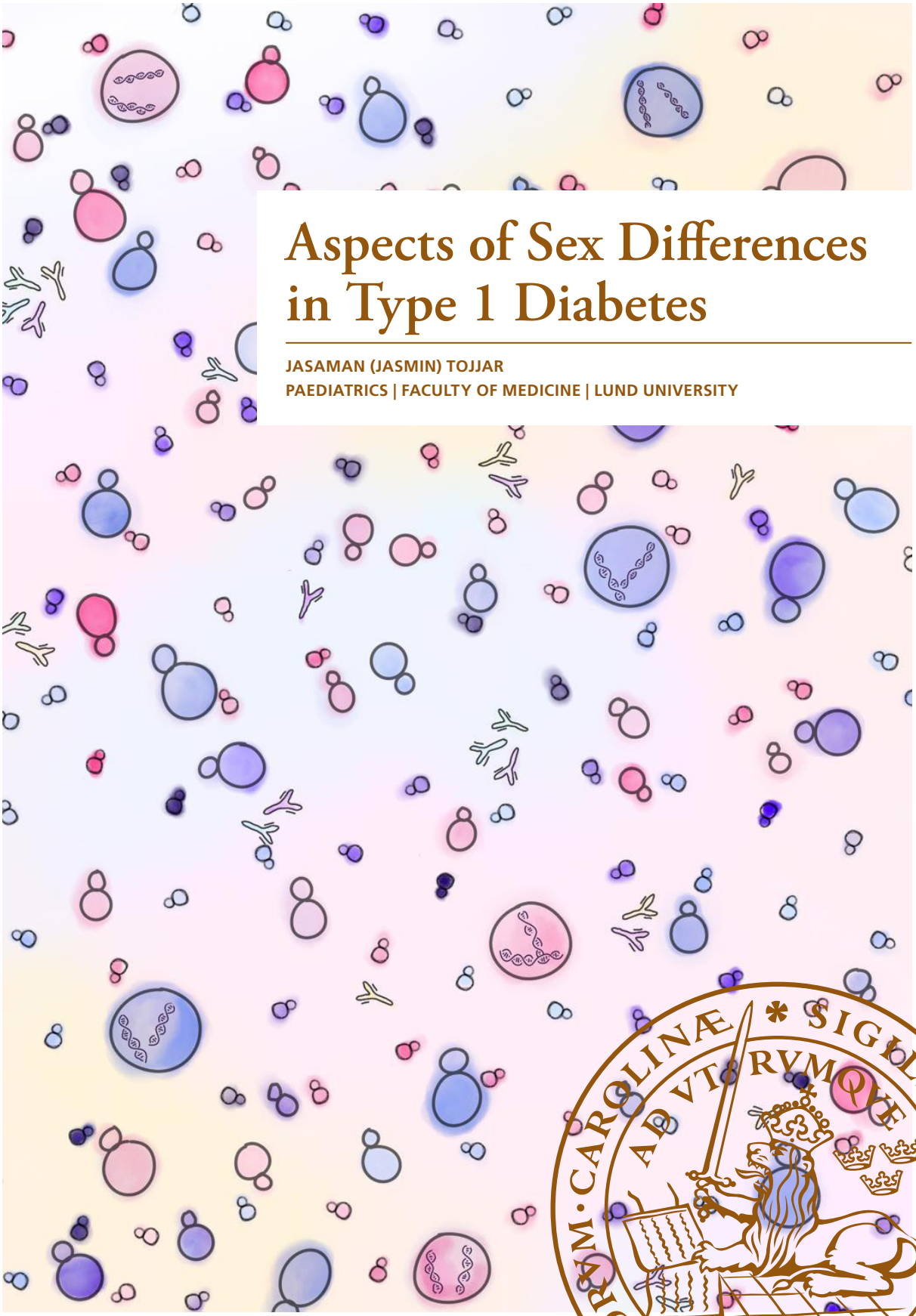

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Abstract:

Background Type 1 diabetes (T1D) is one of the most common childhood autoimmune diseases, with rising incidence worldwide with a male predominance. The etiology behind the disease is mostly unknown and it is essential to understand the factors that impact its development to prevent the disease and personalize the treatment. This thesis aims to examine sex-specific differences in T1D, explore the prevalence of parental diabetes, and the impact of parental diabetes on childhood obesity, as well as the influence of parental diabetes heredity on the clinical profiles of children with T1D.

Methods: Study I examined the relationship between parental diabetes status and childhood obesity risk among 12-year-olds with data obtained from a cross-sectional multicenter national screening study for celiac disease in 11,050 healthy 12-year-old children (The ETICS study). Questionnaires were used to obtain data regarding parental diabetes and Socioeconomic Status, and the children got their height and weight measured by a nurse. Study II investigated sex-specific differences in the clinical and immunological characteristics of children with newly diagnosed T1D, with a T1D population obtained from the nationwide Better Diabetes Diagnosis (BDD) study, an ongoing cohort study including almost all newly diagnosed Swedish patients with diabetes since 2005, where 3,977 children with T1D were included. Study III explored the prevalence of parental diabetes among children with newly diagnosed T1D and examined the potential differences in clinical characteristics based on diabetes heredity. The same population with T1D was used as in Study II, and data from Study I were used as healthy age-matched controls.

Results: Study I findings indicated that only boys with parents affected by T1D had an elevated risk of overweight compared to sex-matched peers without parental T1D. Both girls and boys, with parents with type 2 diabetes (T2D) had an elevated risk of overweight compared to sex-matched peers without parental T2D regardless of the socioeconomic status. Study II showed notable sex differences in the characteristics at the time of T1D diagnosis. Girls demonstrated earlier onset of symptoms and had a higher likelihood of testing positive for various autoantibodies, particularly glutamic acid decarboxylase autoantibodies (GADA). Meanwhile, boys had a higher likelihood of testing positive for Insulin Autoantibodies (IAA). Sex-specific differences in HLA risk factors were also apparent among children under 9 years of age. Study III showed an increased prevalence of parental diabetes (T1D and T2D), in children with T1D compared to healthy controls and that heredity for T1D correlates with younger age at diagnosis and lower HbA1c, while heredity for T2D was associated with a higher risk of being overweight or obese.

Conclusion: This thesis offers insights into the heterogeneity of T1D and the relationship between sex, parental diabetes status, obesity risk, and clinical markers that impact T1D in children. These findings may have implications for new screening strategies when developing tailored preventive interventions and optimizing disease management approaches to improve outcomes in the T1D population.

Key words: Type 1 diabetes, sex differences, autoimmunity, genetics, childhood obesity, parental diabetes

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To my family, friends, and the future.

Table of Contents

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Keywords Type 1 diabetes, sex differences, autoimmunity, genetics, childhood obesity, parental diabetes

List of Abbreviations

ADA	American Diabetes Association
BDD	Better diabetes diagnosis
BSA	Bovine serum albumin
CFRD	Cystic fibrosis-related diabetes
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes control and complications trial
DKA	Diabetic ketoacidosis
EDIC	Epidemiology of diabetes interventions and complications
Equalis	External quality assurance in laboratory medicine in Sweden
ERα	Estrogen Receptor α
ETICS	Exploring the iceberg of celiacs in sweden
GADA	Glutamic acid decarboxylase autoantibodies
GDM	Gestational diabetes mellitus
HbA1c	Hemoglobin A1c
HLA	Human leukocyte antigen
IA-2A	Insulinoma-associated-2 autoantibodies
IAA	Insulin autoantibodies
ICA	Islet Cell Antibodies
IDF	International diabetes federation
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
LADA	Latent autoimmune diabetes in adults
MDI	Multiple daily injections

MODY	Maturity-onset diabetes of the young
NDM	Neonatal Diabetes Mellitus
NDR	Nationella Diabetesregistret
NGSP	National Glycohemoglobin Standardization Program
OGTT	Oral Glucose Tolerance Test
OW/OB	
PCR	Polymerase chain reaction
PCR-SSP	PCR-sequence specific primers
PTDM	Post-Transplant Diabetes Mellitus
SCDR	Swedish Childhood Diabetes Registry
SWEDIABKIDS	
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TEDDY	The environmental determinants of type 1 diabetes in the young
TRIGR	Trial to Reduce Insulin dependent diabetes mellitus in the Genetically at Risk
WHO	World health organization
ZnT8A	Zinc Transporter 8 Autoantibodies

Populärvetenskaplig sammanfattning

Har flickor med typ 1-diabetes ett tuffare tillstånd än pojkar med typ 1-diabetes? Ska de följas upp av vårdpersonalen på samma sätt? Hur kan föräldrarnas diabetes påverka barnen och spelar barnets kön en roll?

Diabetes är en komplex sjukdom som drabbar miljontals människor världen över. Typ 1-diabetes, som främst drabbar barn och unga, kännetecknas av att kroppens immunförsvar angriper de insulinproducerande cellerna i bukspottkörteln, vilket leder till höga blodsockernivåer. Trots intensiv forskning är orsakerna till typ 1-diabetes fortfarande inte helt klarlagda, och det finns ett stort behov av att bättre förstå sjukdomens uppkomst och utveckling för att kunna förbättra diagnostik, behandling och prevention.

I min avhandling har jag undersökt hur typ 1-diabetes skiljer sig mellan pojkar och flickor. Jag har också undersökt om det är vanligare med ärftlighet för diabetes hos barn med typ 1-diabetes jämfört med de barn som inte har typ 1-diabetes alls och om detta påverkar risken för att barnet blir överviktigt. Genom att studera stora grupper av svenska barn så fort de fått diagnosen, såsom från den nationella studien "Better Diabetes Diagnosis" (BDD), har jag kunnat identifiera viktiga skillnader mellan flickor och pojkar när det gäller olika aspekter av typ 1-diabetes. Jag har även använt andra nationella register såsom det Nationella Diabetesregistret (NDR) och information från studien, Exploring the Iceberg of Celiacs in Sweden (ETICS), en skolbaserad screeningstudie av 12-åriga barn genomförd under skolåren 2005/2006 och 2009/2010. Dessa val gjordes på grund av den omfattande studiepopulationen samt för att data samlades in från samma tidsperiod, vilket möjliggör mer tillförlitliga jämförelser.

Jag fann att flickor i genomsnitt diagnostiseras med typ 1-diabetes vid en yngre ålder än pojkar och att de har en mer aggressiv profil med fler typer av så kallade antikroppar mot de insulinproducerande cellerna i bukspottkörteln. Flickor testar oftare positivt för antikroppen som attackerar Glutamate Decarboxylase, vilket brukar kallas för “GADA”, medan pojkar oftare testar positivt för antikroppen som attackerar insulin, vilket kallas för “IAA”. Dessa fynd tyder på att det finns könsskillnader i de immunologiska mekanismer som ligger bakom sjukdomens uppkomst och utveckling, vilket kanske kan hjälpa oss att förstå mekanismerna bakom det som leder till typ 1-diabetes. En spekulation kan vara att könshormonerna möjligtvis spelar en roll.

Vidare undersökte jag hur diabetes hos föräldrarna kan påverka risken för övervikt och fetma hos barnen. Resultaten visade att barn vars föräldrar har typ 2-diabetes löper ökad risk för att vara överviktiga, och pojkar har större risk att vara överviktiga om någon förälder har typ 1-diabetes. Detta understryker vikten av att tidigt identifiera och förebygga övervikt hos barn med ärftlighet för diabetes. Forskarna hoppas på att man i tidig ålder kan fånga upp dessa barn, särskilt pojkar, och informera familjen om betydelsen av en hälsosam kost, motion och mindre tid framför paddan och TV:n.

Jag fann även att det finns samband mellan ärftlighet för olika typer av diabetes och kliniska markörer vid diagnos av typ 1-diabetes hos barn och att det var skillnader beroende på vilken diabetestyp som barnet hade ärftlighet för. Jag fann att barn med typ 1-diabetes oftare hade föräldrar med diabetes, både typ 1-diabetes och typ 2-diabetes, jämfört med barn i den allmänna befolkningen. De barn som hade föräldrar med typ 1-diabetes diagnostiserades tidigare och hade lägre HbA1c-nivåer vid insjuknandet, vilket kan tyda på en ökad medvetenhet om symtom i dessa familjer, vilket är väldigt positivt. Samtidigt visades det att barn till föräldrar med typ 2-diabetes oftare hade övervikt. Dessa resultat visade också på betydelsen av ärftlighet för övervikt hos barnet och behovet av att stödja föräldrar med diabetes angående goda levnadsvanor för att undvika övervikt hos barnet.

Studien undersökte även skillnader i HLA-riskfaktorer mellan könen hos barn under 9 år, vilket kan ge ytterligare insikter i de underliggande mekanismerna bakom typ 1-diabetes.

Avhandlingen bidrar till en ökad förståelse för de komplexa sambanden mellan kön, ärftlighet för diabetes, övervikt och typ 1-diabetes hos barn. Jag hoppas att fynden kan hjälpa till med en preciserad riskbedömning, diagnostik och uppföljning av barn med typ 1-diabetes, med kön som en ny viktig utgångspunkt. Mitt mål är att resultaten och den fortsatta forskningen på sikt ska kunna leda till mer individanpassad vård för barnen samt starkare förebyggande insatser där ärftlighet och könsskillnader ska beaktas.

Overview of the Papers

This doctoral thesis comprises three papers that collectively investigate sex differences in Type 1 Diabetes (T1D) and the impact of parental diabetes on childhood obesity in Swedish populations. Each paper contributes to the overall objectives of the thesis by addressing specific aspects of these topics.

Paper I

Tojjar J, Norström F, Myléus A, Carlsson A.

The Impact of Parental Diabetes on the Prevalence of Childhood Obesity

Childhood Obesity, 2020, Vol. 16, No. 4

This study examined the association between parental diabetes and the risk of overweight and obesity in children. Using data from a population-based study of 12-year-old children, this paper highlights the potential role of genetic, sex, and environmental factors in the development of metabolic disorders. The findings underscore the importance of considering family history when assessing the risk of obesity in children and suggest potential targets for prevention strategies.

Paper II

Tojjar J, Cervin M, Hedlund E, Brahimi Q, Forsander G, Elding Larsson H, Ludvigsson J, Samuelsson U, Marcus C, Persson M, Carlsson A.

Sex Differences in Age of Diagnosis, HLA Genotype, and Autoantibody Profile in Children With Type 1 Diabetes

Diabetes Care, 2023, Volume 46, Issue 11

This study investigated sex-specific differences in the clinical and immunological characteristics of children with newly diagnosed T1D. By analyzing data from a nationwide prospective cohort, this study revealed that girls are diagnosed at a younger age and exhibit a more aggressive autoimmune profile compared to boys. These findings may have important implications for understanding the pathogenesis of T1D and developing sex-specific strategies for diagnosis and management.

Paper III

Hedlund E, **Tojjar J**, Lilja L, Larsson E. H, Forsander G, Ludvigsson J, Samuelsson U, Marcus C, Norström F, Persson M, Carlsson A.

Heredity of Diabetes and Clinical Markers in Children at Diagnosis of Type 1 Diabetes – A Swedish Cohort Study

Submitted to Diabetes Care, 2024

This study explored the prevalence of parental diabetes among children with newly diagnosed T1D compared with age matched children without T1D and examined the potential differences in clinical characteristics based on diabetes heredity. This study provides insight into the complex interplay between genetic and environmental factors in the development of T1D and highlights the importance of considering family history when evaluating the risk and prognosis of the disease.

Together, these three papers provide a starting point to investigate sex differences in T1D and the impact of parental diabetes on childhood obesity. By addressing these topics from different perspectives and using various study designs, this thesis contributes to a deeper understanding of the complex nature of T1D and factors that influence its development and progression. These findings may have important implications for clinical practice and research, and may lay a foundation for a more sex-differentiated view when planning future studies aimed at improving prevention, diagnosis, and management strategies for T1D.

Listed below are the published works during the period of my doctorate that are not included in this thesis.

Borgquist S, Broberg P, **Tojjar J**, Olsson H.

Statin use and breast cancer survival - a Swedish nationwide study.

BMC Cancer, 2019

Magesan K, Gnanaraj R, **Tojjar J**, Amose T, Alagorie AR, Mahalingam M, Sen P, Verma A, Sadda SR.

Fractal analysis of the macular region in healthy eyes using swept-source optical coherence tomography angiography.

Graefe's Archive for Clinical and Experimental Ophthalmology, 2023

Corradetti G, Verma A, **Tojjar J**, Almidani L, Oncel D, Emamverdi M, Bradley A, Lindenberg S, Nittala MG, SriniVas SR.

Retinal Imaging Findings in Inherited Retinal Diseases

Journal of Clinical Medicine - Under review, submitted February 2024

Introduction

Type 1 Diabetes (T1D) is an autoimmune condition that targets and destroys the insulin-producing beta cells within the pancreatic islets, thereby causing an insulin deficiency and hyperglycemia (1). Although the specific etiology of T1D remains unclear, it is widely recognized that both genetic predispositions and environmental influences play a significant role in the disease's manifestation (1, 2). Data from epidemiological studies indicate a greater incidence of T1D in males compared to females, this is particularly evident in high-incidence populations (2, 3). The higher prevalence of T1D in males suggests that there may be sex-specific factors that affect the onset and symptoms of diabetes.

This introduction aims to give a review of Diabetes, its epidemiology, etiology, pathophysiology, clinical characteristics, treatment approaches and much more. Enjoy!

Different types of Diabetes

The classification of diabetes has evolved over time, leading to growing understanding of its etiology, natural progression, and potential future. According to the current classification system, there are basically the following main types of diabetes: T1D, type 2 diabetes (T2D), gestational diabetes, and a group of more specialized types of diabetes caused by other factors (4).

Type 1 Diabetes

T1D is an autoimmune disorder characterized by the loss of pancreatic β-cells, leading to a complete absence of insulin (5). T1D constitutes 5-10% of all diabetes cases and usually appears in children and teenagers, although it can manifest at any stage of life (4). T1D is caused by a multifaceted interplay between genetic susceptibility, environmental influences, and the immune system (5). The treatment of T1D requires continuous injection of insulin, along with extensive education and support for self-management of diabetes (4).

Type 2 Diabetes

As the most common diabetes form worldwide, accounting for all but 5-10% of diagnosed cases, T2D is characterized by the body's resistive response to insulin, by time causing a relative insulin deficiency that results in hyperglycemia (4). Its risk factors include but are not limited to obesity, sedentary lifestyle, advancing age, familial history of diabetes, and specific ethnic demographics (4). Dealing with T2D typically entails behavioral modifications such as dietary and physical activity adjustments along with pharmacological interventions targeting insulin resistance, insulin deficiency, and hyperglycemia (4).

Latent autoimmune diabetes in adults (LADA)

Latent autoimmune diabetes in adults (LADA) is a form of autoimmune diabetes that exhibits characteristics of both T1D and T2D (6). LADA is distinguished by the development of diabetes in adulthood, the presence of islet autoantibodies, and a delayed transition to requiring insulin compared with classic T1D (6). Early management of LADA may include the use of oral glucose-lowering medications, however as the disease advances, insulin therapy is often necessary (5, 6).

Gestational Diabetes

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance with onset during pregnancy (4). GDM affects approximately 7% of all pregnancies worldwide, with varying prevalence rates across different populations (7). GDM is associated with adverse maternal and fetal outcomes, including macrosomia, neonatal hypoglycemia, and an increased risk of future T2D in both the mother and offspring (4). The management of GDM includes dietary modifications, physical activity, and insulin therapy when necessary (4).

Other forms of diabetes

Secondary Diabetes

Secondary diabetes is a type of diabetes that develops as a result of other problems, such as diseases affecting the pancreas, endocrine disorders, or diabetes triggered by certain medications (4). Pancreatic problems, such as pancreatitis, trauma, or neoplasia, may lead to diabetes by inducing the loss or failure of β cells (8). Endocrinopathies, such as Cushing's syndrome, acromegaly, or hyperthyroidism, can lead to the development of diabetes by either increasing the body's resistance to insulin or reducing the production of insulin (8). Drug-induced diabetes can occur as a consequence of taking glucocorticoids, atypical antipsychotics, or immunosuppressive drugs, among other medications (4). The management of

secondary diabetes involves treating the underlying condition and addressing hyperglycemia with appropriate therapies (4).

Drug-induced diabetes

Drug-induced Type 2 diabetes can be induced by specific medications that either obstruct the action of insulin or impede its secretion, making it a variant of secondary diabetes (9).

Diabetes associated with cystic fibrosis (CFRD) is a distinct type of diabetes that is common among patients with cystic fibrosis (CF), a genetic condition that primarily affects the respiratory and digestive systems (10). CFRD is considered the most common coexisting condition in CF, affecting approximately 20% of adolescents and 40-50% of adults (10). The physiological dysfunction of CFRD arises from a combination of inadequate insulin production caused by ongoing fibrosis and fatty infiltration of the pancreas, and insulin resistance, which is linked to persistent infection and inflammation (10). The management techniques for CFRD include the use of insulin medication, reinforcement of nutritional intake, and careful monitoring of the overall health and respiratory function status (4, 10).

Pancreatic diabetes

Pancreatic diabetes, referred to as type 3c diabetes, arises from disorders affecting the exocrine pancreas, such as pancreatitis, trauma, or pancreatic cancer (4). The pathogenesis entails a deficiency in the secretion of both insulin and glucagon, frequently resulting in increased insulin needs. According to the 2024 Standards of Care, it is recommended to screen for diabetes within 3-6 months after experiencing acute pancreatitis, and then annually afterward. The guidelines also suggest that individuals with chronic pancreatitis should have annual monitoring for diabetes (4).

Development of diabetes after an organ transplant is a medical condition recognized as post-transplant diabetes mellitus (PTDM). It is typically seen in patients who are on immunosuppressive treatment after their transplant (4). According to the Standards of Care, it is essential to monitor patients for high glucose levels post-transplantation. A definitive diagnosis of PTDM should be made once the patient has been stabilized on immunosuppressive medication and there is no ongoing infection. As per the 2024 recommendations of the American Diabetes Association Professional Practice Committee, the oral glucose tolerance test (OGTT) is the preferred method of diagnosing PTDM.

Monogenic Diabetes

Monogenic diabetes is a term used to describe a diverse set of illnesses caused by mutations in individual genes that play a role in the creation, function, or control of β-cells (11). Monogenic diabetes encompasses neonatal diabetes mellitus (NDM) and uncommon syndromic types of diabetes, in addition to MODY (4). Neonatal diabetes mellitus (NDM) is a term used to describe the occurrence of diabetes within the first six months of life. It is classified as either transitory or permanent, which means that some of the children diagnosed with neonatal diabetes will only have a transient disease and will not be dependent on insulin. Genetic testing is necessary for the diagnosis of monogenic diabetes. This testing helps tailor treatment plans and provides information about the prognosis and familial risk assessment (4).

Maturity-onset diabetes of the young (MODY) is the most common type of monogenic diabetes and is inherited in an autosomal dominant manner. It is defined by abnormalities in insulin and the onset of diabetes often occurs before the age of 25 years. Most patients are misclassified as having T1D or T2D depending on their phenotype (4). The predominant subtypes of MODY include HNF1A-MODY (MODY3), GCK-MODY (MODY2), and HNF4A-MODY (MODY1), all of which exhibit unique clinical characteristics and implications for treatment (4). Individuals with GCK-MODY experience mild, non-progressive hyperglycemia and typically do not require treatment. In contrast, individuals with HNF1A-MODY and HNF4A-MODY respond positively to sulfonylurea medication. Genetic testing plays a vital role in accurately diagnosing different subtypes of MODY, which is essential for tailoring customized management and providing genetic counseling (4).

Epidemiology of Type 1 Diabetes

International Trends and Incidence of Type 1 Diabetes

The incidence of T1D varies considerably across the globe, with some countries experiencing a much higher burden than others. According to estimates from the International Diabetes Federation (IDF) Diabetes Atlas 9th edition, approximately 98,200 children under the age of 15 years develop T1D annually worldwide as also demonstrated in figure 1. Furthermore, this number has risen to nearly 128,900 when considering those under 20 years of age (12). The corresponding prevalence estimates for existing cases were 600,900 and 1,110,100 for the under 15 and under 20 year age groups, respectively. This further reveals an increase in the number of cases across most IDF regions, covering 45% of the countries, which can be attributed to rising incidence rates (12). The IDF categorizes nations into seven regions: Africa, Europe, the Middle East and North Africa, North America and the Caribbean, South and Central America, Southeast Asia, and the Western Pacific (12).

The highest incidence rates of T1D in children under 15 years are found in the European region, particularly in Nordic countries such as Finland, Sweden, and Norway, as well as in the United Kingdom, Ireland, and Denmark (12). The United States, located in the North America and the Caribbean region, ranks second worldwide for the annual number of incident cases in the 0-14 age group, with an estimated 14,700 new cases per year (12). In contrast, the African region contributes the smallest portion of incident cases, around 2% in both the 0-14 and 0-19 age groups, despite having one of the largest populations (12).

Incidence rates of T1D have been increasing in many countries over the past few decades. A study which analyzed data from 26 European centers representing 22 countries, found a 3.4% (95% CI 2.8%, 3.9%) annual increase in incidence rates during the 25-year period from 1989 to 2013 (13). The study also revealed that the highest rates of increase were observed in the 0-4 year age group for both boys and girls (3.7% per annum) (13).

The disparities in the distribution of T1D incidence and associated mortality across countries with varying income levels are striking. While most new cases occur in high-income and upper-middle-income countries, most deaths related to T1D have been reported in low-income and lower-middle-income countries (12). This finding underscores the urgent need for improved access to insulin, blood glucose monitoring supplies, and trained healthcare professionals in resource-limited settings (12).

The global outbreak of COVID-19 had a substantial influence on the incidence and seriousness of T1D in children and teenagers worldwide. A review of multiple studies has indicated that the worldwide occurrence of newly diagnosed T1D, diabetic ketoacidosis (DKA), and severe DKA increased by 9.5%, 25%, and 19.5%, respectively, in the first year of the COVID-19 pandemic compared to the period before the pandemic (14). The study also revealed that the median glucose levels and HbA1c values in newly diagnosed pediatric T1D patients were 6.43% and 6.42% higher, respectively, after the onset of the pandemic (14).

A study found a notable increase in the occurrence of T1D among children and adolescents aged 0-29 years in the Piedmont area of Italy during the COVID-19 pandemic (15). The study also revealed a significant 31% increase in the incidence rate ratio of T1D in 2021, as opposed to the consistent trend observed from 2017 to 2020 (15).

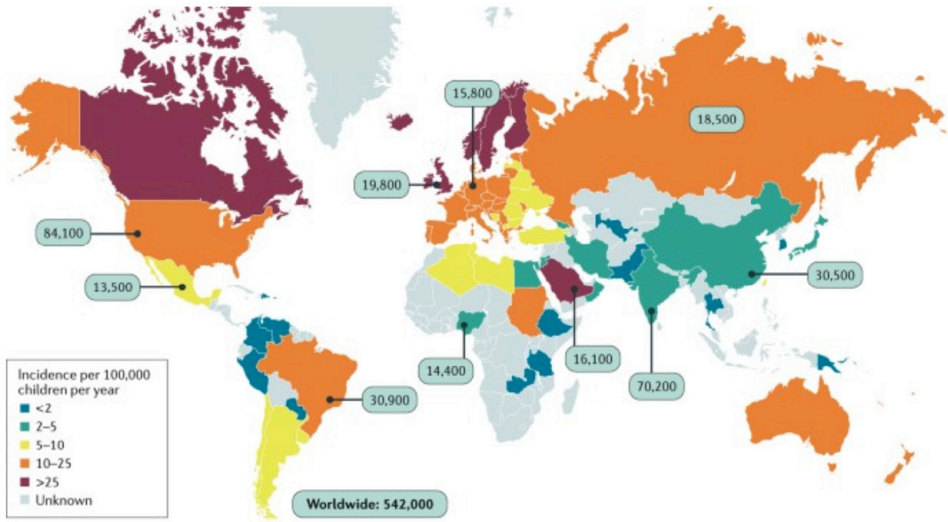

Figure 1: The incidence and prevalence of T1D in children <15 years of age per 100,000 individuals in 2015. Adapted from "Type 1 diabetes mellitus," by A. Katsarou et al., 2017, Nature Reviews Disease Primers. Copyright 2017 by Macmillan Publishers Limited (16)

Type 1 Diabetes Trends and Incidence in Sweden

Sweden ranks second globally, after Finland, in the incidence rates of T1D among children (17). Since 1978, the Swedish Childhood Diabetes Registry (SCDR) has been diligently tracked the incidence of T1D in Swedish children aged 0-14 years (18). The late 20th century saw a dramatic rise in the incidence of childhood-onset T1D in Sweden, with rates more than doubling during the 1980s and 1990s (19, 20). However, a 30-year follow-up of the SCDR data suggested a stabilization of the incidence trend between 2002 and 2007 (20).

The stabilization of the incidence increase appears to have persisted from 2005 to 2019 (17). Interestingly, when comparing the incidence trends of T1D between all children in Sweden and children with both parents born in Sweden, the latter group showed consistently higher rates, although the trends were similar (17). Moreover, when comparing the occurrence patterns over time, it was observed that people with Swedish backgrounds, who are known to have a high predisposition to diabetes, and those with Asian backgrounds, who are known to have a low predisposition to diabetes, showed a consistent increase in diabetes cases in the Asian subgroup (17).

The regression model examined the connections between incidence and demographic factors, such as sex, age at onset, and parental country of birth. The analysis revealed that apart from the well-known influences of calendar year, age, and sex, the specific country indicator had a substantial effect.

An examination of the incidence trends by age at onset revealed that the 0-4 years group exhibited the most pronounced stabilization in incidence after 2000, both in the total population and among "Swedish cases" (17). After 2000, the total population of the 5-9 years age range reached a plateau, while there was more variability among Swedish cases (17). In the 10-14 years group, the incidence continued to rise until around 2015 in both the total population and the Swedish subpopulation, followed by a downward trend in the predicted incidences, with the Swedish subpopulation displaying a higher level and more significant variation (17).

Sex Differences in the Incidence

Accumulating evidence suggests that sex differences play a significant role in the incidence and clinical presentation of T1D. Epidemiological studies have consistently shown a higher incidence of T1D in males compared to females, particularly after the onset of puberty. In a large Finnish study of 4,993 children and adolescents with newly diagnosed T1D, boys were significantly older than girls at clinical diagnosis (mean age 8.3 vs 7.7 years, $P < .001$) (2). This male preponderance in T1D incidence has been observed in various populations worldwide , especially in regions with high disease incidence such as Europe and North America (2).

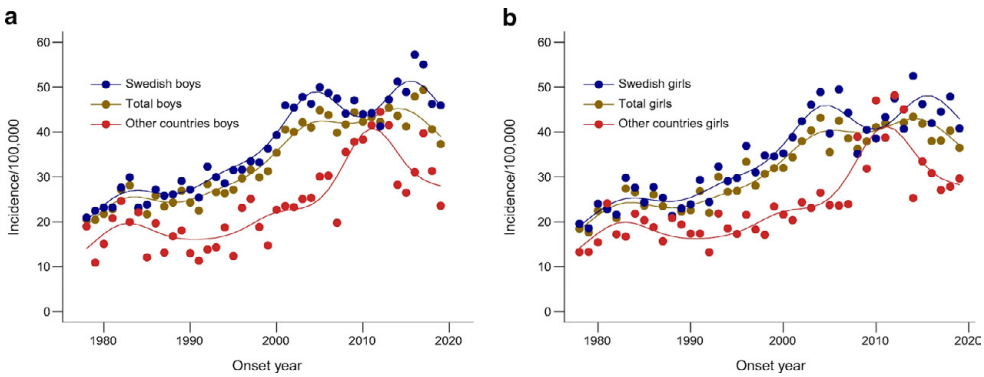

Figure 2: Incidence of childhood-onset type 1 diabetes in Sweden over 40 years distinguished by sex, a) boys and b) girls. From "Incidence of childhood-onset type 1 diabetes in Sweden," by I. Waernbaum, T. Lind, A. Möllsten, and G. Dahlquist, 2023, Diabetologia. Retrieved April 10, 2024, from https://www.examplewebsite.com/incidence-of-type-1-diabetes-in-sweden (21)

Etiology of Pediatric Type 1 Diabetes

The etiology of T1D is complex and involves a combination of genetic predisposition and environmental factors that start the autoimmune process (22). Although there have been significant research endeavors, the exact mechanisms responsible for the development of T1D are still not completely known. This section will provide a comprehensive overview of the current knowledge on the etiology of T1D, focusing on genetic susceptibility, environmental factors, and the interplay between these components in the pathogenesis of the disease.

Genetic Susceptibility

Genetic factors play a significant role in the development of T1D. The condition is closely linked to human leukocyte antigen (HLA) genes, specifically the DQA and DQB genes. The specific combinations of DQ2 and DQ8 have been found to significantly increase the likelihood of developing T1D (23). Nevertheless, having a genetic predisposition is not enough to cause the development of T1D, as shown by the fact that not all persons with high-risk HLA genotypes actually develop the disease (24).

The HLA region contributes to the genetic susceptibility to T1D, but it accounts for a portion of the total genetic risk, as estimated from studies of affected sibling pairs (25). Additional genetic variables beyond the HLA area also contribute significantly to the susceptibility of developing T1D. HLA class II genes, specifically HLA-DQ and HLA-DR, exhibit the most significant correlation with the likelihood of developing T1D (26). The HLA-DQ heterodimers, which are produced by the HLA-DQA1 and HLA-DQB1 genes, and the HLA-DR heterodimers, which are produced by the HLA-DRA and HLA-DRB1 genes, are the primary factors that determine vulnerability to T1D. These molecules are expressed on the surface of antigen-presenting cells and play a central role in the presentation of peptides to CD4+ T cells, which are key mediators of the autoimmune response in T1D (27).

The HLA-DQ2 (DQA1*05:01-DQB1*02:01) and HLA-DQ8 (DQA1*03:01-DQB1*03:02) haplotypes, in short the HLA-DQ2/DQ8 genotype, confer the highest risk for T1D (23). People who carry both HLA-DQ2 and HLA-DQ8 in a heterozygous state have a five times higher chance of developing T1D compared to the general population (24). Children with T1D have a higher prevalence of the HLA-DQ2/DQ8 genotype, which is linked to an increased risk of T1D, compared to the general population (28). Furthermore, some HLA-DR alleles also play a role in increasing the risk of developing T1D. The HLA-DR3 (DRB1*03:01) and HLA-DR4 (DRB1*04:01) alleles are associated with an increased risk of T1D, particularly when present in combination with the high-risk HLA-DQ alleles (29).

In addition, certain HLA alleles, such as HLA-DQ6 (DQA1*01:02-DQB1*06:02), provide protection against T1D (30). The protective effect of these alleles is thought to be related to their ability to present peptides that promote the development of regulatory T cells, which help to maintain immune tolerance (31). The HLA area exhibits a high degree of genetic variation, and the relationship between certain HLA alleles and the likelihood of developing T1D differs among various ethnic groups (32). Additionally, HLA-A*24 has been reported as an independent predictor of 5-year progression to diabetes in autoantibody-positive first-degree relatives of patients with T1D, and it is associated with a younger age at onset of T1D in white European patients (32).

Genes located in the HLA class III region, such as TNFA and MIC-A, have been investigated for their potential connection to T1D. However, it is believed that most of the identified connections are the result of linkage disequilibrium with HLA class II genes (26). Outside of the HLA region, polymorphisms in the insulin (INS), protein tyrosine phosphatase non-receptor type 22 (PTPN22), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) genes have been associated with T1D susceptibility (26). Both CTLA4 and PTPN22, which are immunological regulators, have repeatedly been linked to the likelihood of developing T1D in several ethnic groups (26).

Killer-cell Immunoglobulin-like receptor (KIR) genes, which encode receptors on natural killer cells, are also being investigated for their association with T1D due to their interaction with HLA class I ligands. Nevertheless, existing research has yielded conflicting results, and it is necessary to conduct larger studies with detailed KIR and HLA genotyping in order to establish the exact influence of KIR on susceptibility to T1D (26).

Sex Differences in HLA Genotypes

HLA genotypes are essential in determining the genetic susceptibility to T1D. The two main high-risk haplotypes, HLA-DR3-DQ2 and HLA-DR4-DQ8, are present in the majority of children diagnosed with T1D (28). Research has demonstrated that the HLA-DR3-DQ2 haplotype is more frequently found in boys, but the HLA-DR4-DQ8 haplotype is more prevalent in girls (2). More research is needed to elucidate the potential contribution of HLA genotypes to the observed sex differences in T1D.

The involvement of HLA genotypes in the development of T1D is complex and may include interactions with environmental factors and other genetic loci. For instance, the HLA-DR3-DQ2 haplotype has been correlated with a more severe autoimmune response and an earlier age of onset, whereas the HLA-DR4-DQ8 haplotype has been connected to a slower course of the disease and a later age at onset (28).

Additional research is needed to understand the complex relationship between HLA genotypes, sex hormones, and environmental factors in the development of T1D. Large-scale studies with well-characterized populations and standardized genotyping methods are required to clarify the role of HLA genotypes in the observed sex differences. Furthermore, functional studies exploring the molecular mechanisms underlying the interactions between HLA molecules, autoantigens, and immune cells may provide insights into the differential effects of HLA genotypes in males and females.

Environmental Factors

The rising incidence of T1D in recent decades, particularly among children under the age of 5 years, suggests that harmful changes in the environment in which contemporary children live may contribute to the development of the disease. However, the specific environmental factors that predispose to or protect against islet autoimmunity and T1D are not yet clear and require further research. Collaborative international cohort studies, such as the Environmental Determinants of T1D in the Young (TEDDY), aim to provide conclusive answers regarding these environmental influences (33).

Virus

Viral infections have consistently been associated with the possibility of triggering T1D. Research in epidemiology and molecular biology has shown that enteroviruses, specifically coxsackievirus B (CVB), may play a role in the development of islet autoimmunity (34).

Diet

Researchers have also examined dietary components as possible environmental causes of T1D. Cow's milk proteins, including bovine serum albumin (BSA), have been shown to trigger an autoimmune reaction in individuals who are genetically prone to it (35-37). The TRIGR trial, which compared hydrolyzed infant formula and regular cow's milk-based formula, discovered no notable disparity in the likelihood of developing islet autoimmunity or T1D (38). The role of vitamin D in T1D etiology has also been explored, with some studies suggesting that vitamin D supplementation may improve outcomes in children with T1D by potentially preserving residual endogenous insulin secretion, suggesting a connection between vitamin D and the management of T1D (39).

Gut microbiome

Gut microbiome has been identified as a potential environmental component in the development of T1D. Studies have reported alterations in the gut microbial

composition of individuals with islet autoimmunity or T1D compared to healthy controls (40, 41). These changes could affect immune regulation and the development of tolerance to self-antigens. However, the precise microbial composition and mechanisms that connect the gut microbiome to the risk of developing T1D have still to be fully understood.

Overweight/Obesity

One of the most important risk factors for T1D in children may be overweight or obesity. There have been many publications in the last few decades, both case-control and cohort studies, which have shown a link between childhood obesity/high BMI and an increased risk of developing T1D. One of the first case-control studies on children (1994) showed a clear relationship between faster weight gain from birth and the risk of T1D (42), and a review of case-control and cohort studies on children showed evidence of an association between increased BMI in childhood and the development of T1D (43). Worldwide, the prevalence of childhood obesity has increased from <1% in 1975 to 7.8% and 5.6% in 2016 in boys and girls, respectively (44). The World Health Organization (WHO) estimates that at present, at least one in five children is overweight. The increase in the prevalence of childhood overweight has been dramatic and the trend appears to be global, coinciding with the increase in the incidence of T1D.

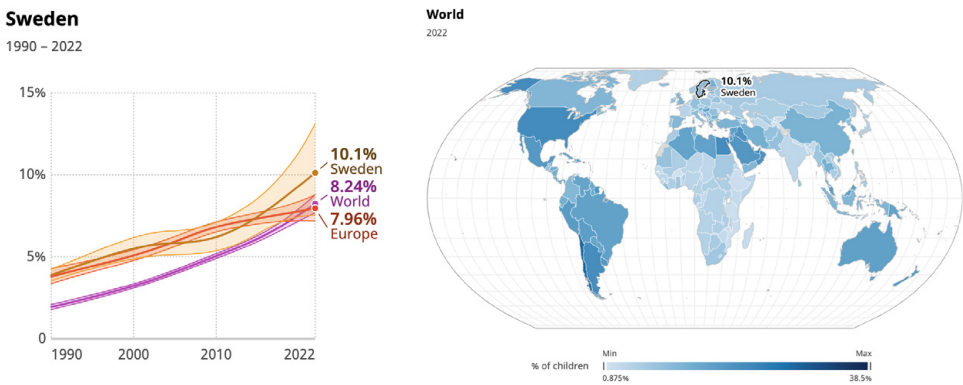

Figure 3. Obesity in children and adolescents (age 5 to 19). Percentage of children and adolescents with a body mass index greater than 2 standard deviation above the median. In Sweden, the prevalence of obesity among children and adolescents aged 5 to 19 years has worsened by an increase of 6.23% from 3.89% [3.54% - 4.26%] in 1990 to 10.1% [7.53% - 13.1%] in 2022. From 1990 to 2022. Adapted from World Health Organization - WHO, 2024. Retrieved April 12, 2024, from https://data.who.int/indicators/i/EF93DDB (17)

Pathophysiology of Type 1 Diabetes

Pancreatic Islet Dysfunction

Pancreatic islets, or islets of Langerhans, are specialized structures in the pancreas that play crucial roles in maintaining glucose the balance in the body. The islets comprise various endocrine cells, such as beta cells that produce insulin, alpha cells that produce glucagon, delta cells that produce somatostatin, and PP cells that produce pancreatic polypeptide (45). In T1D, the main physiological alteration occurs in the pancreatic islets, namely in the beta cells, which are targeted and destroyed by an autoimmune assault. The process described leads to a gradual decrease in the amount and effectiveness of beta cells, ultimately leading to a lack of insulin (46).

The process of beta cell loss in T1D is believed to occur gradually, with several stages of disease progression (47). In the early stages, islet autoantibodies appear in the circulation, indicating the initiation of an autoimmune response. As the disease progresses, beta cell mass and function gradually decline, leading to impaired glucose tolerance and eventual overt hyperglycemia. The rate of beta cell loss can vary among individuals, with some experiencing a rapid decline and others showing more gradual progression (48).

Furthermore, the impairment of surviving beta cells also plays a role in the pathophysiology of T1D, in addition to the direct effects of autoimmune destruction. Exposure to chronic hyperglycemia and inflammatory mediators can lead to beta cell dedifferentiation, a process in which beta cells lose their specialized function and revert to a more primitive cellular state (49). This dedifferentiation further impairs insulin production and secretion, exacerbating the insulin deficiency in T1D.

Autoimmune Destruction of Beta Cells

The autoimmune response in T1D is mostly controlled by T cells, specifically CD4+ (helper) and CD8+ (cytotoxic) T cells, which are significantly involved in beta cell death.

The development of autoimmunity in T1D is thought to involve a breakdown of central and peripheral tolerance mechanisms, allowing autoreactive T cells to escape deletion and regulate the immune response (50). Environmental factors, such as viral infections, dietary antigens, and microbiome alterations, have been proposed as potential triggers for the initiation of autoimmune responses (51). These environmental stimuli can trigger the release of beta cell antigens, which in turn activates autoreactive T lymphocytes that identify these antigens.

Upon activation, CD8+ T lymphocytes specifically and directly eliminate beta cells by releasing cytotoxic granules containing perforin and granzymes (52). CD4+ T cells assist B cells in generating autoantibodies that target beta cell antigens, including insulin, glutamic acid decarboxylase (GAD), islet antigen-2 (IA-2), and zinc transporter 8 (ZnT8) (46). These autoantibodies act as diagnostic indicators of T1D and can be identified years prior to the appearance of clinical symptoms.

In T1D, destroyed beta cells lead to inflammation in the pancreatic islets. This inflammation is characterized by the presence of immune cells and release of pro-inflammatory cytokines, including interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) (53). The cytokines contribute to the development of a harmful environment that exacerbates beta cell malfunction and death, hence accelerating the progression of T1D.

Autoantibodies in T1D

Autoantibodies against different islet cell antigens are characteristic features of T1D and are useful for predicting, diagnosing, and understanding the development of T1D (54).

Islet cell autoantibodies are detectable in the serum of individuals with T1D and in those at risk of developing the disease, often appearing months to years before the clinical onset of T1D (55). These autoantibodies serve as predictive biomarkers and are used to identify individuals who have a high likelihood of developing T1D. This allows for early intervention and the possibility of implementing prevention strategies (47). The major islet cell autoantibodies discussed in this review include Islet Cell Antibodies (ICA), Insulin Autoantibodies (IAA), Glutamate Decarboxylase Autoantibodies (GADA), Insulinoma-Associated-2 Autoantibodies (IA-2A), and Zinc Transporter 8 Autoantibodies (ZnT8A) (56).

Islet Cell Antibodies (ICA) were initially identified in 1974 by Bottazzo et al. (57) as the first autoantibodies discovered in patients with T1D. ICA are polyclonal antibodies that react with multiple islet cell antigens, including GAD65 and IA-2, and are detected using indirect immunofluorescence on human pancreatic tissue sections (58). Although ICA have been widely used for T1D prediction and have shown a high diagnostic sensitivity, prior publications have shown that their use has declined in recent years due to the development of more specific autoantibody assays and the requirement for human pancreatic tissue substrates (59).

Insulin Autoantibodies (IAA) are directed against endogenous insulin and are often the first autoantibodies to appear in young children with T1D, particularly in those under the age of 5 years (60). IAA are more prevalent in children than in adults and are associated with a more rapid progression to clinical T1D (61). The detection of IAA can be challenging due to their low affinity, and interference from insulin antibodies may occur in patients treated with exogenous insulin (62). Therefore,

IAA assays require sensitive and specific methods such as radiobinding assays to accurately detect these autoantibodies (62).

Glutamate Decarboxylase Autoantibodies (GADA) target the 65 kDa isoform of glutamate decarboxylase (GAD65), an enzyme involved in the synthesis of the neurotransmitter γ-aminobutyric acid (GABA) in pancreatic β-cells (63). GADA are found in a significant proportion of children with T1D (64). Single GADA positivity is associated with a slower progression to clinical T1D compared to multiple autoantibody positivity (65). The presence of GADA in combination with other autoantibodies such as IA-2A or ZnT8A confers a higher risk of developing T1D (66).

Insulinoma-Associated-2 Autoantibodies (IA-2A) recognize the protein, tyrosine phosphatase-like protein IA-2 (also known as ICA512), which is expressed in neuroendocrine cells, including pancreatic β-cells (67). IA-2A are highly specific for T1D and are often detected in combination with GADA or IAA (68). The presence of IA-2A in combination with other autoantibodies is associated with a higher risk of developing T1D (69).

Zinc Transporter 8 Autoantibodies (ZnT8A) specifically bind to the zinc transporter 8 protein, which plays a crucial role in the storage and release of insulin granules in pancreatic β-cells (70). ZnT8A is the most recently discovered autoantibody that, when used together with other autoantibodies, has been proven to enhance the accuracy of diagnosing T1D (71). ZnT8A antibodies are also linked to a more severe clinical manifestation of T1D, which is defined by an earlier age of diagnosis, lower C-peptide levels, and increased insulin needs (72).

Having several islet cell autoantibodies increases the likelihood of developing T1D more than having only one autoantibody (73). In the prospective TEDDY (The Environmental Determinants of Diabetes in the Young) study, children with multiple autoantibodies had a 70% cumulative risk of developing T1D by 10 years of age, compared to a 15% risk in those with a single autoantibody (55). The risk of progression to T1D increases with the number of autoantibodies, with a 5-year risk of 11%, 36%, and 47% for one, two, and three autoantibodies, respectively (74).

The pattern of appearance of autoantibodies and progression to T1D varies among individuals. IAA or GADA are typically the initial autoantibodies to emerge, with further development of additional autoantibodies occurring over time (75). The sequence in which autoantibodies arise may have consequences for the advancement of the disease, since individuals who develop islet cell autoantibodies (IAA) first tend to experience a faster development to T1D compared to those who develop glutamic acid decarboxylase autoantibodies (GADA) first (75). The age at autoantibody seroconversion also influences the risk of progression, with a younger age at seroconversion associated with a higher risk of developing T1D (76).

The use of islet cell autoantibodies as predictive biomarkers has enabled the development of staging criteria for T1D (47). The presence of two or more autoantibodies, regardless of glycemic status, defines stage 1 T1D, whereas the presence of two or more autoantibodies with dysglycemia (impaired fasting glucose or impaired glucose tolerance) defines stage 2 T1D (47). Below, figure 4 illustrates landmark models that define the age-adjusted risk of developing stage 1 T1D across childhood and adolescence by illustrating the cumulative risk of developing islet autoantibodies and predictions for the risk of developing any islet autoantibodies in the next 6 years.

The detection of islet cell autoantibodies has also enabled the advancement of disease-modifying treatments for T1D. Several clinical trials have investigated the use of immunomodulatory agents, such as anti-CD3 monoclonal antibodies, in individuals with newly diagnosed T1D or those at a high risk of developing the disease (77). These therapies aim to preserve residual β-cell function and delay the progression of T1D by targeting the autoimmune response (78). The effectiveness of these therapies relies on the promptly identification of individuals at risk through the use of islet cell autoantibodies and other biomarkers (79).

To summarize, islet cell autoantibodies play a critical role as predictive biomarkers and diagnostic tools for T1D. The presence of several autoantibodies, especially IAA, GADA, IA-2A, and ZnT8A, increases the likelihood of developing T1D and helps to identify individuals who could benefit from early intervention and prevention methods. The pattern of autoantibody appearance and influence of HLA genotypes on autoantibody development provide insights into the complex pathogenesis of T1D. The utilization of islet cell autoantibodies in staging criteria and as indicators of disease progression has aided the advancement of tailored therapeutics with the goal of preserving β-cell function and postponing the onset of clinical T1D. Further research on the mechanisms underlying the development of islet cell autoantibodies and their role in the pathogenesis of T1D will continue to inform the development of novel prevention and treatment strategies for this chronic autoimmune disorder.

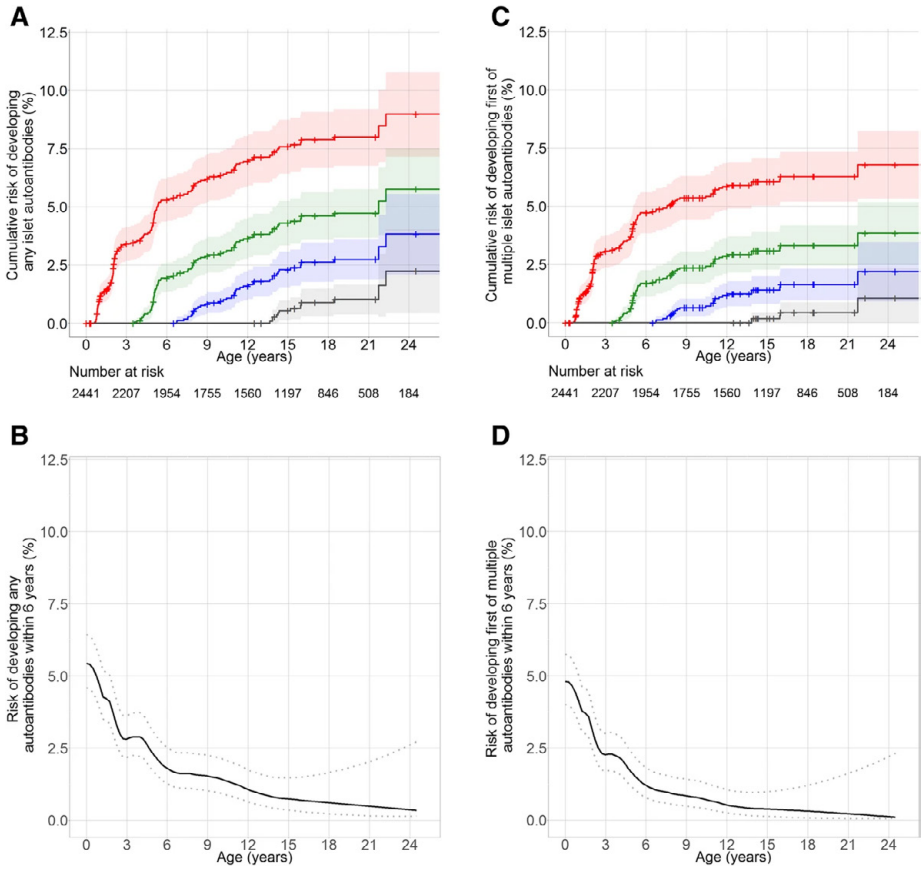

Figure 4: These graphs illustrate the cumulative risks of developing islet autoantibodies over time. Panels (a) and (c) present the cumulative risks of developing any (a) or multiple (c) islet autoantibodies in the total cohort, starting from birth (red), 3.5 years (green), 6.5 years (blue), and 12.5 years (grey) of age. Panels (b) and (d) offer dynamic predictions for the risks of developing any (b) or multiple (d) islet autoantibodies within the next 6 years of life. From World Health Organization. (2024). Obesity in children and adolescents (age 5 to 19). Retrieved April 12, 2024, from https://data.who.int/indicators/i/EF93DDB (80)

Sex Differences in Autoantibody Profile

A comprehensive study conducted in Finland examined 4,993 children and adolescents who were recently diagnosed with T1D. The researchers discovered notable variations between males and females in terms of the occurrence and levels of different islet autoantibodies (2). These differences remained significant even after accounting for the age at which the diagnosis was made. Boys had a higher prevalence of positive test results for IAA, IA-2A, and ZnT8A in comparison to girls. On the other hand, girls exhibited a greater occurrence of GADA positive and higher GADA titers. There was no significant difference in the frequency of islet cell antibodies (ICA) between males and females, although girls had greater ICA

titers. These data indicate that the immune response to autoantibodies in T1D may vary between girls and boys. Girls seem to have a stronger reaction to GADA, whereas males have a larger occurrence of IAA, IA-2A, and ZnT8A.

The higher frequency of IAA in boys reported by Turtinen et al. is consistent with previous studies showing a male predominance of IAA positivity in children and adolescents with newly diagnosed T1D (2). However, some studies have interpreted conflicting results, with a higher IAA frequency in girls, particularly in younger age groups (81). These variations can be linked to disparities in the demographics of the study participants, the sizes of the samples, and the distributions of age groups.

Sex difference in presence of multiple autoantibodies

Having numerous islet autoantibodies is linked to an increased likelihood of developing clinical T1D and experiencing a more severe disease progression (61, 82). In the Finnish study by Turtinen et al., the proportion of children with multiple (≥2) autoantibodies was similar between girls and boys (2). This finding contrasts with a previous report a study which found a higher frequency of multiple autoantibody positivity in girls compared to boys at T1D diagnosis (83). The variation among these investigations could be attributed to disparities in sample sizes, age distributions, and the autoantibody assays employed.

Sex differences in the relationship between Autoantibodies and HLA Genotypes

The human leukocyte antigen (HLA) region is the major genetic determinant of T1D risk, with specific HLA class II haplotypes conferring susceptibility or protection (84). The HLA-DR3-DQ2 and HLA-DR4-DQ8 haplotypes are the strongest genetic risk factors for T1D, and their combination confers the highest risk (28). In previous reports, the frequency of the HLA-DR3-DQ2 haplotype was slightly higher in boys, while the HLA-DR4-DQ8 haplotype was more common in girls, although these differences were not statistically significant (2). Interestingly, the authors found that the HLA-DR3-DQ2 homozygosity was more frequent in boys while the HLA-DR4-DQ8 homozygosity was more frequent in girls after adjusting for age at diagnosis (2).

The association between HLA genotypes and islet autoantibodies in T1D is intricate and may encompass interactions between genes as well as between genes and the environment (85). Several studies have documented connections between particular HLA haplotypes and patterns of autoantibodies. For instance, the HLA-DR4-DQ8 haplotype has been connected to the presence of IAA and IA-2A antibodies, as indicated by research (86). Similarly, the HLA-DR3-DQ2 haplotype has been associated with the presence of GADA antibodies (87). A higher frequency of the HLA-DR4-DQ8 haplotype in girls has been shown to not translate into a higher frequency of IAA or IA-2A, as these autoantibodies were more common in boys (2). Similarly, the higher frequency of the HLA-DR3-DQ2 haplotype in boys did

not result in a higher frequency of GADA, which was more prevalent in girls. These findings suggest that the relationship between HLA genotypes and autoantibody patterns may be influenced by sex-related factors, such as hormonal or environmental exposures.

Hypotheses for the Development of Type 1 Diabetes

Although the precise origin of T1D in children is still unknown, various suggestions have been suggested to elucidate its development. There are two well-known hypotheses: the hygiene theory and the accelerator hypothesis.

Hygiene Hypothesis

The hygiene hypothesis suggests that reduced exposure to infections and microorganisms during early childhood may increase the risk of developing autoimmune diseases, including T1D. This idea proposes that a deficiency in early immunological activation results in an asymmetry in the immune system, rendering it more prone to attacking the body's own cells (88).

It has been reported that children with a greater incidence of infections in their first year of life had a reduced likelihood of acquiring T1D (89). This discovery provides evidence that early exposure to viruses can contribute to the education of the immune system and prevention of autoimmune illnesses.

Accelerator Hypothesis

The accelerator hypothesis, proposed by Terence J. Wilkin (90), suggests that T1D and T2D are essentially the same disorder, with T1D being an accelerated form of T2D. This hypothesis suggests that three primary factors that lead to the onset of diabetes:

1. Insulin resistance: Elevated body weight and lack of physical exercise can result in insulin resistance, a condition that places greater strain on the beta cells.
2. Beta-cell apoptosis: Insulin resistance and glucose toxicity can result in apoptosis of beta-cells, which in turn decreases the production of insulin.
3. Autoimmunity: In genetically susceptible individuals, the increased need for insulin caused by insulin resistance can activate an immunological response, resulting in the death of beta cells and the onset of T1D.

Clinical Presentation, Diagnosis, and Treatment

T1D is characterized by a set of symptoms known as the classic trio: polydipsia (excessive thirst), polyphagia (excessive appetite), and polyuria (excessive urine), together with high blood sugar levels (46). These symptoms occur because the body is unable to effectively use glucose due to insufficient insulin, resulting in elevated blood glucose levels and excretion of glucose in the urine. The diagnostic criteria for diabetes are as follows: fasting blood glucose level over 7 mmol/L (126 mg/dL), a random blood glucose level of 11.1 mmol/L (200 mg/dL) or higher accompanied by symptoms of hyperglycemia, or an abnormal oral glucose tolerance test (91).

Treatment of T1D Insulin Injections and Insulin Pumps

The management of T1D primarily involves exogenous insulin replacement therapy, which is crucial for patient survival (46). Insulin therapy can be administered by multiple daily injections (MDI) using insulin pens or continuous subcutaneous insulin infusion (CSII) using insulin pumps (92). MDI commonly entails the administration of a mixture of long-acting basal insulin, once or twice daily and rapid-acting insulin boluses prior to meals. In contrast, CSII, on the other hand, delivers rapid-acting insulin continuously through a subcutaneous catheter, with the ability to administer bolus doses at mealtimes (93).

Artificial Pancreas: Closed-Loop Systems

Recent advancements in diabetes technology have led to the development of closed-loop systems, also known as artificial pancreas systems (94). These devices integrate continuous subcutaneous insulin infusion (CSII) with continuous glucose monitoring (CGM) and an algorithm that automatically modulates insulin administration based on real-time glucose levels (95, 96). Closed-loop systems aim to mimic the function of a healthy pancreas by continuously monitoring glucose levels and adjusting insulin delivery, thereby reducing the burden of diabetes management and improving glycemic control (97). Research has demonstrated that closed-loop systems are more effective than conventional insulin therapy in terms of improving the time spent within the desired glucose range, reducing instances of hypoglycemia, and enhancing overall glycemic control (95, 96, 98).

Diabetes Medical care in Sweden

In Sweden, specialized pediatric diabetes teams oversee the care of children with diabetes. These teams are composed of pediatric endocrinologists, diabetic nurses, nutritionists, and psychologists. These teams collaborate closely with families to

offer personalized care plans, education, and assistance. Advanced diabetes technologies, such as continuous glucose monitoring (CGM) and insulin pumps, are common in Sweden (99).

Sweden has a highly advanced healthcare system that offers extensive and thorough care for children diagnosed with diabetes. In Sweden, the management of childhood diabetes emphasizes patient education, self-care, and support from a multidisciplinary team. The Swedish Childhood Diabetes Registry (SWEDIABKIDS) gathers information on every child and teenager with diabetes in Sweden, allowing healthcare professionals to track patterns and enhance quality of care which has enhance the diabetes care in Sweden with very good results in metabolic control (100).

Comparison of Diabetes treatment in Other Countries

Sweden's approach to pediatric diabetes care has been internationally acclaimed for its excellence. A previous study compared the glycemic control of children with T1D in seven high-income countries: Sweden, Denmark, England, Wales, United States, Germany, and Austria. This study found that Sweden had the lowest average HbA1c level (7.4%) and the highest proportion of children who achieved the target HbA1c level (101).

Key factors contributing to Sweden's effectiveness in managing pediatric diabetes include:

1. Thorough and all-encompassing norms are established at a national level, together with registries that ensure the quality of services.
2. Implementation of extensive patient education and self-management assistance
3. Extensive availability of advanced diabetes technologies
4. Regular follow-up and multidisciplinary team support

It is important to acknowledge that nations such as Denmark and Germany also have well-developed systems for pediatric diabetes care and obtain favorable results. The United States, despite its advanced medical technology, exhibits higher average HbA1c levels in children with diabetes than Sweden. This disparity may be attributed to variations in healthcare accessibility and socioeconomic characteristics (102).

Sex Differences in Metabolic Control and Insulin Requirements

A comprehensive analysis of 90 papers has revealed multiple differences between sexes in children diagnosed with T1D. Female children had higher HbA1c levels at diagnosis and during treatment, higher BMI, and a higher prevalence of overweight/obesity, dyslipidemia, ketoacidosis, hospitalizations, pump therapy use, insulin dose requirements, comorbidities (thyroid and celiac disease), and lower quality of life. In contrast, male children exhibited a greater prevalence of hypoglycemia and partial remission (103).

Metabolic control and insulin requirements are important aspects of T1D management that exhibit notable sex differences. Multiple studies have consistently found that girls tend to have worse glycemic control, as indicated by greater levels of HbA1c, both at the time of diagnosis and during the period of follow-up (104). The elevated levels of C-peptide in females may be a contributing factor to the reported variations in glycemic control between the sexes. In a large Swedish cohort, girls had significantly higher C-peptide levels than boys ($p<0.05$), especially in early puberty (105). Similar findings have been reported for HbA1c, with teenage girls showing significantly higher levels compared to boys (106). The reasons for this sex difference in glycemic control are likely multifactorial, involving biological, behavioral, and psychosocial factors.

Biological factors, such as hormonal changes during puberty, may contribute to the observed sex differences in glycemic control. Insulin resistance has been shown to increase immediately at the onset of puberty, and significant differences in insulin resistance has shown to be present between boys and girls, where girls have shown to be significantly more insulin resistant than boys (107). The rise in growth hormone and insulin-like growth factor-1 levels during puberty can lead to increased insulin resistance, making glycemic control more challenging (108).

Behavioral and psychosocial factors may also play a role in the sex differences in glycemic control. Girls have higher rates of eating disorders, depression, and anxiety compared to boys (109). The presence of mental health disorders can have a detrimental effect on the ability to effectively manage diabetes, including following insulin therapy, monitoring blood glucose levels, and maintaining healthy eating habits. Moreover, girls may face unique social pressures and challenges related to body image, peer relationships, and family dynamics, which can further complicate diabetes management.

Addressing the sex differences in metabolic control and insulin requirements requires a multidisciplinary approach that takes into account the biological, behavioral, and psychosocial factors influencing diabetes management. Healthcare practitioners should possess knowledge about the distinctive obstacles encountered

by females with T1D and deliver personalized medical attention that caters to their particular requirements. This may involve increased frequency of monitoring glycemic control, doing screenings for mental health conditions, and delivering age-appropriate education and support. Additionally, research efforts should focus on identifying the underlying mechanisms driving the sex differences in metabolic control and developing targeted interventions to improve outcomes in girls with T1D.

Adverse effects of Type 1 Diabetes

Despite improvements in insulin therapy and diabetes technology, people with T1D still face the possibility of long-term problems. The complications can be categorized as either microvascular, which refers to the involvement of tiny blood vessels, or macrovascular, which refers to the involvement of big blood vessels (110).

Microvascular complications

Microvascular problems include retinopathy (vascular damage in the retina), nephropathy (renal damage), and neuropathy (nerve damage) (110). Retinopathy can result in loss of vision or complete blindness, while nephropathy can advance to end-stage renal disease, necessitating dialysis or kidney transplantation. Neuropathy can result in discomfort, loss of sensation, and reduced limbs strength. It can also affect the autonomic nervous system, causing problems in the digestive, urinary, and cardiovascular systems (111, 112).

Macrovascular complications

Macrovascular problems largely encompass cardiovascular disorders, including coronary artery disease, stroke, and peripheral artery disease (113). Individuals with T1D are at a considerably greater risk of developing cardiovascular disease compared to the overall population. This risk becomes even higher as they age and the duration of their diabetes grows (113, 114).

Intensive diabetes management and maintaining optimal glycemic control can decrease the likelihood of having both microvascular and macrovascular problems (115, 116). The Diabetes Control and Complications Trial (DCCT) and its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), have shown that intensive insulin therapy, which aims to achieve glycemic control close to normal levels, significantly decreases the likelihood of microvascular and macrovascular complications in individuals with T1D (115, 116).

Sex Differences in Long-term Complications

Sex differences are seen in the long-term complications of T1D. Studies consistently show that women with T1D have a significantly higher risk for mortality from any cause and cardiovascular events compared to men. This excess risk in women is particularly pronounced for coronary heart disease (117). Studies have found that there are differences between males and females in the development of microvascular problems, including retinopathy, in patients with T1D. It has been observed that females tend to experience retinopathy at an earlier age compared to males (118).

Comorbidities of Type 1 Diabetes

Individuals with T1D have a higher likelihood of developing additional autoimmune conditions, including celiac disease, autoimmune thyroid disease, and Addison's disease (119). These other medical conditions can affect the regulation of blood sugar levels, overall well-being, and overall health in patients with T1D.

Celiac Disease

Celiac disease is an autoimmune condition characterized by an immunological reaction to gluten in the diet, resulting in harm to the small intestine (119). The incidence of celiac disease in patients with T1D is expected to be 5-10 times greater than that in the general population (120). Screening for celiac disease in individuals with T1D is recommended, as untreated celiac disease can lead to poor glycemic control, nutrient deficiencies, and an increased risk of complications (119, 120).

Autoimmune Thyroid Disease

Individuals with T1D have a higher prevalence of autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease, compared to the general population (119). Thyroid dysfunction can affect glycemic control and overall health of individuals with T1D, making regular screening for thyroid disorders an important part of diabetes management (119, 121).

Adrenal insufficiency

Addison's disease, also known as primary adrenal insufficiency, is an uncommon autoimmune illness that affects the adrenal glands and results in a shortage of cortisol and aldosterone synthesis (122). The prevalence of Addison's disease is higher in individuals with T1D than in the general population (122).

Conclusion

The issue of sex differences in T1D is a complicated and nuanced topic that requires additional research. By comprehending the biological, behavioral, and psychosocial elements that contribute to these disparities, we can formulate more efficient and individualized strategies for managing and preventing T1D. This dissertation aimed to provide a comprehensive overview of the current state of knowledge on sex differences in T1D.

Aims and Objectives

The overall aim of this thesis was to investigate the impact of sex on different aspects of T1D. This includes incidence, age at diagnosis, genetic susceptibility, autoimmune profile, and the influence of parental diabetes on childhood obesity.

The specific objectives were the following:

1. To examine sex-specific differences in the incidence and age at diagnosis of T1D among Swedish children.
2. To investigate the association between sex, human leukocyte antigen (HLA) genotypes, and autoantibody profiles in children with a newly diagnosed T1D.
3. To explore the impact of parental diabetes on the prevalence of childhood obesity and its potential role in the development of T1D.
4. To study the prevalence of parental diabetes in children with T1D and its impact on clinical markers at diagnosis of the disease.
5. To discuss the implications of sex differences in T1D in terms of diagnosis, management, and future research directions.

By addressing these objectives, this thesis may contribute to a better understanding of the nature of T1D.

Methods

Study design and participants

The current dissertation incorporates data from three distinct studies, each employing a specific study design and participant selection criteria to investigate the relationships between sex, heredity and clinical markers, in children and adolescents with T1D.

Study 1: "The Impact of Parental Diabetes on the Prevalence of Childhood Obesity"

Study 1 utilized data from the Exploring the Iceberg of Celiacs in Sweden (ETICS) study, a two-phase cross-sectional multicenter screening study for celiac disease in 12-year-old children.

The study was approved by the Regional Ethical Review Board of Umeå University (Dnr 04-156) and conducted in two field phases: the first in the years 2005–2006 and the second in 2009–2010, thus including two birth cohorts of 12-year-olds (those born in 1993 and those in 1997). The study design was consistent across both screening phases.

Children in the sixth grade from five study sites (Lund, Umeå, Norrtälje, Norrköping, and Växjö) were invited to participate. Informed consent was obtained from at least one legal guardian before enrollment. The first field phase included 7,567 children, while the second enrolled 5,712, covering approximately 10% of the 12-year-old population in Sweden. The proportion of girls was similar in both cohorts (48% in the 1993 cohort and 49% in the 1997 cohort).

For the purpose of this study, information on weight, height, parental diabetes, and highest parental education level was required. Children lacking this data were excluded from the analysis (n=2,229; 16.8%), resulting in a final sample of 11,050 participants.

Study 2: "Sex Differences in Age of Diagnosis, HLA Genotype, and Autoantibody Profile in Children With Type 1 Diabetes"

Study 2 used data from the nationwide Better Diabetes Diagnosis (BDD) study, an ongoing project in Sweden since 2005. The BDD study aimed to improve the classification of diabetes and understanding of factors contributing to diabetes

development. Diagnostic criteria for T1D were based on the presence of classic symptoms of hyperglycemia and casual plasma glucose ≥200 mg/dL (11.1 mmol/L), fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), or 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test, according to the American Diabetes Association (ADA) guidelines. Type 2 diabetes, monogenic diabetes, and other diabetes subtypes were diagnosed based on clinical features, family history, and genetic testing, as appropriate.

Between May 2005 and December 2010, 4,601 children were diagnosed with diabetes, of which 3,977 (87%) were included in the BDD study. Until December 2010, all BDD participants were analyzed for a comprehensive panel of autoantibodies, including GADA, IA-2A, ZnT8RA, ZnT8WA, ZnT8QA, and IAA. After this period, participants were only analyzed for IAA or zinc transporter autoantibodies if GAD and IA-2A were negative. Consequently, only participants enrolled before 2011 were included in this study to ensure a consistent autoantibody assessment.

The current study analyzed data from 3,645 children with a confirmed T1D diagnosis according to the ADA criteria. Ethical approval for the BDD study was granted by the Regional Ethics Board at Karolinska Institute in Stockholm, Sweden. Patients and caregivers provided written informed consent/assent for participation.

Study 3: "Heredity of diabetes and clinical markers in children at diagnosis of Type 1 diabetes – a Swedish cohort study"

Study 3 is a cohort study also consisting of children from the BDD study, but also from the national longitudinal Swedish quality register for pediatric diabetes, Swediabkids, where all children are registered and followed.

A reference group of healthy 12-year-olds (n=11,050) from the ETICS study was used to compare the prevalence of parental heredity for diabetes between children with and without T1D. For this comparison, only records from children without T1D or celiac disease were used to ensure a valid reference population. Clinical parameters such as BMI, HBA1c, and ketoacidosis were collected from the national Swediabkids study.

Data collection and variables

Study 1

Anthropometric measurements were performed by a research nurse, using standardized methods. Newly calibrated scales were used to weigh children wearing light clothes, and a wall-mounted stadiometer was used to measure height. Body

mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m2). Overweight was defined according to Cole's international age and gender-adjusted cutoff values for age 12, which correspond to an adult BMI of 25 kg/m2.

A parent or legal guardian of each child was asked to complete a questionnaire regarding parental diabetes diagnosis and highest education level. The questionnaire used Swedish common language, referring to insulin-dependent diabetes as T1D and non-insulin-dependent diabetes as T2D. Parental diabetes was defined as having a mother and/or father with either T1D or T2D. Education level was categorized as low (≤9 years of schooling), middle (12 years of schooling), or high (>12 years of schooling).

Validation and Reliability of Questionnaires in the ETICS Study:

The ETICS study utilized semi-quantitative questionnaires to collect data on sociodemographic factors and perinatal outcomes, including parental diabetes and education level. To ensure the validity and reliability of the questionnaires, several measures were taken.

To minimize potential biases associated with self-reported data, the questionnaires were designed using clear and concise language, avoiding complex medical terminology. The questions were framed in a neutral manner to reduce the likelihood of socially desirable responses. Additionally, the confidentiality of the collected data was emphasized to encourage honest and accurate reporting.

Furthermore, the use of a large, representative sample in the ETICS study helped to mitigate the impact of potential biases associated with self-reported data. The large sample size allowed for the detection of significant associations even in the presence of some degree of misclassification or bias.

Despite measures such as these and more, it is essential to acknowledge the inherent limitations of self-reported data, such as the possibility of recall bias, particularly for events that occurred in the past, such as parental diabetes diagnosis and educational attainment. However, the impact of such biases is expected to be non-differential between the groups being compared, thus minimizing the overall effect on the study results.

Study 2

Autoantibodies were analyzed using radio-ligand binding assays with methods described in detail elsewhere. Cut-off levels for positivity were established for each autoantibody: GADA >50 U/mL, IA-2A >10 U/mL, ZnT8RA >75 U/mL, ZnT8WA >75 U/mL, ZnT8QA >100 U/mL, and IAA ≥1.0 U/mL. HLA typing was performed on dried blood spots using PCR with a DELFIA hybridization assay (PerkinElmer, Boston, MA). Sequence-specific oligonucleotide probes of HLA-DQB1 were used

to define the presence of specific alleles, and another set of HLA-DQA1 probes was used to define additional alleles. HLA genotypes were classified into different risk groups (high, moderate, and low risk) using normative data from the general population.

Study 3

The cohort was categorized by heredity for diabetes among parents and grandparents into four groups: only T1D, only T2D, both type 1 and T2D, and no heredity for diabetes. Information on heredity was collected at diagnosis by a diabetes nurse or physician and recorded in the BDD registry. Inquiries about first-degree (parents) and second-degree (maternal and paternal grandparents) relatives regarding diabetes of different types, cardiovascular diseases, and other autoimmune diseases were made.

BMI was calculated using weight and height measured at a clinical visit 5-6 months post-diagnosis. Based on BMI, children were categorized as normal weight, overweight (ISO-BMI >25 kg/m2), or obese (ISO-BMI >30 kg/m2). BMI was not calculated for children under the age of two (n=106), who were excluded from BMI analyses.

HbA1c was analyzed at different hospitals according to various laboratory methods, which are quality-assured through Equalis (External Quality Assurance in Laboratory Medicine in Sweden), enabling the comparison of HbA1c values across different clinics. HbA1c is presented as International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol) and as a percentage (% HbA1c) according to the National Glycohemoglobin Standardization Program (NGSP). Clinical parameters such as BMI, HBA1c, and ketoacidosis were collected from the national Swediabkids study.

The pH value at diagnosis was used to identify diabetic ketoacidosis (DKA), defined as venous pH <7.30 combined with hyperglycemia and ketonemia or ketonuria, according to the ISPAD guidelines.

Autoantibodies (GADA, IA-2A, IAA, ZnT8RA, ZnT8WA, ZnT8QA) were analyzed as previously described in Study 2. HLA-DQA1 and HLA-DQB1 genotypes were determined, and HLA-genotypes were classified into 4 different risk groups: 1: HLA-DQ2/8, 2: HLA-DQ8/X (where X is not 2), 3: HLA-DQ2/X (where X is not 8), 4: HLA-DQX/X (where X is neither 2 nor 8).

BDD Study Methods (Studies 2 and 3)

Autoantibody analyses

GAD65A and IA-2A were analyzed using radio-ligand binding assays with recombinant human GAD65 and IA-2 labeled with [35S] methionine. Serum samples were incubated with the labeled antigens, and antibody-bound radioactivity was counted in a β-counter. Levels were expressed in units per milliliter derived from the WHO standard 97/550. The intra-assay CV for duplicates was 7% in the GADA assay and 11% in the IA-2A assay.

IAA was analyzed using a non-competitive method with [125I] insulin. Serum samples were incubated with labeled insulin, and antibody-bound radioactivity was counted in a β-counter. Positive samples were further analyzed using a competitive method with unlabeled insulin. IAA levels were calculated as relative units related to positive controls, with positivity set at 1.0 relative units. The intra-assay CV was 6.0% for IAA, and the inter-assay CV was 13.2%.

ZnT8A (ZnT8RA, ZnT8WA, ZnT8QA) were analyzed using separate radio-binding assays with COOH-terminal constructs of ZnT8 prepared using site-directed mutagenesis. [35S] methionine-labeled antigens were incubated with serum samples, and antibody-bound radioactivity was counted in a β-counter. Levels were estimated from a known standard curve. The intra-assay CV was 5.5% for ZnT8-RA, 5.3% for ZnT8-WA, and 4.9% for ZnT8-QA, while the inter-assay CV was 13.8% for ZnT8-RA, 6.7% for ZnT8-WA, and 11.0% for ZnT8-QA.

HLA-typing

In BDD1 (2005-2010), HLA-DQA1-DQB1 genotypes were determined using PCR amplification of DQA1 and DQB1 alleles from dried blood spots. Single-stranded DNA was hybridized with two sets of probes containing specific alleles. Samples positive for DQB1*02 were further analyzed for DQA1*02:01 and DQA1*05:01 alleles to separate subjects with DR7 from DR3. 'X' represents expected haplotypes due to linkage disequilibrium, and 'Z' represents haplotypes not tested. HLA-DQ genotypes were reported to the clinics on the remittance of each patient, including information on levels of islet autoantibodies as well as cumulative statistics.

In BDD2 (2011 onwards), DNA was extracted from EDTA-blood, and HLA typing was obtained by PCR-sequence specific primers (PCR-SSP), which distinguish different DRB1, DQA1, and DQB1-alleles. PCR-SSP for DQA1 *01, *02, *03, *04, *05, *06 and DQB1 *02, *03:01, *03:02, *03:03, *03:04, *05, *06, and *06:02 were used. PCR-sequence specific primers detecting the specific alleles DRB1 *01, *03/*11/*13/*14, *04, *07, *08/*12, *09, *10, and *15/*16 were also used to confirm risk alleles, though they are linked with known haplotypes together with

DQ2 and DQ8 due to linkage disequilibrium and to confirm results that are difficult to interpret. Information from the IMGT/HLA database, version 3.12.0, was used to find the DNA-sequences for the different primers to detect the HLA alleles.

Statistical analysis

The choice of statistical methods in each study was based on the research questions, the nature of the variables, and the underlying assumptions of the data. The studies employed a combination of descriptive statistics, hypothesis testing, and regression analyses to investigate the associations between various factors and the outcomes of interest.

In Study 1 which examined the impact of parental diabetes on the prevalence of childhood obesity, the relative risk (RR) and 95% confidence intervals (CIs) were calculated to assess the strength and precision of the associations. The chi-square test was used to determine significant differences between categorical variables, while the Student's t-test was used for continuous variables. A significance level of 0.05 was chosen, which is a widely accepted threshold in medical research, as it strikes a balance between type I and type II errors. Stratified analyses were performed to explore potential effect modification by factors such as the child's gender, field phase, maternal and paternal diabetes, and highest parental education level. All statistical calculations were performed using SPSS 11.0.5 software (SPSS, Inc., TX).

Study 2 investigated sex differences in age at diagnosis, autoantibody positivity, and HLA risk in children with T1D. Independent-samples t-tests were used for age at diagnosis, one-sample binomial tests for the proportion of boys/girls in separate age groups, logistic regression for autoantibody positivity, and ordinal regression for HLA risk. To account for multiple comparisons, a more conservative α level of 0.01 was used as an indicator of statistical significance, reducing the likelihood of type I errors. However, for analyses in separate age groups, where statistical power was lower, an α level of 0.05 was used to balance the risk of type I and type II errors. As boys have been shown to be older at T1D diagnosis, age at diagnosis was controlled for in all models where it was not the dependent variable. Statistical analyses were performed using SPSS 25 and R Studio 1.1.447 software.

In Study 3, which assessed the prevalence of parental diabetes among children with T1D and examined potential differences in clinical characteristics based on diabetes heredity, relative risk with 95% CIs was used to compare the prevalence of diabetes heredity between children with and without T1D, using the reference group from the ETICS study. Relative risk was also used to compare the presence of autoantibodies,diabetic ketoacidosis (DKA), and overweight or obesity at T1D diagnosis between children with and without a heredity of diabetes, presented for

the age groups 0–5.99 years, 6–11.99 years, and 12–17.99 years to minimize age-related differences. Analysis of variance (ANOVA) and the Kruskal-Wallis test were used to compare age at diagnosis and HbA1c levels between different heredity groups and age groups, respectively. The Bonferroni correction was applied to adjust for multiple testing in these analyses, reducing the likelihood of type I errors. Chi-square tests were used to compare HLA genotypes and the prevalence of diabetes among parents and grandparents, with a significance level of 0.05. Complete data on age, sex, and autoantibodies were obtained. The main analyses were repeated for the subgroup of participants with missing data for any variable, and results were similar to those of the main cohort. Patients with more than two missing variables were excluded (n=44).

The significance levels and adjustments for multiple comparisons in each study were chosen based on the balance between minimizing type I errors (false positives) and type II errors (false negatives), while considering the specific research questions and the nature of the analyses. The use of 95% CIs provided a measure of the precision of the estimates, allowing for the assessment of the statistical and clinical significance of the findings.

Ethical considerations

The BDD study was approved by the Regional Ethics Review Board at Karolinska Institute in Stockholm, Sweden (Dnr 2009/1684-32, Dnr 2006/1082-32, Dnr 04-826/1, and Dnr 2009/1684-32). Oral and written information about the study was provided to all potential participants and the parents and children gave informed consent to participate in the study. Study participants can opt out of the study at any time. (Papers II, and III).

The ETICS study was approved by the Regional Ethical Review Board of Umeå University, Umeå, Sweden. (Paper III, and I)

The ETICS study and the ethical reflection on conducting data sampling on a healthy population:

Conducting research involving children not in need of direct care, raises several ethical concerns. At this age, children are highly susceptible to bullying in school settings. Measuring weight or height could be a sensitive matter. Additionally, blood sampling is generally considered an unpleasant experience. Before approving such sampling and measurement of children, the ethical board carefully considered these and numerous other factors, ultimately concluding that the study's benefits outweigh the potential risks.

The study's results should not pose any harm to the participating individuals, as it is highly improbable to connect a specific result to a particular person and the data has been securely protected since completion of the study.

Methodological considerations

The strengths of the BDD study include the large, nationwide sample of children with newly diagnosed T1D, which allowed for comprehensive analyses of sex differences in clinical and immunological factors at disease onset. The use of standardized data collection methods and quality control measures, such as regular monitoring and feedback to maintain data integrity, ensured the reliability of the findings. However, the cross-sectional design of the study limits the ability to infer causality (Paper II).

The relatively small number of islet autoantibody-positive children may have reduced the statistical power to detect associations in some subgroup analyses (Paper II).

The inclusion of parental diabetes and obesity data in Papers I and III allowed for the exploration of potential associations between familial factors and the child's risk of T1D and related outcomes. However, the reliance on self-reported data for parental diabetes and the lack of detailed information on parental obesity may have introduced some measurement error or bias.

Results

Impact of parental diabetes on the prevalence of childhood obesity (Paper I)

Prevalence of overweight and obesity in children with parental diabetes

Children with parental T1D and children with parental T2D had a significantly higher prevalence of overweight and obesity (31%) compared to children without parental diabetes (21%, $p < 0.001$). The risk of being overweight or obese was significantly increased in children with parental T1D (RR 1.50, 95% CI 1.24-1.82) and in children with T2D (RR 1.48, 95% CI 1.20-1.82) compared to those without parental diabetes.

Sex-specific associations between parental diabetes and childhood obesity

Boys with parental T1D had a significantly higher risk of overweight and obesity compared to boys without parental diabetes (RR 1.61, 95% CI 1.28-2.04). Girls with parental T1D had a non-significantly higher risk of overweight and obesity compared to girls without parental diabetes (RR 1.32, 95% CI 0.95-1.84). Both boys and girls with parental T2D had a significantly higher risk of overweight and obesity compared to those without parental diabetes (boys: RR 1.48, 95% CI 1.11-1.95; girls: RR 1.51, 95% CI 1.12-2.04).

Role of parental education in the association between parental diabetes and childhood obesity

The highest prevalence of overweight was observed among children with parents with low education (31%, n = 519), whereas the lowest prevalence was found among children with at least one highly educated parent (17%, n = 5,496). Children with parental T1D and at least one highly educated parent had a higher risk of being overweight (RR 1.70, 95% CI 1.23-2.35) compared to their counterparts without parental diabetes. Parental education level did not significantly influence the

associations between parental diabetes and childhood overweight and obesity among children with parents with low education.

Sex differences in clinical and immunological factors at type 1 diabetes onset (Paper II)

Demographic characteristics

The study population consisted of 3,645 children with confirmed T1D, of which 55.9% (n = 2,037) were boys and 44.1% (n = 1,608) were girls. Girls had a significantly lower mean age at diagnosis compared to boys (9.53 ± 4.28 years vs. 10.23 ± 4.48 years, $p < 0.001$). The proportion of boys was significantly higher in the age groups 3-5 years (55.0%, $p = 0.017$), 12-14 years (62.0%, $p < 0.001$), and 15-17 years (64.0%, $p < 0.001$).

Islet autoantibodies

Girls had a higher prevalence of islet autoantibody positivity compared to boys (94.7% vs. 92.0%, age-adjusted OR = 1.529, 95% CI: 1.164-2.008, $p = 0.002$). The mean number of positive islet autoantibodies was significantly higher in girls than in boys (2.36 ± 1.09 vs. 2.21 ± 1.12, age-adjusted OR = 1.273, 95% CI: 1.131-1.432, $p < 0.001$). This difference remained significant even after excluding those without autoantibodies (age-adjusted OR = 1.201, 95% CI: 1.062-1.359, $p = 0.003$).

The prevalence of GADA was higher in girls than in boys (64.9% vs. 49.0%, age-adjusted OR = 2.041, 95% CI: 1.783-2.342, $p < 0.001$), with significant differences across all age groups ($p < 0.001$).

Boys had a marginally higher prevalence of IAA compared to girls (33.8% vs. 32.3%, age-adjusted OR = 1.197, 95% CI: 1.034-1.387, $p = 0.016$), but this difference was only significant among 15-17-year-olds ($p = 0.005$).

No significant sex differences were observed for IA-2A (72.9%) or ZnT8A (65.6%) positivity.

Older age at diagnosis was associated with a higher risk of GADA (sex-adjusted OR = 1.068, 95% CI: 1.051-1.084, $p < 0.001$) and ZnT8A (sex-adjusted OR = 1.043, 95% CI: 1.027-1.059, $p < 0.001$) and a lower risk of IAA (sex-adjusted OR = 0.854, 95% CI: 0.840-0.869, $p < 0.001$). Age at diagnosis was not associated with IA-2A ($p = 0.959$).

HLA genotypes

Sex differences in HLA risk were found in children aged 3-5 years and 6-8 years.

Boys aged 3-5 years had a higher prevalence of the high-risk HLA-DQ2/DQ8 genotype compared to girls (OR = 0.647, 95% CI: 0.427-0.979, p = 0.040).

Girls aged 6-8 years had a higher prevalence of the high-risk HLA-DQ2/DQ8 genotype than boys (OR = 1.442, 95% CI: 1.017-2.042, p = 0.040).

Older age at diagnosis was associated with a higher probability of being classified as having a low HLA risk (sex-adjusted OR = 1.058, 95% CI: 1.033-1.084, p < 0.001).

Parental diabetes and clinical characteristics at the child's type 1 diabetes onset (Paper III)

Prevalence of parental diabetes

Among children with T1D (n = 3,603), 8.4% (n = 303) had a parent with T1D, and 3.5% (n = 126) had a parent with T2D. In contrast, among children without diabetes (n = 11,050), 2.1% (n = 235) had a parent with T1D, and 1.9% (n = 206) had a parent with T2D. Children with T1D had a significantly higher prevalence of parental T1D (RR 3.93, 95% CI 3.03-5.11) and T2D (RR 1.88, 95% CI 1.27-2.76) compared to children without diabetes.

Association between parental diabetes and clinical characteristics

Children with parental T1D were significantly younger at diagnosis (mean age 9.2 ± 4.5 years, p < 0.0001) and had lower HbA1c levels (mean 84.7 ± 25.2 mmol/mol, p < 0.0001) compared to those with parental T2D (mean age 10.2 ± 4.1 years; mean HbA1c 88.9 ± 25.0 mmol/mol) or no parental diabetes (mean age 9.9 ± 4.4 years; mean HbA1c 92.8 ± 29.7 mmol/mol). Children with parental T2D had a higher risk of being overweight or obese compared to those without parental diabetes (crude RR 1.41, 95% CI 1.13-1.76). This increased risk was statistically significant in boys (RR 1.48, 95% CI 1.11-1.95) but not in girls (RR 1.34, 95% CI 0.95-1.88). Children with both parental type 1 and T2D had a lower risk of DKA at diagnosis compared to those without parental diabetes (RR 0.58, 95% CI 0.35-0.96).

Parental diabetes and islet autoantibodies

No significant associations were found between parental diabetes and islet autoantibody profile at T1D diagnosis.

Parental diabetes and HLA genotypes

No statistically significant differences were observed in HLA proportions between the children with parental T1D and those with parental T2D. Children with parental T2D were less likely to have the high-risk HLA-DQ2/DQ8 genotype compared to those without parental diabetes ($p = 0.02$).

Discussion

This dissertation aimed to mainly investigate the differences between sexes in the etiology of T1D but also the potential links between type 1 and T2D. The three articles included in this dissertation highlights a complex interplay between sex, heredity, overweight, and the clinical presentation of T1D in children.

Overview of the articles

Article 1: Parental Diabetes and the Risk of Overweight in Children

Article 1 examined the relationship between parental diabetes and the likelihood of being overweight in 12-year-old children. The study included a large, population-based sample of 11,050 children from various cities and environments in Sweden, ensuring a representative and diverse cohort. The findings indicated that having a parent with diabetes, regardless of the specific kind, was associated with an increased likelihood of children being overweight. The increased proneness to obesity in children with parents who have diabetes remained constant regardless of the parents' level of education, underscoring the potential impact of genetic variables on body mass index (BMI) in this particular group. This finding is particularly important, as it suggests that the impact of parental diabetes on childhood overweight may be independent of socioeconomic factors, which are known to influence obesity risk. The study's strengths include the large sample size, the population-based design, and the inclusion of children from diverse backgrounds, which enhance the generalizability of the findings. Nevertheless, it is important to acknowledge the limitations of this study, such as the absence of data regarding parental weight status and the use of questionnaire-based information for diagnosing parental diabetes. These limitations should be taken into account when interpreting the findings. The presence of these constraints may have resulted in the misdiagnosis of diabetes in certain family members, which could have impacted the observed relationships.

Article 2: Sex Differences in Age at Diagnosis, HLA Genotype, and Autoantibody Profile

Article 2 investigated the differences in age at diagnosis, HLA genotype, and autoantibody profile between boys and girls with recently diagnosed T1D. The research utilized a large group of children and adolescents with T1D from all around Sweden, ensuring a thorough and representative sample. The findings indicated that girls were diagnosed at a younger age and had a higher prevalence of glutamic acid decarboxylase antibodies (GADA) compared to boys. This observation aligns with prior research that has documented a higher occurrence of GADA positive in females. It emphasizes the potential influence of gender on the autoimmune mechanisms that contribute to the development of T1D. Furthermore, girls were more likely to be autoantibody-positive and have multiple autoantibodies at diagnosis, suggesting a more aggressive autoimmune response in females. These sex differences in autoantibody profiles may reflect differences in the immune system's response to the triggers of T1D in girls and boys. The study additionally discovered that the age groups showing a significant overrepresentation of boys at the time of T1D diagnosis (3-6 years and over 12 years) aligned with the age ranges in which boys were more prone to test negative for all autoantibodies. This observation may reflect the impact of puberty on the clinical onset of T1D, with increased insulin resistance and insulin demand potentially contributing to the sex differences observed in these age groups. Boys experience a greater rate of growth during puberty than females, which may make them more susceptible to acquiring T1D during this stage of life. Additionally, data from the general population of 12-year-olds in Sweden show that overweight/obesity is more common in prepubertal boys than in girls, which could further impact the risk of T1D in adolescent boys. The study's merits lie in its extensive, countrywide sample and its meticulous examination of sex differences in autoantibody profiles and HLA genotypes. These aspects offer important insights into the diverse nature of T1D and the potential influence of sex on the development of the disease. Nevertheless, the absence of data about pubertal status and BMI may be considered as constraints, as these variables could have impacted the observed disparities between sexes and the understanding of the findings.

Article 3: Heredity of Diabetes and Clinical Markers in Children at T1D Diagnosis

The study in Article 3 investigated the correlation between genetic predisposition for diabetes and clinical indicators in children after they were diagnosed with T1D. The study conducted a thorough analysis of the influence of familial diabetes history on the clinical manifestation of T1D by comparing a large sample of children with T1D to a reference group from the general population who were of comparable ages and born during the same time periods. The findings indicated a higher prevalence of genetic inheritance for both type 1 and T2D among children diagnosed with T1D,

as compared to healthy children. This finding indicates that there could be common genetic elements that contribute to both type 1 and T2D. Additionally, having a family history of diabetes may make individuals more prone to getting T1D. Children with heredity for T1D presented with diabetes at a younger age and had lower HbA1c at clinical onset, which may reflect a more aggressive disease course or increased awareness of diabetes symptoms among families with a history of T1D. On the other hand, children who have a genetic predisposition for T2D were diagnosed at a later age, had a higher likelihood of being overweight or obese, and had a lower likelihood of having the DQ2/8 HLA genotype, which is a recognized risk factor for T1D. These findings underscore the heterogeneity of T1D and the importance of considering familial diabetes history when assessing the clinical presentation of the disease. The higher prevalence of T2D heredity in children with T1D compared to 25 years ago suggests that heredity for T2D, along with overweight and obesity, may be contributing factors to the increased incidence of T1D in recent decades. This observation provides evidence for the accelerator hypothesis, which suggests that higher BMI can cause increased insulin resistance, leading to stress on the beta-cells and an elevated chance of developing T1D. The study's strengths include the large, nationwide cohort and the comparison to a general population reference group, which allows for a comprehensive assessment of the impact of familial diabetes history on the clinical presentation of T1D. However, the lack of a matched control group and the potential for misclassification of diabetes among family members are limitations to consider when interpreting the findings.

Connections between Diabetes heredity, Overweight, and Sex

Paper I, found a statistically significant association between parental T1D and overweight and obesity in boys (RR 1.61, 95% CI 1.28-2.04), while the association in girls was not statistically significant (RR 1.32, 95% CI 0.95-1.84). However, without further statistical analysis, it cannot be conclusively stated that the influence of parental T1D on childhood overweight and obesity is more pronounced in boys than in girls. Additional research is needed to explore potential sex-specific differences in this association. However, both boys and girls with parental T2D had a significantly higher risk of overweight and obesity compared to their counterparts without parental diabetes (boys: RR 1.48, 95% CI 1.11-1.95; girls: RR 1.51, 95% CI 1.12-2.04). This indicates that the association between parental T2D and childhood overweight and obesity is consistent across both sexes, which points to involvement of environmental and genetic factors not necessarily connected to the sex, for the child to be overweight (123-125). These children will despite their sex, have a relatively strong likelihood of receiving a T2D diagnosis, since two important

risk factors for receiving a T2D diagnosis in young age are OW/OB and a family history for the disease (126-129)

Type 1 Diabetes and Sex differences in proportion, age, HLA and autoantibodies

Paper II confirm the proportion of boys/girls with T1D and the male predominance in T1D onset is most pronounced in older children, specifically in adolescents, as reported by a Finnish study which is the only prior study using a comparable sample size to examine sex differences in pediatric T1D (2). Our results further add that an increased rate of boys in the 3-6-year-old group is specifically also seen. This further overlaps with our findings of 3-6-year-old boys (and 6-9-year-old girls) being more likely to have high-risk HLA. We consider these findings preliminary and in need of replication because of the small groups these subset analyses made up.

Further, the age groups with a clear overrepresentation of boys at T1D diagnosis (3-6 years, and above 12 years of age) also coincide with the age groups where boys were more likely to be negative for all autoantibodies. It is possible that the impact of different exposures varies with sex, which is mirrored in these groups where boys are overrepresented, demonstrate a high HLA risk, and also commonly lack autoantibodies. For example, pubertal growth velocity is higher in boys compared to girls during puberty, which may contribute to their increased vulnerability to develop T1D during puberty. Further, paper I showed that overweight/obesity is more common in prepubertal boys than in girls, which could also impact risk of T1D in adolescent boys. This hypothesis is supported by recent publications showing an association between increased growth and beta cell autoimmunity (130, 131) and between increased BMI and risk of T1D (132-135). In conclusion, the sex difference in prevalence shown in 3-6-year-olds remains unclear and needs to be further studied and confirmed in other populations. It is worth adding that HLA-risk was not associated with sex or age at diagnosis in relation to positivity/negativity for any of the autoantibodies in paper II.

The mean age at diagnosis was lower for girls than boys in paper II, which is also in line with results from previous studies (136, 137). This could partly reflect the fact that pubertal onset is earlier in girls, with elevated levels of growth hormones and sex steroids increasing insulin resistance and insulin demand. This is also consistent with earlier findings from Sweden, where girls diagnosed with T1D in these ages were shown to have a higher C-peptide than age-matched boys (105). Interestingly, the mean age at T1D diagnosis in our study was about two years higher than in the study from Finland discussed above (1). However, the Finnish study only included children under 15 years of age. To be able to make a direct comparison, we excluded all participants in our sample that were over 15 years of

age at T1D diagnosis (results not reported), and still found that the mean age at T1D diagnosis was about one year higher than the mean age reported in the Finnish study. It is possible that the lower age at onset in the Finnish population may reflect exposure to more aggressive genetic and/or environmental risk factors, as this country has the highest prevalence of T1D in the world (138).

Circling back to positivity/negativity for any of the autoantibodies, paper II showed that girls were positive for a higher number of autoantibodies than boys at diagnosis of T1D, which is consistent with earlier reports (139-141), but this has not been found in all studies (2). As shown in previous studies based on the BDD cohort (142, 143), 6.8% of the participants were not positive for any of the analyzed autoantibodies. In the present study, boys were more likely than girls to be autoantibody negative compared to girls. Studies from other countries, which have included a limited number of individuals with T1D, have shown that 2.3-9.3% of children and adolescents with T1D are negative for autoantibodies when analyzing for at least GADA, IA2A, and IAA (144-146). In line with our results, these studies also show that autoantibody negativity is more common in boys than in girls. In the only study with a comparable sample size to ours (2), no sex differences with respect to the number of autoantibodies were present, and this study also showed a slightly lower overall prevalence of autoantibody negativity in children with T1D (5.1% compared to 6.8% in the present study). We found no association between age at T1D diagnosis and autoantibody negativity.

Overall, paper II showed us that girls have more autoantibodies when diagnosed with T1D and have an earlier diagnosis which may reflect a more aggressive disease. However, boys with fewer autoantibodies seem to be more prone to develop diabetes than girls and more boys with a T1D diagnosis lack autoantibodies. Therefore, we think that the earlier onset of T1D in girls is more likely to be due to an earlier puberty enhancing the clinical onset than an increased number of autoantibodies. Countries with a high incidence of T1D show a male dominance of the disease regardless of the increased incidence of diabetes. We therefore consider if differences in the autoantibody pattern between the sexes is also influenced by differences in susceptibility for new environmental triggers the last decades.

Implications for Understanding Sex Differences and Links Between Type 1 and Type 2 Diabetes

The findings of these three articles collectively support the existence of sex differences in the etiology and clinical presentation of T1D. The results highlight the complex interplay between genetic susceptibility, environmental factors, and metabolic changes in the development of T1D and underscore the potential links between type 1 and T2D. The observed differences in autoantibody profiles and age

at diagnosis between sexes indicate that the immune system may exhibit distinct responses to the causes of T1D in females and males. This understanding is crucial for developing targeted prevention and intervention strategies for children at risk of developing T1D. For example, the identification of sex-specific risk factors and biomarkers could facilitate the development of personalized screening and prevention programs, which may improve the early detection and management of T1D in children.

Moreover, the increased prevalence of parental T2D may support the accelerator hypothesis, which proposes that increased insulin resistance due to higher BMI may lead to beta-cell stress and an increased risk of developing T1D. This finding highlights the importance of considering the interplay between genetic susceptibility, environmental factors, and metabolic changes in the development of T1D. Future research should focus on further elucidating the mechanisms underlying these sex differences and the potential links between type 1 and T2D. This may involve investigating the role of hormonal changes during puberty, the impact of environmental exposures on the immune system, and the genetic and epigenetic factors that contribute to the development of T1D. A better understanding of these factors may lead to the development of more effective prevention and treatment strategies for children at risk of developing T1D.

Sex differences in Type 1 Diabetes and parental diabetes

The results from paper III underscored the link between parental diabetes and the likelihood of children developing T1D, with some notable differences between boys and girls. The study found that children diagnosed with T1D had a higher probability of having a parent with the same condition compared to children without diabetes. This relationship was evident in both male and female children, implying that the impact of parental T1D on a child's risk of developing the disease is not dependent on the child's sex. Moreover, these findings corroborate previous research indicating a higher prevalence of diabetes heredity among children with T1D (147-149). Dahlquist et al.'s earlier Swedish study demonstrated that heredity for either type 1 or T2D was more prevalent in children with T1D compared to a healthy control group (148). However, while the prevalence of parental heredity for T1D was comparable to our study, heredity for T2D was more common in our research than it was 25 years ago (2.5% vs 1.7%). This suggests that children with T1D are more likely to have a family history of T2D today, although this could also be a reflection of the increasing prevalence of T2D in the general population in recent years. We hypothesize that heredity for T2D, along with overweight and obesity, are risk factors for the development of T1D and have contributed to its rising incidence over the past few decades.

Furthermore, the study revealed that children with T1D were more likely to have a parent with T2D compared to children without diabetes. This association was observed in both girls and boys, suggesting that heredity for T2D elevates the risk of T1D in both sexes or that there may be shared genetic risk factors. Heredity for T2D was linked to overweight and obesity, but only among boys. Previous research has shown that more men develop T2D at a lower BMI than women (150). While other studies have identified increased BMI as a risk factor for T1D (90, 151-153), potential sex differences have not been explored. Based on our study's findings, we speculate that boys might be more susceptible to developing T1D if they are overweight or obese. We have previously reported that an increased BMI in combination with low-risk HLA DQ2.5/DQ2.5 is associated with a higher risk of T1D, supporting the notion that obesity associated with genetic susceptibility can be a risk factor for T1D (154). These findings may support the accelerator hypothesis, which posits that high BMI leads to increased insulin resistance, resulting in β-cell stress and an increased risk of developing T1D (90, 155). A crucial question is whether heredity for T2D alone, or in combination with other immunological factors such as increased weight or sex, heightens the risk of beta cell destruction.

Our study confirms earlier findings that heredity for T1D is more common on the paternal side than the maternal side of the family of children with T1D (148, 156, 157), and this was also observed for heredity for T2D. Similarly, Parkkola et al. showed that children with T1D were more likely to have a father or grandfather with T2D than a mother or grandmother (152). The reason why paternal heredity seems to increase the risk of developing T1D compared to maternal heredity remains unclear.

Potential Biological Mechanisms Underlying Sex Differences in Type 1 Diabetes

The observed differences in the incidence, clinical manifestation, and risk factors of T1D between males and females indicate the presence of distinct biological pathways that impact males and females in different ways. Although the precise mechanisms are not yet fully understood, recent research has shed light on probable elements that may contribute to these sex differences.

An important field of research focuses on the involvement of sex hormones in the development of T1D. Research has demonstrated that estrogens can provide protection to pancreatic β-cells, potentially by activating estrogen receptor α (ERα) (158). Studies conducted on both human and genetic mice models have demonstrated that estrogen possesses antidiabetic properties (159). Additionally, research has indicated that estrogen replacement therapy can enhance insulin

sensitivity in postmenopausal women (160, 161). Testosterone has been documented to possess protective properties against autoimmune disorders, maybe via inhibiting the production of pro-inflammatory cytokines (162). The complex interplay between sex hormones and the immune system may contribute to the sex-specific risk of developing T1D and the differences in clinical presentation between males and females.

As stated earlier, another possible explanation involves disparities between males and females in the gut microbiota, which has been linked to the onset of T1D (163). Research has demonstrated that there are variations in the makeup of the gut microbiome between males and females (164). These changes have the potential to impact the likelihood of developing autoimmune illnesses, such as T1D. For example, alterations in the gut microbial composition have been associated with GADA positivity in children with T1D (165). Additional investigation is required to comprehend how sex-specific disparities in the gut microbiome may influence the varying susceptibility and development of T1D in males and females.

Epigenetic factors may contribute to the sex differences reported in T1D. Both DNA methylation and histone alterations can impact gene expression and have been linked to the onset of autoimmune disorders (166). Sex-specific epigenetic alterations have been documented across several organs, including pancreatic islets (167). These epigenetic differences may contribute to the differential expression of genes involved in insulin secretion, immune regulation, and β-cell survival between males and females. Further studies are needed to investigate the role of sex-specific epigenetic modifications in the pathogenesis of T1D and how they may be influenced by environmental factors.

Moreover, variations in the immune system across sexes may play a role in the varying susceptibility and clinical manifestation of T1D. Females generally exhibit a more strong immune response compared to males, which may increase their susceptibility to autoimmune diseases (168). The increased immune response in females may be affected by sex hormones, genetic factors, and environmental exposures. Understanding the mechanisms underlying sex differences in immune regulation may potentially provide insights into the pathogenesis of T1D and guide the development of sex-specific prevention and treatment strategies, though further research is needed to establish direct links.

Potential Mechanisms Underlying Sex Differences in Autoantibody Profile

The mechanisms underlying the observed sex differences in the autoantibody profile of T1D are not fully understood but may involve a complex interplay of genetic, hormonal, and environmental factors. Estrogens and androgens, which are sex hormones, have been demonstrated to regulate the immune system and perhaps play

a role in the gender disparity observed in autoimmune illnesses (169). Estrogens exhibit dual effects on inflammation, with both pro-inflammatory and anti-inflammatory actions, which are contingent upon the concentration, receptor subtype, and specific target cell (170). Estrogens have demonstrated a protective effect against β-cell apoptosis and insulin-deficient diabetes in animal models of autoimmune diabetes (171). Androgens, on the other hand, have been reported to have protective effects on autoimmune diseases, possibly by suppressing the production of pro-inflammatory cytokines (162).

Environmental variables, such as nutrition, infections, and microbiome composition, may also affect the variations in the autoantibody profile of T1D between sexes (163). For instance, the study conducted by Turtinen et al. found that males have a higher occurrence of IAA (2). This could be attributed to variations in baby feeding methods, as early consumption of cow's milk proteins has been linked to a greater likelihood of IAA positive (36). The increased prevalence of GADA in females may be attributed to sex-related disparities in the gut microbiome, as changes in the composition of gut microbes have been connected to GADA positive in children with T1D (172).

Strengths and Limitations

While this dissertation provides valuable insights, it is essential to acknowledge and address the limitations of the included studies. These limitations may impact the generalizability and interpretation of the findings and highlight potential avenues for future research.

One limitation of Studies 1 and 3 is the reliance on self-reported data. This may be subject to recall bias or misclassification, potentially leading to an underestimation or overestimation of the true associations between parental factors and childhood diabetes and obesity. It should be considered to use objective measures, such as medical records or direct diagnostic testing, in future studies to confirm parental diabetes status and minimize the risk of misclassification.

Another limitation is the cross-sectional design of Studies 1 and 2, which precludes the establishment of causal relationships between the investigated factors and the development of T1D and obesity. While the findings suggest associations, the temporal sequence of these factors cannot be determined. A prospective cohort study which follows children from birth to the onset of T1D and may assess the influence of sex and parental factors over time and could provide additional strength in evidence for causal relationships and help identify potential mechanisms underlying the observed associations.

The lack of data on pubertal status and BMI in Study 2 may have limited the ability to fully explore the potential influence of these factors on the observed sex differences in autoantibody profiles and HLA risk genotypes. Future studies can possibly collect detailed information on pubertal development and body composition to better understand how these factors may interact with sex and contribute to the heterogeneity of T1D in children.

The generalizability of the findings may also be limited by the specific characteristics of the Swedish population studied. While Sweden has one of the highest incidence rates of T1D worldwide, the associations observed in this population may not be directly applicable to other geographical regions or ethnic groups with different genetic backgrounds as well as environmental exposures. A collaborative international study that would include diverse populations could help validate the findings and explore potential variations in sex differences globally.

Clinical Implications

The findings of this dissertation have important clinical implications for the screening, prevention, and management of T1D and obesity in children. The observed sex differences in the incidence, clinical presentation, and risk factors for T1D highlight the need for sex-specific approaches to the prevention and early detection of this chronic condition.

The findings also underscore the importance of considering family history and parental diabetes status in the risk assessment and management of T1D in children. Children with a family history of T1D, particularly those with affected fathers or paternal grandparents, may benefit from closer monitoring and more aggressive prevention strategies. This could include education on the signs and symptoms of T1D, regular screening for islet autoantibodies, and counseling on lifestyle factors that may influence disease risk, such as diet and physical activity.

Furthermore, the association between parental T2D and increased risk of overweight and obesity in children, particularly boys, highlights the need for targeted interventions to prevent and manage obesity in this population. Healthcare providers should routinely assess the weight status and body mass index of children with a family history of T2D and provide appropriate counseling on healthy eating habits, regular physical activity, and strategies for maintaining a healthy weight. Family-based interventions that involve both parents and children may be particularly effective in promoting sustainable lifestyle changes and reducing the risk of obesity and related metabolic disorders.

The sex differences observed in the autoantibody profiles and HLA risk genotypes of children with T1D suggest that sex-specific approaches to disease management

may also be warranted. Girls with T1D, who were found to have a higher prevalence of GADA positivity and a more aggressive autoimmune profile, may require closer monitoring for the development of other autoimmune conditions and may benefit from closer insulin therapy monitoring to achieve optimal glycemic control.

Potential Future Research Directions

Although the dissertation offers valuable insights into the sex differences in T1D and obesity, the precise processes behind these differences have yet to be completely understood. Future research is needed on investigating the biological pathways that may contribute to these differences, such as the role of sex hormones. Experimental studies in animal models could help to unravel the complex interplay between sex, genetics, and environmental factors in the pathogenesis of T1D and obesity.

Thesis Conclusion

This thesis, comprising three studies, provides insights into the complex interplay between sex, parental diabetes, and the development of T1D in children. The findings underscore the importance of considering sex-specific differences and familial factors in the etiology and clinical presentation of T1D.

Study I revealed that boys with parental T1D had an increased risk of being overweight compared to their peers without parental T1D, while both boys and girls with parental T2D had an elevated risk of being overweight regardless of socioeconomic status. These findings suggest that sex and the type of parental diabetes may differentially influence the risk of childhood obesity, which is a known risk factor for T1D.

Study II highlighted significant sex differences in the clinical and immunological characteristics of children at T1D diagnosis. Girls exhibited an earlier onset of symptoms and a higher prevalence of autoantibodies, particularly GADA, while boys were more likely to test positive for IAA. Additionally, sex-specific differences in HLA risk factors were observed among children under 9 years of age. These findings emphasize the heterogeneity of T1D and the potential role of sex in shaping the immune response and genetic susceptibility to the disease.

Study III showed an increased prevalence of parental T1D and T2D in children with T1D compared to healthy controls. Heredity for T2D was linked to overweight and obesity, but only among boys, suggesting potential sex-specific effects of parental diabetes on T1D risk factors in children. These findings support the accelerator hypothesis, which proposes that high BMI leads to increased insulin resistance, resulting in β-cell stress and an increased risk of developing T1D. The study also confirmed that heredity for both T1D and T2D is more common on the paternal side.

Collectively, these studies highlight the importance of considering sex and parental diabetes status in the understanding of T1D pathogenesis and clinical presentation. The findings support the notion that T1D is a heterogeneous disease, with sex-specific differences in immune response, genetic susceptibility, and the influence of parental diabetes on obesity risk. These insights may have implications for the development of personalized screening strategies, preventive interventions, and disease management approaches tailored to the individual characteristics of children at risk for or diagnosed with T1D.

Future research should focus on further elucidating the biological mechanisms underlying these sex-specific differences and the potential interactions between genetic, immunological, and environmental factors in the pathogenesis of T1D.

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