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Diabetes Mellitus Type 1 in Adolescents: A Narrative Review

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Abstract

Diabetes mellitus type 1 is the most common type of diabetes seen in children and adolescents. It is a chronic autoimmune condition in which the insulin producing pancreatic ß-cells are destroyed resulting in hyperglycemia due to absolute insulin deficiency. patients usually present with polydipsia, polyuria, polyphagia, and weight loss. Rapid diagnosis is essential to prevent metabolic decompensation to diabetic ketoacidosis which could be fatal. There is no cure, but a life-long self-management is required. This could be challenging as daily monitoring of the blood glucose levels is needed with insulin replacement therapy. Poor adherence and resultant poor control could have a negative impact on the psychology and physical well-being of the adolescent. An integrated team of health professionals should work with the adolescents and their families to educate them about the disease, management and the challenges that come with it. As diabetes is a progressive disease that goes through several stages before the actual onset of symptoms, several ongoing studies and trials show promising results in some interventions that could prevent disease progression and maintain functional ß-cells in the future.

Keywords*: Type 1 Diabetes, Adolescents, Juvenile Diabetes, Management, Chronic Disease.*

Introduction

Diabetes is a chronic disease that is classified into many types **(**Tan et al., 2019**)**. According to the IDF, there are currently 537 million adults living with diabetes and by 2045, this number is expected to reach 784 million **(**IDF, 2021**)**. The most common diabetes type is the type 2 diabetes **(**T2D**)** which involves insulin resistance and reduced insulin production **(**Tan et al., 2019**)**. The second most common type accounting only for 10% of the cases is the type 1 diabetes **(**T1D**)**, which is more common among the young and it affects more than 1.1 million diabetics under 20 years of age globally **(**IDF, 2021**)**. In T1D a chronic autoimmune destruction of the pancreatic ß-cells occurs as a result of a complex interplay between genetics, microbiome, environmental factors and the immune system. It is not solely an autoimmune disease, but recent findings suggest that it is also a disease of the ß-cells itself **(**Brawerman & Thompson, 2020**)**. This destruction leads to insulin deficiency which is normally

produced by the ß-cells (Tan et al., 2019). T1D does not have a cure, it requires a lifelong self-management with several daily tasks such as measuring the blood glucose levels frequently to ensure that it is within the required range and also making sure that insulin injections are being taken when needed. This could be very challenging especially for adolescents who lead a considerably busy lifestyle and spend lots of time at school or in other social contexts (Morrissey et al., 2021). Fear of stigmatization could affect the psychology of the adolescents negatively (Liu et al., 2017). Hence a multidisciplinary team is assigned to an adolescent upon diagnosis, to educate the adolescent about the disease, the treatment, the importance of exercise and nutrition in management, ways to deal with any stress and some coping mechanisms (Delamater et al., 2018). T1D diabetes is classified into 3 distinct stages. Patients presenting to the doctor with the classical symptoms and signs of T1D including polydipsia, polyuria and high blood glucose levels, are already in the 3rd stage of the disease and the only thing that can be done is initiating the insulin replacement therapy. However, studies discovered that it is possible to identify T1D in earlier stages by detecting islet related autoantibodies and high-risk genes in the individual and ongoing studies are trying to find proper interventions or preventions that could be done in these earlier stages to control the disease before it progresses to the 3rd symptomatic stage (Akil et al., 2021). In this review we will take about how T1D could be challenging for adolescents and what updates have been made in the pathogenesis and prevention of T1D.

Methods (Search Strategy)

This narrative review on T1D in adolescents was conducted by searching EBSCO, Medline, Pubmed and UNIC library for articles published only in the last 5 years in the English language. The keywords used were: “T1D”, “adolescents”, “T1D management”, “psychoeducation”, “stigma”, “prevention”. Advanced search was done and the used Boolean operators were: “type 1 diabetes or t1d or diabetes mellitus or juvenile diabetes or insulin-dependent diabetes” AND “adolescents or teenagers or young adults or teen or youth” AND “management or treatment or intervention or therapy”.

Body

Disease Presentation

T1D in children presents with the classical signs and symptoms of polyuria, polydipsia, polyphagia, weight loss, fatigue, glycosuria, ketonemia and blurred vision (Chiang et al., 2018). Some additional symptoms include shortness of breath, abdominal pain, vomiting and impaired general state of health (Ziegler & Neu, 2018). It is imperative to diagnose T1D as early as possible and start treatment to

prevent rapid deterioration of the metabolic state, known as diabetic ketoacidosis (DKA). DKA is the leading cause of morbidity and mortality in children with diabetes. Unfortunately, the number of cases presenting with DKA at or near diagnosis is increasing at a rate of 2% per year (Jensen et al., 2021). DKA occurs when the insulin concentration is so low that glucose can't enter the cells of the body. The liver then starts to break down fat resulting in the production of ketones to be used as energy. These ketone acids build up and cause symptoms including severe thirst, frequent urination, kussmaul breathing, dehydration, fruity-smelling breath, vomiting, stomach pain and muscle pain (Wolfsdorf et al., 2009).

Some of the common mistakes that delay diagnosis include confusing the kussmaul breathing of ketoacidosis with asthma or pneumonia, the abdominal pain could be misdiagnosed as appendicitis, vomiting could be thought to be gastroenteritis or sepsis, polyuria may be misdiagnosed as urinary tract infection and obese patients misdiagnosed as having type 2 DM (Couper et al., 2018)

Diagnosis

In symptomatic children, a random plasma glucose ≥200 mg/dl is enough to confirm the diagnosis (table 1). However, having hyperglycemia without any other symptoms does not indicate diabetes, as hyperglycemia can occur in acute illnesses. Also, it's important to not solely rely on a single sign to make the diagnosis. For example, glycosuria (in the absence of other signs) could be caused by a low renal glucose threshold (Chiang et al., 2018).

when it comes to screening asymptomatic children that are at high risk for T1D, a fasting plasma glucose (FPG) ≥126 mg/dl, or a 2-hour plasma glucose (2-h PG) ≥200 mg/dl, or A1C ≥6.5% would confirm the diagnosis only if the test is repeated with a new blood sample on another day, and similar results are obtained. It is preferred to repeat the same exact test. However, using two different tests could also confirm the diagnosis (Chiang et al., 2018). A1C has some advantages over the others, as there is no fasting, less affected by stress or illness and has greater preanalytical stability. But because A1C measures the average blood glucose levels indirectly, several factors and conditions like age, race, pregnancy and hemoglobinopathies can affect the hemoglobin glycation independent of glycemia hence FPG or 2-h PG should be used in patients with marked discordance between the measured A1C and plasma glucose values. The FPG and 2-h PG blood samples should be centrifuged immediately after being drawn to prevent preanalytical variability (ADA, 2021a).

Distinguishing T1D from T2D in overweight patients could be difficult. Hence islet autoimmunity, family pedigree and plasma or urine C-peptide levels should be measured. Positivity for islet autoantibodies always confirms T1D **(**Chiang et al., 2018**)**.

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 1.75 g/kg up to a maximum of 75 g anhydrous glucose dissolved in water.*

OR

A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified† and standardized to the DCCT assay.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG ≥200 mg/dL (11.1 mmol/L).

Definitions are based on venous PG levels. WHO, World Health Organization. *In the absence of unequivocal hyperglycemia, the first three criteria should be confirmed by repeat testing. †See www.ngsp.org.

(*Chiang et al., 2018****)***

Table 1- diabetes diagnosis criteria

Epidemiology

Globally, T1D is increasing in both incidence and prevalence with an annual incidence increase of 2-3%. T1D accounts for 5-10% of individuals with diabetes. According to the international diabetes federation **(**IDF**)** 1.110,100 children and adolescents younger than 20 were diagnosed with T1D In 2019 **(**IDF, 2021**)**. Overall, approximately 128,900 children and adolescents under 20 years of age are estimated to develop T1D annually worldwide. T1D accounts for more than 90% of childhood and adolescent diabetes in most western countries **(**Mayer-Davis et al., 2018**)**. According to the CDC, in 2018, 26.9 million people were diagnosed with diabetes in the US. For diabetes patients under 20 years of age **(**210,000 patients**)**, the vast majority were diagnosed with T1D **(**187,000 patients**) (**CDC, 2018**)**. T1D is more common in males than females **(**Mayer-Davis et al., 2018**)**. The rapid and dramatic increase in T1D incidence globally especially in those who are not genetically susceptible, implies that environmental factors also play an important role in T1D **(**Xia et al., 2018**)** Acute diabetes complications such as DKA and hypoglycemia were the leading cause of mortality in young patients with T1D. however, in older patients the mortality is mainly due to the late complications of the disease such as renal and cardiovascular diseases. Patients diagnosed with T1D during their first 15 years of life have 3 folds increased mortality risk compared to the general population **(**Morgan et al., 2017**)**.

Pathophysiology

T1D is a chronic multifactorial metabolic disease. It is caused by a complex interaction between genetics, environmental factors, microbiome, and the immune system, that differ between individuals

hence contributing to the clinical heterogeneity of T1D. The specific roles of these factors are not fully understood yet **(**Mayer-Davis et al., 2018**)**.

Islet autoimmunity and T1D stages:

Autoimmune T1D, also known as type 1A diabetes, occurs due to the progressive autoimmune destruction of the insulin producing pancreatic ß-cells **(**Brawerman & Thompson, 2020**)**. The destruction rate varies among individuals. Upon the loss of more than 90% of the ß-cells, the clinical symptoms appear **(**Mayer-Davis et al., 2018**)**. On the other hand, in the type 1B diabetes, known as idiopathic or nonautoimmune, beta cell loss and insulin deficiency occur without autoimmunity. However, this type is rare **(**Brawerman & Thompson, 2020**)**.

T1D can be diagnosed way before the onset of its classical symptoms. This is the clinically silent phase in which islet cell autoimmunity, ß- cell dysfunction and glucose intolerance are developing. The duration of this phase varies greatly among individuals and can last from several months to decades **(**Akil et al., 2021**)**. Islet autoimmunity occurs in genetically susceptible people after being exposed to triggering environmental factors **(**Klak et al., 2020**)**. Following the onset of autoimmunity, the progression towards the clinical manifestation of T1D can be classified into three distinct stages **(**table-2**)**; Stage 1: Asymptomatic, Normoglycemia and ß-cell autoimmunity with 2 or more autoantibodies such as islet cell antibodies **(**ICA**)**, insulinoma-associated proteins **(**IA-2A and IA-2β**)**, zinc transporter 8 **(**ZnT8A**)** and GAD65 **(**GADA**)**. Stage 2: Asymptomatic, dysglycemia, due to loss of function of the ß- cell mass, and ß-cell autoimmunity with 2 or more autoantibodies. Stage 3: symptomatic, dysglycemia and autoimmunity **(**Akil et al., 2021**)**. In t1D, there is decreased regulatory immune function and increased frequency of the autoreactive cytotoxic CD8+ T lymphocytes and to a lesser extent CD4+T cells which are responsible for the ß-cell destruction **(**Dimeglio et al., 2018**)**.

	Stage 1	Stage 2	Stage 3
Stage	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• ≥2 autoantibodies • No IGT or IFG	• ≥2 autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

(**Chiang et al., 2018**)

Table 2- Staging of type 1 diabetes

Genetics:

T1D is heritable and polygenic. the human leukocyte antigen **(**HLA**)** genotype confers approximately 50% of T1D risk **(**Couper et al., 2018**)**. The haplotypes with the highest risk are the HLA-DR4-DQ8 and HLA-DR3-DQ2 which are associated with IAA and GAD primary islet autoantibodies respectively **(**Klak et al., 2020**)**. Interestingly, the HLA-DR15-DQ6 haplotype reduces the T1D risk **(**Mayer-Davis et al., 2018**)**. In addition, more than 60 non-HLA genes have been identified that also contribute to T1D risk. These genes which are the CTLA4, INS, PTPN22 and IL2RA, contribute to the immune system and affect pathways involved in disease development like the expression of insulin gene in the thymus and regulation of T-cell activation. Forming risk scores from the HLA and non-HLA genes enables an enhanced risk prediction for developing T1D and allows discrimination between T1D, T2D and the monogenic diabetes. T1D has an identical twin concordance of 30-70%, sibling risk of 6-7% and children who have a parent with diabetes, 1-9% risk **(**Mayer-Davis et al., 2018**) (**Dimeglio et al., 2018**)**.

Environmental factors:

The role of the environmental components became more evident when the incidence of T1D increased in individuals with low genetic risk and in genetically similar populations that are separated by socioeconomic borders **(**Dimeglio et al., 2018**)**. Viral infections including the enterovirus, rubella and mumps accelerate T1D clinical onset due to the increased insulin demand. The viruses were detected in the islets of diabetics. Low gut-microbiome diversity could be a factor as the microbiota has a role in immune system development. Obesity could increase T1D risk in children with low-risk HLA genotypes. Low levels of vitamin D or omega 3 fatty acids are associated with an increase in T1D **(**Ilonen et al., 2019**)**.

ß-cell dysfunction:

New evidence suggest that T1D is not just an autoimmune process, but it is a disease of the beta cells as well, both contributing to T1D pathogenesis **(**Brawerman & Thompson, 2020**)**. Endoplasmic reticulum **(**ER**)** in the ß-cells is very important in producing and folding proteins such as insulin. An increase in insulin demand can impose stresses on the ER leading to its decompensation or stress. This stress stops the ER from producing and processing the proteins efficiently, leading to unfolded protein

accumulation and eventually cell apoptosis and death (Sims et al., 2020). In addition, ß- cells overexpression of HLA class I acts as a signal for cytotoxic T lymphocytes leading to their destruction, however whether this overexpression occurs as a primary ß-cell defect or if it is secondary to a stimulus like a viral infection is not yet known (Dimeglio et al., 2018).

Management

It is imperative to start insulin treatment immediately after establishing the diagnosis to prevent metabolic decompensation and DKA (Danne et al., 2018). In addition, an integrated healthcare team composed of a pediatric endocrinologist, diabetes nurse educator, dietician, social worker, and mental health professional should be assigned to the adolescent and their family to educate them about insulin injection, blood glucose monitoring, nutrition, physical activity and hypoglycemia. The goal is to achieve optimal metabolic control, prevent acute or long-term complications and improve psychological aspects of the adolescents and their family (Wherrett et al., 2018).

Insulin therapy ang glycemic targets:

insulin is needed for T1D survival. Intensive insulin replacement therapy is used to stimulate the normal physiological insulin secretion patterns. Normally, there is an increased secretion after meals (postprandial) and decreased secretion overnight or when fasting (Chiang et al., 2018). Insulin regimen should be tailored depending on the adolescent's age, lifestyle, school support, socioeconomic factors, glycemic target, and preferences. This individualization minimizes hypoglycemia, enables A1C target achievement, and enhances the quality of life. There are two intensive insulin regimes, either the basal-bolus where long-acting basal insulin and rapid-acting bolus insulin is given, or the continuous subcutaneous insulin infusion (CSII) which is also known as insulin pump (Wherrett et al., 2018). Some studies suggest that the usage of CSII in adolescents in associated with lower A1C levels, lower hypoglycemia rates, better life quality and higher treatment satisfaction (Chiang et al., 2018). The insulin dose should be frequently adjusted for ingested carbohydrates, illness, physical activity or stress (Dimeglio et al., 2018). The typical maintenance total daily doses of insulin is 1) less than 0.5 units/kg/day during the partial remission "honeymoon" phase, 2) 0.7 to 1 units/kg/day for prepubertal children and, 3) 1 to 2 units/kg/day during puberty. Detemir, glargine and NPH are examples of basal insulins which provide insulin to maintain euglycemia between meals and overnight. Prandial insulins which are given to control the high glucose after meals, include aspart, lispro and glulisine insulins (Danne et al., 2018). The only drug that has been approved to be used as an adjunct therapy in

adolescents is metformin which is primarily used for insulin resistance during puberty and in obesity. Its usage is associated with weight loss, decreased insulin needs and cardiovascular disease (Chiang et al., 2018).

According to the ADA, the recommended target HbA1c value for adolescents is <7% (53mmol/mol). A1C targets must be reassessed over time (ADA, 2021b) and are individualized by taking factors such as comorbidities, lifestyles issues, patient age, hypoglycemia unawareness and level of supervision are taken into consideration (Chiang et al., 2018). For example, more relaxed targets like <7.5% (58mmol/mol) or <8% (64mmol/mol) could be set for patients with hypoglycemia unawareness or history, or for those do not have access to most recent insulin delivering or glucose monitoring devices. More strict targets, <6.5% (48mmol/mol), could be set for patients who are able to achieve it without hypoglycemia or other negative impacts (ADA, 2021).The target value should be reached by aggressive attempts to achieve the optimum metabolic control. To assess the overall glycemic control, A1C should be measured every 3 months in adolescents (Wherrett et al., 2018).

Blood glucose and ketone monitoring:

Patients with T1D should monitor their blood glucose, HbA1c and ketone levels. The most common approach is the manual capillary blood glucose measurement by the patient (Self-monitoring of blood glucose, SMBG) which is recommended to be done multiple times daily (6-10 times/day), and to be measured before bedtime, exercise, meals, driving, and when hypoglycemia is suspected (Chiang et al., 2018). Blood glucose target before meals in adolescents is: 90-130 mg/dL (5.0–7.2 mmol/L), the bedtime/ overnight target is: 90–150 mg/dL (5.0–8.3 mmol/L) (ADA, 2021) and before exercise it should be: 90 to 250 mg/dL (5-13.9 mmol/L) (13. Children and Adolescents: Standards of Medical Care in Diabetes-2019.2019). Better clinical outcomes were seen in patients with increased frequency of SMBG (Wherrett et al., 2018). However, nowadays especially in adolescents, continuous glucose monitoring (CGM) which every 2-3 minutes measures the interstitial glucose concentration via a subcutaneous sensor and transmits the results to a readout device, should be considered (Ziegler & Neu, 2018). CGM is advised to be used in patients regardless of which insulin regimen (basal- bolus or insulin pump) is used. Adherence to CGM usage could result in lower A1C levels. Blood or urine ketone levels should only be measured in acute illness or prolonged hyperglycemia to prevent metabolic decompensation and guide insulin therapy (Chiang et al., 2018).

Artificial pancreas "closed loop" system:

It is a combination of insulin pump **(**CSII**)**, CGM and a control algorithm. This combination enables automatic frequent modifications to/of the insulin infusion rate depending on the data obtained from the CGM **(**Boughton & Hovorka, 2019**)**. This automated glucose control can reduce the burden of self-management as less input is needed from patients **(**Akil et al., 2021**)**. This system increased the time spent within target glucose ranges, lowered A1C levels, reduced hyperglycemia or hypoglycemia occurrence and enhanced the quality of life of adolescents. Some models administer glucagon hormone in addition to the insulin so that carbohydrate counting is no longer needed **(**Chiang et al., 2018**)**. Despite its advantages, it is still not widely used due to its high cost, insufficient information about its effectiveness in different patient groups **(**Akil et al., 2021**)** and lack of evidence from large randomized clinical trials in adolescents **(**Wherrett et al., 2018**)**.

Nutrition and physical activity

It is essential to know about the effect that food has on the blood sugar levels especially when it comes to carbohydrates **(**Ziegler & Neu, 2018**)**. Hence, a dietician should educate the adolescent about the importance of maintaining a healthy diet and together should come up with a diet plan taking into consideration the family habits, food preferences, lifestyle, and religious or cultural needs. A well-balanced diet consisting of vegetables, fruits, whole grains and dairy products should be considered with increased intake of fiber rich food and decreased intake of saturated fats. Carbohydrate counting should also be taught so that insulin could be matched to the carbohydrate intake. The dietician should ensure that the caloric intake is adequate for normal growth and development **(**Chiang et al., 2018**)**. A series of sessions should be scheduled initially, and then annual updates and reevaluations are considered. Dietary adherence in adolescents is associated with better glycemic control **(**ADA, 2021**)**.

Exercise is essential as it benefits the adolescents in several ways. It affects the metabolic and psychological health positively, increases insulin sensitivity and prevents complications. Adolescents should perform 60 minutes of moderate to vigorous aerobic physical activity daily and they should also engage in activities that strengthen the muscle and the bone at least 3 times per week. However, it should be kept in mind that exercise could lead dysglycemia. Adolescents and their families should be educated about the prevention and management of hypoglycemia. Some strategies to prevent exercise related hypoglycemia include: ensuring the blood glucose level before starting to exercise is between 90-250 mg/dL, avoid exercise if it is below 95 mg/dL and consume carbohydrates to raise it, reduce the prandial insulin dose for meals before the exercise and for those using CSII, the basal insulin

rates could be reduced by about 10-50% or more, or instead it could be suspended for 1-2 hours during exercise (ADA, 2021). It is essential to keep monitoring the glucose levels before, during and after the exercise frequently and this is best done by using CGM where real time readings of the blood glucose levels could be monitored from a mobile application enabling quick response to any changes (Moser et al., 2020).

Psychological care and psychosocial issues

During adolescence dynamic and rapid cognitive, emotional, and developmental changes occur. This puts adolescents with T1D at a higher risk for developing emotional and psychological problems, including anxiety, depression, eating disorders and diabetes distress (Wherrett et al., 2018). These disorders lead to poor diabetes management and control with an increase in DKA events and hospital admissions (Galler et al., 2020). Early detection and intervention are required and for this reason, meetings with the mental health professionals should be initiated when an adolescent is first diagnosed to start screening for issues. Family involvement and support is necessary for treatment adherence (ADA, 2021). In a recent study which investigated the association between diabetes-related family conflict, parent engagement in care, and child HbA1c levels, concluded that increased conflicts and decreased parent involvement in the care led to an increase in the HbA1c levels. Hence, it is important to screen for conflicts among families (Case et al., 2021). Subtle neurocognitive deficits affecting the parts of the brain involved in information processing and executive skills (planning, problem solving, mental flexibility) were documented in children. Interestingly, these are the skills that are needed for disease management thus weakness in these skills should be suspected in patients with poor metabolic control (Delamater et al., 2018).

Living with T1D can be very challenging especially in adolescence as it is a transition period between childhood and adulthood. Adolescents go through numerous changes including physical, intellectual, personality and social developmental. In adolescence, the focus shifts towards developing independence, creating an identity, and exploring new aspects of life which comes with its own stressors. Hence, finding a balance between T1D management and the developmental tasks could be very challenging. This could explain the nonadherence and poor glycemic control seen in adolescents. Adolescents tend to strive for autonomy in their relationship with their parents and the health care professionals. It's important to encourage their autonomy in self-management and avoid excessive supervision and overinvolvement to prevent conflicts (Ingersgaard et al., 2021). Fear of getting stigmatized is an additional factor affecting the diabetes management negatively. Some patients avoid

taking insulin shots or monitoring their glucose levels in social settings to hide their disease. They avoid disclosure to their peers from the fear of being judged and left out (Liu et al., 2017). Psychological interventions are associated with better glycemic control, increased treatment adherence, enhanced mental health and quality of life (Wherrett et al., 2018).

Prevention

Screening for T1D risk by detecting the presence of autoantibodies currently only occurs in research trials and is not yet recommended to the public due to its low feasibility and lack of approved therapeutic interventions. Many ongoing studies are trying to identify the markers and autoantibodies that are specific for each stage, ways to predict the disease progression through the stages and stage specific interventions that might halt the disease in the pre-symptomatic phase preventing its progression. 3 separate studies carried in Finland, Germany and the U.S were all studying the risk of progression to T1D from the time of seroconversion to autoantibody positivity in children. The Germans chose offspring of parents with T1D while the Americans and the Finnish chose children from the general population. Interestingly they all got to the same conclusion that as the number of autoantibodies increase, the risk for T1D increases and that is because of the children who developed more than two autoantibodies, almost 70% developed T1D within 10 years and 84% within 15 years hence also suggesting that both familial and sporadic cases follow the same sequence of the disease (ADA, 2021)

In a more recent study, Data from five prospective cohort studies in Finland, Germany, Sweden and the U.S. were combined and harmonized to estimate the risk of islet autoimmunity and progression to clinical T1D. Enrolled children were either first- degree relatives of people with T1D or HLA-DR-DQ genotype carriers from the general population that have higher risk for T1D. The study concluded that 1) children who developed multiple autoantibodies at the initial seroconversion have greater cumulative risk of T1D than those with single autoantibodies. Children with one, two, or three autoantibodies at seroconversion had a 45% (95% CI 40–52), 85% (78–90), and 92% (85–97) 15-year cumulative risk respectively. 2) the younger the age of multiple autoantibodies development, the greater the rate of progression to diabetes. 3) in children who remain with a single autoantibody, the HLA-DR-QR gene could be used to refine the progression risk to T1D (Anand et al., 2021)

Another study tried to make the prediction of the disease in pre-symptomatic simpler by using only a single blood sample instead of multiple. We have lots of ongoing studies in this area which are trying to make screening more affordable and less complex because early detection and intervention is

associated with easier disease management, delayed complications, reduced mortality and improved long-term outcomes **(**Bediaga et al., 2021**)**.

The primary prevention of T1D is the prevention of autoimmunity onset. In a randomized placebo-controlled trial babies and children with high T1D genetic risk were administered daily oral insulin to promote immune tolerance, this is due to the fact that the earliest autoantibody that develops in T1D is the IAA **(**Point; www.clinicaltrials.gov identifier NCT03364868**)**. Other possible primary preventions that need to undergo trials include dietary and behavioral prevention in obese children as obesity is a risk factor for T1D. Secondary prevention is the interruption of autoimmunity and prevent/ delay its progression to the symptomatic clinical diabetes. In a study, Teplizumab which causes transient T cell depletion was given to the first-degree relatives of T1D patients and a delay for insulin treatment of at least 3 years was observed. This study proved that immunointervention could delay T1D diagnosis **(**Dayan et al., 2021**)**. In tertiary prevention, the goal is to preserve ß-cell function and delay complications. Low doses of anti-thymocyte globulin **(**ATG**)** were able to ß-cell function and C-peptide production **(**Primavera et al., 2020**)**.

By detecting autoantibodies and calculating genetic risk scores, it is possible to identify the children who are at high risk for developing diabetes while they are still in stage 1 or 2 with functional ß-cells. Primary and secondary preventions have entered large- scale clinical trials and any future success in this area could make a difference in the disease progression and might even end the insulin dependency of this disease **(**Dayan et al., 2021**)**.

Conclusion

Living with T1D is challenging for adolescents and could lead to emotional or psychological problems but proper amount of care and support from the family or the integrated health care could reduce the burden of the disease and make it more possible to control the disease and better cope with the difficulties that come with it. The ongoing trials of primary and secondary prevention give hope for the future. Success in any of them would mean that diabetics will no longer get to the 3rd symptomatic stage, and they will no longer need life-long insulin. Instead, the focus will shift to giving medications or therapies that can maintain and preserve the function of ß-cells. However, in this case, early diagnosis which involves autoantibodies detection and genetic testing will be a necessity and hence, cheap, and more feasible ways to screen the population should be discovered.

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