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Mechanisms and Drivers of Type 2 Diabetes in Children and Adolescents

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Authors' contributions

This work was carried out in collaboration between all authors. Author MCS conceived the topic and structure of the review. Authors MCS, JX and JB performed the literature search and synthesized the content of the paper. Author MCS wrote the first draft and all authors read and approved the final manuscript.

Review Article

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ABSTRACT

The rates of type 2 diabetes (T2D) in children and adolescents are rising globally, and this is closely linked to the obesity epidemic that is affecting millions of youth around the world. In this review, we examine the differences between type 1 diabetes and T2D, and highlight the mechanisms involved in T2D development including genetic, epigenetic and environmental factors. We also highlight the role of inflammation in causing insulin resistance, one of the main drivers of T2D genesis.

Keywords: Type 2 diabetes; obesity; Immunometabolism; inflammation; cytokines; children.

1. INTRODUCTION

1.1 Type 2 Diabetes is a Global Epidemic

Type 2 diabetes (T2D) is a condition characterized by relative insulin deficiency with impaired insulin production in the face of insulin resistance leading to hyperglycemia [1]. This global epidemic is spreading and is mainly driven by the increased prevalence of obesity, increased population growth rate and aging [2].

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In 2011, an estimated 366 million people around the world had T2D; in 2030, this number is projected to rise to 552 million people [3]. Most of these patients are in low-and middle-income countries, and the enormous burden of T2D on the individual, family, community, health care system and society represents one of the most significant public health challenges around the world in the 21st century [4].

The rates of T2D are rising worldwide in all age groups including children [5] and an increasing number of adults with T2D will be diagnosed during childhood. In addition, some patients who will develop T2D in adulthood would have developed the risk factors leading to T2D during childhood [6]. This is significant, as developing T2D may reduce the lifespan and quality of life and increase health care system utilization [7,8]. In addition, T2D is an incurable disease and will require long-term therapy to control blood glucose levels and manage diabetes-related complications [9].

Understanding the mechanisms that lead to T2D in children and designing interventions to reduce its global burden is a priority, but this is a daunting challenge as the major driver of this disease i.e. childhood obesity has been difficult to control due to changes in lifestyle over the past few decades [10].

In making management decisions in the pediatric age group, one needs to balance the incomplete understanding of the mechanisms driving T2D compared to the better studied diabetes in children i.e. type 1 diabetes, the limited treatment options, and the lack of long-term natural history data with the known association of T2D with early comorbidities and complications in children and adolescents [11-13].

1.2 T2D is a Different Disease than Type 1 Diabetes in Children and Adolescents

Most cases (>90%) of diabetes in children and adolescents are type 1 diabetes (T1D), but T2D rates are rising and affects certain populations disproportionately [1,5,14].

There are several significant differences between T1D and T2D (Table 1). T1D is a disease of the adaptive immune system, characterized by T-lymphocyte activation and antibody-mediated islet cell destruction leading to absolute insulin deficiency [15], with insulin treatment required for survival [16]. On the other hand, T2D is initially a disease of insulin resistance, with the evolution of insulin deficiency over time. In addition, T2D may not require insulin therapy at diagnosis, and many newly diagnosed patients have hyperinsulinemia due to insulin resistance. Some newly diagnosed patients may require insulin therapy at diagnosis if they have metabolic decompensation, but it may be possible to withdraw insulin therapy in the majority of patients within few weeks. However, insulin may be needed later in the course of T2D to improve glycemic control.

Some patients with T2D have positive pancreatic antibodies similar to T1D patients, including Glutamic Acid Decarboxylase (GAD), insulin and islet cell autoantibodies (ICA) [17-19]. Patients with antibody-positive disease have reduced insulin secretory capacity and less insulin resistance on clamp studies when compared to the antibody-negative group, implying that they may in fact have T1D and obesity [20]. Another possibility is that islet damage with obesity-related inflammation, glucotoxicity and lipotoxicity exposes cellular antigens to immune cells, and this leads to activation of adaptive immunity and antibody production. The antibody-positive T2D group requires insulin therapy earlier than the antibody-negative

group, and more research is needed to clarify the role of these antibodies in pathogenesis of T2D.

Table 1. Differences between type 1 and type 2 diabetes in children and adolescents

Variable	Type 1 diabetes	Type 2 diabetes
Age	Any	Usually teens
Weight/BMI	Lean (usually, can be Overweight/obese)	Overweight/obese
Autoantibodies	++	-/+
Endogenous Insulin production	Low	High/normal/low
Complications	Late	Early
Pathophysiology	T-lymphocyte-mediated β-cell destruction Insulin deficiency	• Glucotoxicity/lipotoxicity/inflammation/ insulin resistance • ± Insulin deficiency • Immune system activation at pancreatic/metabolic organ levels
Need for insulin	Survival	May not be needed (at least initially) or is needed to achieve/improve control
Autoimmune disease associated with diabetes	Celiac disease Adrenal insufficiency Hypothyroidism	Not usually
Comorbidities	• Proteinuria • Hypertension • Dyslipidemia • Retinopathy • Psychiatric disorders (e.g. eating disorders)	Proteinuria Hypertension Dyslipidemia Psychiatric disorders Non-alcoholic fatty liver disease polycystic ovary syndrome obstructive sleep apnea

In addition, the appearance and progression of complications and comorbidities is different between T1D and T2D. The latter is a more aggressive disease, with proteinuria, hypertension, dyslipidemia, non-alcoholic fatty liver disease, obstructive sleep apnea, and polycystic ovarian syndrome appearing relatively early in the course of disease during childhood. In T1D, macrovascular and microvascular complications, including nephropathy, neuropathy, and retinopathy are less common in the pediatric age group compared to adults [12,13].

2. THE TODAY STUDY: A HINT OF THE CHALLENGES IN MANAGING T2D IN CHILDREN AND ADOLESCENTS

As T2D is a relatively new disease in children, there is a need to identify effective treatment strategies to achieve glycemic targets and manage comorbidities and complications. Some of the most widely used methods in managing T2D in children and adolescents include a combination of lifestyle intervention (LSI), insulin and metformin. Recently, a systematic review concluded that there is no good quality evidence to support the use of one of these cornerstones for managing T2D, lifestyle intervention (LSI), to achieve glycemic goals in

children and adolescents [21]. This emphasizes the need to define effective treatments in this age group.

In an effort to expand treatment strategies for T2D in children and adolescents, the Treatment Options for Type 2 Diabetes in Youth (TODAY) study was conducted and recently published its results [22]. This was a randomized multicenter study that recruited 699 subjects (10-17) year old, 64.7% female, average age 14±2 years) to three intervention arms: metformin alone, metformin plus LSI, and metformin plus rosiglitazone. The mean duration of T2D was around 8 months, with HbA1c<8% at recruitment, and a mean duration of follow-up of 3.9 years [22].

The primary outcomes, defined as failure to maintain HbA1c <8% over 6 months, or metabolic decompensation requiring insulin therapy at diagnosis or restarting after stopping insulin within 3 months, occurred in 51.7%, 46.6% and 38.6% in the above groups, respectively [22]. The metformin monotherapy group had similar outcomes to metformin plus LSI, and combination therapy of metformin plus rosiglitazone offered better success rates especially in girls (P 0.03). Metformin alone had higher failure rates in black participants [22].

In addition to glycemic control endpoints, other outcomes studied including significant weight loss rates, defined as weight loss of 7% or more, were low. These rates were higher in the metformin alone (24.3%) and metformin plus LSI groups (31.2%) and significantly lower in the metformin plus rosiglitazone group (16.7%) [22].

This study revealed that even with intensive LSI and combination pharmacotherapy, many T2D patients fail to achieve glycemic targets. In addition, many treatment options available to adults with T2D are scantily studied in children and adolescents; for example, rosiglitazone held promise in TODAY study, but it use was linked to adverse cardiac outcomes in adults that resulted in restricted use. Although this restriction was recently lifted, its reuse in children and adolescents will likely be relatively slow [23].

3. INCIDENCE AND PREVALENCE OF T2D

The rates of T2D in children and adolescents vary widely around the world, but its incidence and prevalence are rising [24]. This is due to differences among the populations studied in age range, country, timeline, ethnicity, and the methods used to derive these measures [14,17,25,26].

In a recent systematic review that examined global incidence and prevalence in children and adolescents, the reported incidence varied from 0-330/100,000 person-years and prevalence rates from 0-5,300/100,000 [14]. The populations with the highest rates of T2D encompassed mainly native populations in North America including Pima and Navajo Indians in the USA and the aboriginal community in Canada, but African American, Pacific Islanders, Caucasian, Japanese, and Taiwanese children were also among those represented [14,17,25,26].

In the next sections of this review, we discuss the drivers of the T2D epidemic, and describe the mechanisms of insulin resistance involved in the genesis of T2D.

4. FACTORS DRIVING THE RISK FOR T2D

Type 2 diabetes is a heterogeneous disease propelled by the global obesity epidemic with genetic, epigenetic and environmental factors contributing to the risk of developing the disease (Fig. 1).

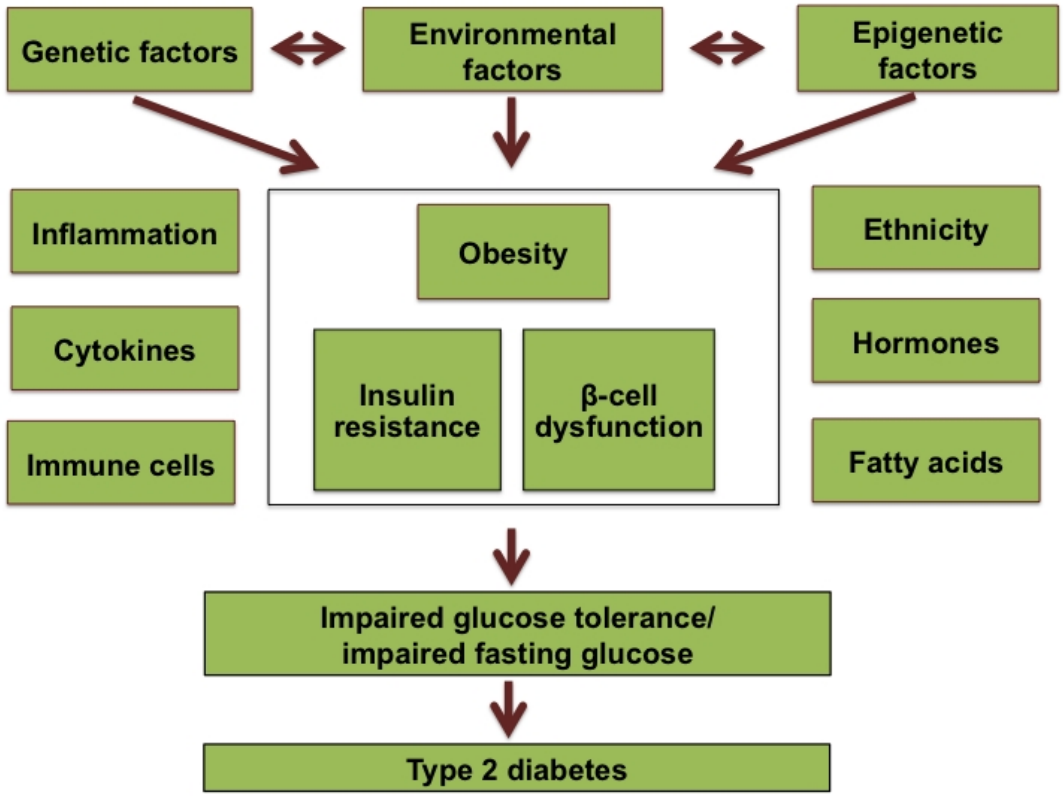

Fig. 1. Mechanisms & drivers of type 2 diabetes

The interactions among genetic, epigenetic, and environmental factors contribute to the risk of obesity and subsequent insulin resistance. In addition, these interactions also result in impairment in pancreatic β-cells function to mount a compensatory response to excess demand for insulin. These interactions are influenced by many factors including ethnicity, endocrine factors, immune system activation and cytokines. All these factors will contribute to increased insulin demand coupled with diminished insulin supply, which leads to the development of T2D

4.1 Genetic Factors

The heritability of type 2 diabetes is estimated to be more than 50%, based on rates noted in twin studies and in patients who have 1st degree relatives with T2D [27]. The data in twin studies need to take into account the kind of shared exposure in utero in dizygotic and monozygotic twins, which may confound the interpretation of the exposure status of the baby [28].

A recent study showed that having 2 siblings with T2D increases the risk of the disease without the need for parental history of T2D, indicating that recessively inherited rare variants and shared environmental factors may contribute to the risk more than parental disease [29].

Furthermore, genome-wide association studies have revealed multiple loci for T2D, the majority of which are related to β-cell dysfunction and reduced insulin production rather than obesity or insulin resistance [30,31]. This indicates that there are yet unidentified genes with small effect that mediate the T2D phenotype.

4.2 Epigenetic Factors

In addition to genetic factors, epigenetic factors play a critical role in the development of T2D. There is considerable evidence that exposure to adverse intrauterine environment will reprogram the fetus for future adverse metabolic and cardiovascular risks [32].

When the fetus faces in-utero nutrient restriction (e.g. maternal malnutrition, placental insufficiency) or excess (diabetic mothers, obese mothers), metabolic pathways are reprogrammed to adapt to this environment. What begins as an adaptive process becomes maladaptive after birth, whereby the obesogenic environment ex-utero result in a higher risk of obesity and T2D later in life [33].

4.3 Environmental Factors

Significant changes to lifestyle have resulted in a dramatic shift in dietary and exercise habits over the past few decades, which increased the risk of obesity. The consumption of high calorie foods [34] and sugary drinks [35], sedentary lifestyle with less physical activity and increased screen time are associated with higher risk of obesity in children [36,37]. Obesity results in insulin resistance, which is a critical step on the path to T2D [38].

5. PATHOGENESIS OF T2D: INSULIN RESISTANCE AND INSULIN DEFICIENCY ARE THE CENTRAL MECHANISMS IN T2D

Over the past three decades, breakthroughs in our understanding of adipose tissue biology and its crosstalk with metabolic organs and the immune system, and the alterations of these interactions in obesity have provided critical insights into obesity-driven downstream outcomes including T2D.

The increase in adipose tissue mass noted in obesity results in adipose tissue hypoxia as its size outstrips its vascularity, and this activates the inflammatory response. The hallmark of inflammation in the adipose tissue is the production of hypoxia-related factors e.g. HIF-1α, and molecules called ‘chemokines’ that attract circulating, bone marrow-derived monocytes into the adipose tissue [38,39]. When monocytes enter the adipose tissue, they respond to the local tissue microenvironment by differentiating to new cells called ‘macrophages’ and these cells will secrete inflammatory molecules called ‘cytokines’; this process leads to the propagation of inflammation which interferes with insulin signaling and lead to insulin resistance in the adipose tissue [40-44].

Obesity is also associated with excess dietary fatty acid delivery to the adipose tissue, but there is a limited capacity to uptake this supply. In addition, adipose tissue insulin resistance

secondary to inflammation propagates lipolysis and fatty acid release [45]. Both cytokines and fatty acids will enter the systemic circulation, and are transported to distant metabolic organs including skeletal muscle and liver and activate inflammation in both organs.

Inflammation is associated with insulin resistance in several ways through its mediators in metabolic organs i.e. cytokines and fatty acids. Cytokines signal through cell surface cytokine receptors to activate the inflammatory pathways within cells, which further propagate the secretion of inflammatory cytokines which interfere with insulin signaling. In addition, fatty acids can interfere with insulin signaling either directly by signaling through receptors in muscle and liver cells called Toll-Like Receptors 2 & 4 [46,47], which activate the inflammatory pathways. Alternatively, fatty acids enter the cells and generate intracellular mediators including Diacylglycerol and Ceramide; both of them can interfere with several steps of insulin signaling leading to insulin resistance [48]. Muscle insulin resistance is associated with reduced glucose uptake, while hepatic insulin resistance is associated with impaired insulin-mediated curbing of hepatic glucose production, and both are significant contributors to hyperglycemia [49].

Clinically, the impaired muscle and liver insulin responses are part of a phase called 'prediabetes', which include impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or IFG/IGT combination [50]. IFG is associated with hepatic insulin resistance, impaired first-phase insulin secretion and normal muscle insulin responses, while IGT is associated with muscle insulin resistance and normal or slightly reduced hepatic insulin resistance and reduced first phase insulin secretion. When both IFG and IGT are present, the second phase insulin secretion is also impaired [50] and these defects in insulin secretion indicate impaired β-cell function.

Prediabetes is an intermediate step between normal glucose tolerance and diabetes, and while there is evidence that prediabetes can revert to normal glucose tolerance with intervention, many patients with prediabetes will develop diabetes [51,52].

In order to respond to impaired insulin action, the natural compensatory mechanism to insulin resistance involves increasing insulin production to overcome insulin resistance, which leads to hyperinsulinemia. The capacity of the β-islet cells to increase insulin production in the face of sustained insulin resistance is limited, and these cells are exposed to inflammatory cytokines, fatty acids (Lipotoxicity) and glucose (Glucotoxicity), which impacts their function and triggers apoptosis [53]. Inflammation, lipotoxicity, and glucotoxicity cooperate to impair β-cell's ability to produce sufficient insulin to meet the body's needs, and this results in the development of T2D.

6. CONCLUSION

Pediatric & adolescent T2D is a relatively new disease that is driven by the obesity epidemic, and its rates will likely continue to rise.

This is an aggressive disease in the young, with complications seen early in the course of the disease that require ongoing monitoring and aggressive intervention to control T2D and prevent or at least delay the onset of its complications.

It is critical that further research into youth T2D is focused on understanding the mechanisms that drive its initiation and progression, so that effective treatment approaches can be devised to limit its devastating impact.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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