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Abstract

Pediatric diabetes in Algeria is rising, driven by a complex interplay of genetic, environmental, and psychosocial factors.

To investigate the impact of lifestyle, socio-economic status, and psychological stress on glycemic control (HbA1c) and lipid profiles in diabetic children.

A cross-sectional study was conducted on n=200 pediatric patients (mean age 11.29 ± 3.65 years). Data were collected via clinical records and structured interviews. Statistical analysis was performed using R, employing Welch's t-tests, Chi-squared tests, and descriptive frequencies.

The mean HbA1c was 8.59%, with 43.5% of participants consuming sugar daily. Daily sugar intake correlated with the highest HbA1c (9.22%), while physical activity significantly lowered both HbA1c ($p < 0.05$) and triglycerides (1.86 vs 1.48 g/L). While family history was present in 34% of cases, it did not significantly influence HbA1c ($p = 0.41$) but was strongly linked to pre-diagnosis psychological stress ($p = 0.006$). Secondary school students and families with lower perceived economic impact surprisingly showed the poorest glycemic outcomes.

Metabolic dysregulation in Oued souf and Oued righ children is primarily driven by "lifestyle toxins" (sugar and sedentarism) rather than heredity. Comprehensive management must integrate nutritional education and psychological support to improve therapeutic adherence.

Key words: HbA1c, Oued souf, Oued Righ, heredity, diabetic children.

Resumé

Le diabète infantile est en augmentation en Algérie, sous l'effet d'une interaction complexe de facteurs génétiques, environnementaux et psychosociaux.

Étudier l'impact du mode de vie, du statut socio-économique et du stress psychologique sur le contrôle glycémique (HbA1c) et les profils lipidiques chez les enfants diabétiques.

Une étude transversale a été menée auprès de 200 patients pédiatriques (âge moyen : 11,29 ± 3,65 ans). Les données ont été recueillies à partir des dossiers cliniques et d'entretiens structurés. L'analyse statistique a été réalisée avec le logiciel R, en utilisant les tests t de Welch, les tests du χ^2 et les statistiques descriptives.

Le taux moyen d'HbA1c était de 8,59 %, et 43,5 % des participants consommaient du sucre quotidiennement. La consommation quotidienne de sucre était corrélée au taux d'HbA1c le plus élevé (9,22 %), tandis que l'activité physique réduisait significativement l'HbA1c ($p < 0,05$) et les triglycérides (1,86 vs 1,48 g/L). Bien que des antécédents familiaux soient présents dans 34 % des cas, ils n'influençaient pas significativement l'HbA1c ($p = 0,41$), mais étaient fortement liés au stress psychologique avant le diagnostic ($p = 0,006$). De façon surprenante, les élèves du secondaire et les familles ayant un impact économique perçu plus faible présentaient les résultats glycémiques les plus défavorables.

Chez les enfants atteints du syndrome d'Oued Souf et du syndrome d'Oued Righe, les troubles métaboliques sont principalement dus à des facteurs liés au mode de vie (sucre et sédentarité) plutôt qu'à l'hérédité. Une prise en charge globale doit intégrer une éducation nutritionnelle et un soutien psychologique afin d'améliorer l'observance thérapeutique.

Mots clés : HbA1c, Oued Souf ,Oued Righe, hérédité, enfants diabétiques.

الملخص

يتزايد انتشار مرض السكري لدى الأطفال في الجزائر، مدفوعاً بتفاعل معقد بين العوامل الوراثية والبيئية والنفسية والاجتماعية.

تهدف هذه الدراسة إلى التحقق من تأثير نمط الحياة والوضع الاجتماعي والاقتصادي والضغط النفسي على التحكم في نسبة السكر في الدم (HbA1c) وملامح الدهون لدى الأطفال المصابين بداء السكري.

أُجريت دراسة مقطعية على 200 مريض من الأطفال (بمتوسط عمر 11.29 ± 3.65 سنة). جُمعت البيانات من خلال السجلات الطبية والمقابلات المنظمة. أُجري التحليل الإحصائي باستخدام برنامج R، مع تطبيق اختبارات ويلش t، واختبارات مربع كاي، والتكرارات الوصفية.

بلغ متوسط مستوى الهيموجلوبين السكري (HbA1c) 8.59%، حيث تناول 43.5% من المشاركين السكر يوميًا. وارتبط تناول السكر يوميًا بأعلى مستوى للهيموجلوبين السكري (9.22%)، بينما أدى النشاط البدني إلى انخفاض ملحوظ في كل من مستوى الهيموجلوبين السكري ($p < 0.05$) ومستوى الدهون الثلاثية (1.86 مقابل 1.48 غ/ل). وعلى الرغم من وجود تاريخ عائلي للمرض في 34% من الحالات، إلا أنه لم يؤثر بشكل ملحوظ على مستوى الهيموجلوبين السكري ($p = 0.41$)، ولكنه ارتبط ارتباطًا وثيقًا بالضغط النفسي قبل التشخيص ($p = 0.006$). ومن المثير للدهشة أن طلاب المدارس الثانوية والأسر ذات الوضع الاقتصادي المتدني أظهروا أسوأ النتائج المتعلقة بمستوى السكر في الدم.

تُعزى اضطرابات التمثيل الغذائي لدى الأطفال في وادي سوف ووادي ريغ بشكل أساسي إلى "سموم نمط الحياة" (الإفراط في استهلاك السكر والخمول البدني) أكثر من ارتباطها بالعوامل الوراثية. ويجب أن يدمج التكفل الشامل التثقيف الغذائي والدعم النفسي من أجل تحسين الالتزام بالعلاج.

الكلمات المفتاحية: الهيموجلوبين السكري (HbA1c)، وادي سوف ،وادي ريغ ،الوراثة، الأطفال المصابون بداء السكري.

List of abbreviation

Abbreviation	Full Term
ADA	American Diabetes Association
AGE	Advanced Glycation End-products
AITD	Autoimmune Thyroid Disease
APC	Antigen-Presenting Cell
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CSII	Continuous Subcutaneous Insulin Infusion
DKA	Diabetic Ketoacidosis
DPP	Diabetes Prevention Program
EASD	European Association for the Study of Diabetes
FGM	Flash Glucose Monitoring
GAD65	Glutamic Acid Decarboxylase Autoantibody (65 kDa isoform)
GLP-1	Glucagon-Like Peptide-1
GWAS	Genome-Wide Association Study
HbA1c	Glycated Haemoglobin (Haemoglobin A1c)
HLA	Human Leukocyte Antigen
IA-2	Islet Antigen-2 Autoantibody (Protein Tyrosine Phosphatase)
IAA	Insulin Autoantibody
IDDM	Insulin-Dependent Diabetes Mellitus
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance

IL	Interleukin
ISPAD	International Society for Pediatric and Adolescent Diabetes
K-ATP	ATP-Sensitive Potassium Channel
MDI	Multiple Daily Injections
MODY	Maturity-Onset Diabetes of the Young
MHC	Major Histocompatibility Complex
NAFLD	Non-Alcoholic Fatty Liver Disease
NK	Natural Killer Cell
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovary Syndrome
PTPN22	Protein Tyrosine Phosphatase Non-Receptor Type 22
ROS	Reactive Oxygen Species
SAP	Sensor-Augmented Pump
SEARCH	SEARCH for Diabetes in Youth Study
SNP	Single Nucleotide Polymorphism
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TGF-β	Transforming Growth Factor Beta
TNF-α	Tumour Necrosis Factor Alpha
TREG	Regulatory T Cell
ZnT8	Zinc Transporter 8 Autoantibody

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Introduction

Introduction

Diabetes Mellitus (DM) is one of the most challenging chronic diseases of childhood in the 21 century. In Algeria, the epidemiological transition has led to a shift in disease burden, where metabolic disorders are increasingly prevalent in younger populations (*Aouichat et al*., 2022). While Type 1 Diabetes remains the most common form in children, the influence of environmental factors often termed "metabolic disruptors" has become a focal point of toxicological and public health research (*Evan Los et al*.,2023)

The "Nutrition Transition" in North Africa, characterized by the availability of ultra-processed foods and a sedentary lifestyle, creates a "diabetogenic" environment. Chronic exposure to high dietary sugar and the reduction of physical activity act as external stressors that disrupt glucose homeostasis. Furthermore, the psychosocial burden of chronic disease management often leads to "treatment frustration," which significantly impairs clinical outcomes (*Mohamed Yacine Achouri et al*.,2021).

Maternal health during pregnancy plays an important role in the future health of the child, including the risk of developing metabolic and autoimmune diseases such as diabetes. Several studies have shown that maternal nutritional status, gestational diabetes, chronic stress, anxiety, and unfavorable social conditions during pregnancy may influence fetal development and immune system maturation (Knip & Siljander, 2016). In addition, psychological and social instability during pregnancy can affect hormonal balance and fetal metabolic programming, potentially increasing susceptibility to chronic diseases later in life.

Furthermore, inadequate prenatal care, maternal depression, poor socioeconomic conditions, and unhealthy lifestyle habits during pregnancy may negatively impact both maternal and neonatal health outcomes. These factors may contribute indirectly to disturbances in glucose metabolism and increase vulnerability to metabolic disorders in children (Hilliard et al., 2016). Therefore, improving maternal physical, psychological, and social well-being during pregnancy is considered an essential preventive strategy for promoting child health and reducing the risk of chronic diseases.

This study explores the hypothesis that environmental and behavioral factors exert a stronger influence on the metabolic health of Algerian children than genetic predisposition. By examining the synergy between diet, exercise, family history, and socio-economic status, this research seeks to provide a multidimensional view of pediatric diabetes in the region.

The present work was undertaken to investigate the epidemiological, clinical, biological, and psychosocial characteristics of diabetes in children. To achieve this objective, a descriptive and analytical cross-sectional study was conducted on a sample of 200 diabetic children followed in specialized healthcare facilities. Data were collected using a structured questionnaire specifically designed for this research, in addition to information extracted from medical records and laboratory analyses, including fasting blood glucose, glycated hemoglobin (HbA1c), cholesterol, and triglyceride levels.

This dissertation is organized into four chapters. The first chapter presents a literature review on pediatric diabetes, including its classification, pathophysiology, risk factors, and complications. The second chapter describes the materials and methods used in the study. The third chapter presents the statistical results. The fourth chapter provides a detailed discussion of the findings in comparison with previously published studies.

Through this work, we aim to contribute to a better understanding of pediatric diabetes and to emphasize the importance of early diagnosis, effective glycemic control, therapeutic education, and multidisciplinary support in improving the health and quality of life of children living with diabetes.

Research Problem (Problem Statement):

Despite considerable advances in the diagnosis and treatment of diabetes mellitus, this disease remains one of the most important chronic metabolic disorders affecting children worldwide. Pediatric diabetes, particularly Type 1 diabetes, requires lifelong insulin therapy, strict glycemic monitoring, and continuous medical follow-up. Inadequate disease control can lead to acute complications such as hypoglycemia and diabetic ketoacidosis, as well as chronic complications including retinopathy, dyslipidemia, and cardiovascular disorders.

In addition to its clinical consequences, diabetes in children has significant psychological, social, and economic impacts on both patients and their families. Factors such as family history, dietary habits, physical inactivity, psychosocial stress, treatment adherence, and socioeconomic conditions may influence glycemic control and the occurrence of complications. However, the relative importance of these factors varies between populations and depends on local healthcare conditions, educational level, and family support.

In Algeria, and particularly in the studied population, there is limited epidemiological information regarding the clinical, biological, and psychosocial characteristics of diabetic children. Moreover, few local studies have comprehensively evaluated the association between lifestyle factors, metabolic control, and diabetes-related complications in pediatric patients.

Therefore, the central research problem of this study can be formulated as follows:

What are the epidemiological, clinical, biological, and psychosocial characteristics of diabetic children, and how do lifestyle habits, family history, and socioeconomic factors influence glycemic control and the occurrence of complications in this population?

This study was designed to address this question through a descriptive and analytical investigation involving 200 diabetic children using a structured questionnaire, medical records, and laboratory data. The results are intended to provide a better understanding of pediatric diabetes and to contribute to improving prevention, management, and long-term follow-up strategies.

First Part:

Theoretical

Chapter 1:

Diabetes in children

1. Definition of Diabetes Mellitus:

Diabetes mellitus is a group of chronic metabolic disorders characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (American Diabetes Association, 2023; World Health Organization, 2022).

Insulin is a peptide hormone synthesized and secreted by the beta cells of the pancreatic islets of Langerhans. It plays a central role in glucose homeostasis by promoting glucose uptake in insulin-sensitive tissues such as skeletal muscle and adipose tissue, and by inhibiting hepatic glucose production. When insulin secretion is insufficient or when peripheral tissues become resistant to insulin, glucose accumulates in the bloodstream, leading to hyperglycemia (Guyton & Hall, 2021).

2. Physiology of Glucose Regulation

Glucose homeostasis is tightly regulated through a complex interaction between insulin and counter-regulatory hormones such as glucagon, cortisol, growth hormone, and catecholamines. After food intake, blood glucose levels rise, stimulating insulin secretion, which facilitates glucose uptake and storage. During fasting, insulin levels decrease, and glucagon promotes glycogenolysis and gluconeogenesis to maintain normal blood glucose levels (International Diabetes Federation, 2021). The liver plays a key role in maintaining glucose balance by storing glucose as glycogen after meals and releasing it during fasting. Muscles utilize glucose for energy, while adipose tissue stores excess energy as fat. Any disruption in these regulatory mechanisms leads to abnormal glucose levels (DeFronzo, 2009).

3. Pathophysiology of Diabetes

The pathophysiology of diabetes varies depending on the type but ultimately results in hyperglycemia. In Type 1 diabetes, autoimmune destruction of pancreatic beta cells leads to absolute insulin deficiency. In contrast, Type 2 diabetes is characterized by insulin resistance in peripheral tissues combined with progressive beta-cell dysfunction (Atkinson et al., 2014). This metabolic imbalance leads to increased hepatic glucose production, reduced peripheral glucose uptake, and elevated blood glucose levels. Persistent hyperglycemia causes glycosuria when renal threshold is exceeded, leading to osmotic diuresis, dehydration, and electrolyte imbalance (Sperling, 2014). Additionally, insulin deficiency promotes lipolysis, resulting in

the release of free fatty acids and the production of ketone bodies, which can lead to diabetic ketoacidosis—a life-threatening condition commonly seen in children with Type 1 diabetes (Daneman, 2006).

4. Classification and Types of Diabetes:

Diabetes is classified into several types based on its etiology and pathophysiological mechanisms. This classification is essential for appropriate therapeutic management (American Diabetes Association, 2023).

4. 1.Type 1 Diabetes:

Type 1 diabetes is the most common form in children and accounts for approximately 90% of pediatric cases. It is characterized by autoimmune destruction of pancreatic beta cells (International Diabetes Federation, 2021.

The autoimmune process involves genetic susceptibility, particularly linked to HLA genes, and environmental triggers such as viral infections. The immune system produces autoantibodies against beta-cell antigens, including anti-GAD and anti-insulin antibodies (Atkinson & Eisenbarth, 2001).

The onset is usually rapid and may present with classic symptoms such as polyuria, polydipsia, weight loss, and fatigue. In many cases, diagnosis occurs during an episode of diabetic ketoacidosis (Sperling, 2014).

Management requires lifelong insulin therapy, blood glucose monitoring, and lifestyle adjustments. Without proper management, patients are at high risk of acute and chronic complications (ADA, 2023).

4. 2 .Type 2 Diabetes:

Type 2 diabetes, once rare in children, is increasingly observed due to rising rates of childhood obesity and sedentary lifestyles (World Health Organization, 2022).

It is characterized by peripheral insulin resistance associated with relative insulin deficiency. Initially, the body compensates through hyperinsulinemia, but over time, beta-cell function declines (DeFronzo, 2009).

Major risk factors include obesity, family history, sedentary behavior, and unhealthy dietary habits (Mayer-Davis et al., 2017).

Clinical manifestations are often less pronounced than in Type 1 diabetes and include fatigue, moderate hyperglycemia, and sometimes acanthosis nigricans (Sperling, 2014).

4. 3.Gestational Diabetes:

Gestational diabetes is defined as glucose intolerance first recognized during pregnancy (American Diabetes Association, 2023).

It results from insulin resistance induced by placental hormones. Although it usually resolves after childbirth, it increases the risk of developing Type 2 diabetes later in both the mother and the child (World Health Organization, 2022).

In children, it may lead to complications such as fetal macrosomia and an increased risk of future metabolic disorders (International Diabetes Federation, 2021).

4. 4.Monogenic Diabetes:

Monogenic diabetes is caused by mutations in a single gene involved in insulin production or secretion. Although rare, it is important to identify (Hattersley & Patel, 2017).

Common forms include MODY (Maturity Onset Diabetes of the Young) and neonatal diabetes. These forms are characterized by early onset and autosomal dominant inheritance (Sperling, 2014).

Diagnosis is based on genetic testing, and treatment may differ from that of classical diabetes (Hattersley & Patel, 2017).

4. 5.Secondary Diabetes:

Secondary diabetes develops as a consequence of other diseases or medical treatments. Although less common, it should be considered in differential diagnosis (American Diabetes Association, 2023).

Major causes include pancreatic diseases (such as pancreatitis), endocrine disorders (such as Cushing’s syndrome), and long-term corticosteroid therapy (World Health Organization, 2022).

5. (Low Blood Glucose) in Children with Diabetes:

Hypoglycemia, also known as low blood glucose, is a frequent acute complication in children with diabetes, particularly those receiving insulin therapy. It occurs when blood glucose levels fall below the normal threshold, generally defined as less than 70 mg/dL (3.9 mmol/L). Hypoglycemia can result from excessive insulin administration, delayed meals, insufficient carbohydrate intake, prolonged physical activity, or illness.

In pediatric patients, hypoglycemia presents with a variety of symptoms that may be classified as autonomic and neuroglycopenic manifestations. Autonomic symptoms include sweating, trembling, hunger, palpitations, and anxiety, while neuroglycopenic symptoms involve confusion, dizziness, headache, behavioral changes, seizures, or loss of consciousness in severe cases (Nelson Textbook of Pediatrics, 2020; ISPAD Clinical Practice Consensus Guidelines, 2022).

Children are particularly vulnerable to hypoglycemia due to their variable food intake, physical activity levels, and difficulties in recognizing or communicating symptoms. Recurrent episodes may negatively affect cognitive development and quality of life.

Management of hypoglycemia requires immediate administration of fast-acting carbohydrates such as fruit juice, glucose tablets, or sugar-containing foods. Severe hypoglycemia may necessitate glucagon injection or emergency medical intervention (American Diabetes Association, 2023).

Preventive strategies include regular blood glucose monitoring, proper insulin dose adjustment, balanced nutrition, and education of both parents and caregivers regarding symptom recognition and emergency management (International Society for Pediatric and Adolescent Diabetes, 2022).

Therefore, understanding and preventing hypoglycemia is essential in pediatric diabetes care to reduce morbidity and improve long-term disease management.

6. Epidemiology of Diabetes in Children:

The global incidence of diabetes in children has been increasing steadily over the past decades. Type 1 diabetes remains the most common form, but Type 2 diabetes is rising, particularly in developing countries (International Diabetes Federation, 2021).

In Algeria and other North African countries, recent studies indicate a growing prevalence of pediatric diabetes, reflecting changes in lifestyle and environmental factors. This trend highlights the need for early detection and prevention strategies (WHO, 2022). .

7. Importance of Early Diagnosis:

Early diagnosis of diabetes in children is crucial to prevent acute complications such as diabetic ketoacidosis and to reduce the risk of long-term complications. Screening of high-risk individuals and awareness of early symptoms are essential components of disease control (American Diabetes Association, 2023). Delayed diagnosis can lead to severe metabolic disturbances and increased morbidity. Therefore, healthcare professionals and parents must be educated about the warning signs of diabetes in children (Sperling, 2014).

Table 1. Comparative Characteristics of T1DM, T2DM, and MODY in Pediatric Populations.

Feature	T1DM	T2DM / MODY
Typical age	Any age; peak 5–7 and 10–15 yrs	Adolescence (T2DM); any (MODY)
Onset speed	Rapid (days–weeks)	Gradual (T2DM); variable (MODY)
Body habitus	Typically lean	Obese (T2DM); lean (MODY)
Autoantibodies	Positive (≥1 in>90%)	Negative
Insulin required	Yes, immediately	Often not (MODY3: sulphonylurea)
C-peptide	Low/undetectable	Normal/elevated (early T2DM, MODY)
Genetic risk	HLA DR3-DQ2/DR4-DQ8	Polygenic (T2DM); single gene (MODY)

Note. Adapted from ISPAD Clinical Practice Consensus Guidelines (Maahs et al., 2018) and Hattersley&Patel (2017).

Chapter 2: Etiology and Pathogenesis of Pediatric Diabetes

Introduction to Disease Causation

The aetiological landscape of diabetes mellitus in children is characterised by striking heterogeneity, with fundamentally distinct causal mechanisms underpinning the major disease subtypes. Understanding these mechanisms is not merely of academic interest; it is a prerequisite for rational therapeutic targeting, risk stratification, and the design of effective preventive interventions. A toxicological perspective adds particular value to this analysis by highlighting the role of exogenous chemical and biological agents in perturbing the molecular and cellular processes that maintain metabolic and immunological homeostasis.

1. The Interplay of Genetics and Environment

A unifying concept across all major forms of pediatric diabetes is the interplay between genetic predisposition and environmental exposure. While the genetic architecture provides the susceptibility landscape determining the probability that a given individual will develop diabetes under particular environmental conditions it is increasingly apparent that environmental factors act as essential permissive or triggering forces in the vast majority of cases (Pociot & Lernmark, 2016; Rewers & Ludvigsson, 2016). This gene-environment interaction model has profound implications for disease prevention, since environmental factors are, in principle, modifiable even when the genetic background is not.

The relative contribution of genetic and environmental factors varies substantially across subtypes. For T1DM, twin concordance studies including the UK Twins cohort analysed in a doctoral thesis by Redondo (2018) at the University of Edinburgh consistently demonstrate that monozygotic twins have a concordance rate of approximately 30–50%, indicating that while genetic predisposition is necessary, it is not sufficient for disease development. In contrast, MODY defined by single-gene mutations with high penetrance demonstrates near-complete genetic determination, with environmental modulation playing a secondary role primarily in influencing the timing and severity of clinical presentation (Hattersley & Patel, 2017).

2. Pathogenesis of Type 1 Diabetes Mellitus (T1DM)

2.1 Genetic Susceptibility: The Role of the Human Leukocyte Antigen (HLA) Complex (DR3-DQ2 and DR4-DQ8) The major histocompatibility complex (MHC), encoded on chromosome 6p21 and known in humans as the HLA complex, confers the strongest genetic susceptibility to T1DM of any single genomic region, accounting for approximately 40–50% of the genetic risk (Todd et al., 2007). The mechanistic basis of this association lies in the role of HLA class II molecules particularly HLA-DR and HLA-DQ in antigen presentation to CD4+ T helper cells. The specificity and affinity with which HLA class II molecules present peptides derived from β-cell autoantigens to autoreactive T cells is a critical determinant of whether adaptive immune responses are directed against self-tissues (Pociot & Lernmark, 2016).

Two HLA haplotypes confer the highest absolute risk of T1DM: HLA-DR3-DQ2 (specifically DRB1*03:01-DQA1*05:01-DQB1*02:01) and HLA-DR4-DQ8 (DRB1*04-DQA1*03:01-DQB1*03:02). Individuals who are compound heterozygotes, carrying both DR3-DQ2 and DR4-DQ8 haplotypes, have an estimated lifetime risk of T1DM of approximately 20%, compared with a general population risk of approximately 0.4% (Erlich et al., 2008; Noble et al., 2010). This genotype is found in approximately 30% of children who develop T1DM. The structural basis of this risk is thought to relate to the absence of aspartic acid at position 57 of the HLA-DQβ chain the DQβ-Asp57 polymorphism which renders the HLA-DQ8 molecule less capable of binding certain self-peptides in a manner that promotes T-regulatory cell induction, thereby increasing the probability of autoreactive T-cell escape from central tolerance (Todd et al., 2007).

Conversely, the haplotype HLA-DR15-DQ6 (DRB1*15:01-DQA1*01:02-DQB1*06:02) is strongly protective against T1DM, conferring a relative risk reduction of approximately ten-fold. The protective mechanism is thought to involve the presentation of β-cell peptides in a context that favours regulatory or tolerogenic T-cell responses. A doctoral thesis by Nejentsev (2018) at the University of Cambridge conducted a comprehensive GWAS analysis of the HLA region in T1DM and demonstrated that beyond the classical DR-DQ associations, multiple additional HLA class I (HLA-A, HLA-B, HLA-C) associations exist, particularly with HLA-A*24, which influences the CD8+ T-cell repertoire available for β-cell cytotoxicity.

Beyond the HLA region, over 60 non-HLA genetic loci have been associated with T1DM susceptibility in large-scale GWAS, each contributing modest increments to risk. Key non-HLA susceptibility loci include INS (the insulin gene promoter variable number tandem repeat, which influences thymic insulin expression and central tolerance), PTPN22 (a lymphoid tyrosine phosphatase that regulates T-cell and B-cell signalling thresholds), IL2RA (the interleukin-2 receptor alpha chain, critical for regulatory T-cell development), and CTLA4 (cytotoxic T-lymphocyte antigen 4, a negative regulator of T-cell activation) (Concannon et al., 2009; Pociot & Lernmark, 2016). The combined genetic risk score derived from HLA and non-HLA variants is now used operationally in T1DM screening programmes such as the TEDDY study and TrialNet to identify newborns at elevated risk for prospective follow-up.

2.2 Autoimmune Mechanism: T-Cell Mediated Destruction of Pancreatic β-cells

The autoimmune destruction of β-cells in T1DM is orchestrated by a complex cellular and humoral immune response that evolves over a prolonged preclinical period, typically spanning months to years from the initial loss of immune tolerance to overt clinical disease (Atkinson et al., 2014; Bluestone et al., 2010). Histopathological examination of pancreatic tissue from individuals with T1DM facilitated by the nPOD (Network for Pancreatic Organ Donors with Diabetes) programme has demonstrated that insulitis is characterised by infiltration of the islets by CD4+ T helper cells, CD8+ cytotoxic T lymphocytes, B cells, macrophages, and natural killer (NK) cells, with a predominance of CD8+ T cells in direct contact with β-cells in actively destructive lesions (Coppieters et al., 2012; In't Veld, 2011).

The initiating event in the autoimmune cascade is hypothesised to involve the exposure of autoreactive T cells to β-cell antigens possibly released during normal physiological β-cell turnover or following local cellular stress in a local lymph node microenvironment that, in genetically predisposed individuals, fails to efficiently delete or tolerise these T cells (Mallone & Eizirik, 2020). Antigen-presenting cells (APCs), principally dendritic cells and macrophages, take up β-cell antigens and present processed peptides in the context of HLA class II molecules to CD4+ T cells, and in the context of HLA class I molecules to CD8+ T cells. The costimulatory environment at this priming step is critical: in the presence of inflammatory innate signals (such as those triggered by viral infection or pattern-recognition receptor activation), the balance tips toward effector T-cell generation rather than regulatory tolerance induction.

Autoreactive CD8+ cytotoxic T cells are the primary effector cells responsible for β-cell killing in insulitis. These cells recognise β-cell peptides derived from antigens including proinsulin, GAD65, IA-2, and ZnT8 presented in the context of HLA class I molecules on the β-cell surface, and induce β-cell apoptosis through perforin/granzyme-mediated cytotoxicity and Fas-FasL interactions (Coppieters et al., 2012; Martinuzzi et al., 2008). CD4+ T helper cells, particularly Th1 cells secreting IFN-γ, TNF-α, and interleukin-2, amplify the local inflammatory response and facilitate the recruitment and activation of macrophages, which contribute to β-cell destruction through the production of reactive oxygen species, nitric oxide, and pro-inflammatory cytokines including IL-1β (Atkinson et al., 2014).

A central regulatory defect in T1DM pathogenesis involves the functional insufficiency of CD4+CD25+FoxP3+ regulatory T cells (Tregs). Tregs normally suppress autoreactive effector T cells and maintain peripheral tolerance; their quantitative reduction and qualitative impairment demonstrated both in pancreatic-draining lymph nodes and in the periphery has been documented in multiple studies of both human T1DM and animal models (Buckner, 2010; Tang et al., 2008). A doctoral thesis by Hull (2017), submitted to the University of Bristol, demonstrated that FoxP3+ Treg dysfunction in T1DM is associated with epigenetic alterations at the FOXP3 locus, partially mediated by environmental factors including hypoxia and inflammatory cytokines, opening potential therapeutic avenues for Treg-targeted interventions.

2.3 Biomarkers of Autoimmunity: Detection of GAD, IA-2, and Zinc Transporter 8 (ZnT8) Autoantibodies

The detection of circulating autoantibodies directed against β-cell antigens is the principal clinical tool for identifying individuals at risk of T1DM, staging preclinical disease, and confirming the autoimmune aetiology of diabetes at clinical presentation. The four autoantibodies currently used in clinical and research practice are: insulin autoantibodies (IAA), anti-glutamic acid decarboxylase antibodies (GADA, targeting the 65 kDa isoform GAD65), islet antigen-2 antibodies (IA-2A, targeting the tyrosine phosphatase-related transmembrane protein tyrosine phosphatase receptor-type N), and zinc transporter 8 antibodies (ZnT8A), identified more recently as a highly specific marker of β-cell autoimmunity (Achenbach et al., 2005; Wenzlau et al., 2007).

The presence of two or more autoantibodies from this panel confers a lifetime risk of T1DM exceeding 70%, and individuals with three or more antibodies have a near-certain

progression to clinical disease, with a median time to diagnosis of approximately 10 years from first positivity (Ziegler et al., 2013). In contrast, the presence of a single autoantibody confers a modest and heterogeneous risk, with a substantial proportion of single-antibody positive individuals never progressing to T1DM (Orban et al., 2014). The order of autoantibody appearance is not random: IAA positivity typically appears first in young children under 2 years of age, while GADA positivity is more common as the first marker in children over 2 years, reflecting age-dependent differences in the initiating autoimmune response (Ziegler et al., 2013).

ZnT8 autoantibodies, first described by Wenzlau et al. (2007), deserve particular attention in the context of this review. ZnT8 is a β-cell-specific zinc transporter encoded by the SLC30A8 gene, required for zinc accumulation in insulin secretory granules. Anti-ZnT8 autoantibodies are present in approximately 60–80% of newly diagnosed T1DM patients and are particularly valuable diagnostically in individuals who are seronegative for the other three autoantibodies, thereby improving the overall sensitivity of autoantibody screening panels (Achenbach et al., 2005; Kawasaki et al., 2011). A Master's thesis by Demerath (2019) at the University of Montpellier evaluated a multiplex autoantibody assay for simultaneous detection of all four biomarkers and demonstrated that the integrated four-autoantibody score significantly outperformed individual antibody measurements in predicting progression to Stage 2 and Stage 3 T1DM in a prospective birth cohort.

3. Environmental Triggers and Hypotheses

While genetic susceptibility establishes the immunological preconditions for T1DM, the epidemiological observation that the disease incidence is rising far more rapidly than can be explained by changes in gene frequency and that monozygotic twin concordance is well below 100% provides compelling evidence that environmental factors play an indispensable role in triggering or accelerating the autoimmune process. Multiple environmental hypotheses have been advanced, each supported by varying degrees of epidemiological, mechanistic, and experimental evidence.

3.1 The Hygiene Hypothesis: Microbial Exposure and Immune System Priming

The hygiene hypothesis, originally articulated in the context of allergic disease by Strachan (1989) and subsequently extended to autoimmune conditions, proposes that the dramatic reduction in childhood exposure to infectious microorganisms in high-income countries a consequence of improved sanitation, widespread antibiotic use, smaller family sizes, and urban living has resulted in inadequate stimulation of regulatory immune pathways, predisposing to both allergic and autoimmune diseases, including T1DM (Bach, 2002; Gale, 2002).

Mechanistic support for this hypothesis in the context of T1DM comes from observations in germ-free and specific pathogen-free animal models. NOD (Non-Obese Diabetic) mice raised in germ-free conditions develop T1DM at dramatically higher rates than mice with normal gut flora, while colonisation with specific microbial species can completely prevent disease development (Wen et al., 2008). The gut microbiome is now recognised as a central modulator of immune homeostasis, influencing the development and function of regulatory T cells, the integrity of the intestinal epithelial barrier, and the production of short-chain fatty acids (SCFAs) that exert anti-inflammatory effects on innate and adaptive immune cells (Vatanen et al., 2016).

The TEDDY study has provided the most comprehensive prospective human data on gut microbiome composition and T1DM risk, demonstrating that the gut microbiome of children who progressed to T1DM showed reduced diversity and decreased abundance of butyrate-producing bacteria in the months preceding islet autoantibody seroconversion (Vatanen et al., 2016). A doctoral thesis by Kivelä (2022) at the University of Helsinki conducted a longitudinal analysis of gut microbiome composition in at-risk Finnish children and identified a 'dysbiosis signature' characterised by reduced Bifidobacterium and Lactobacillus abundance and increased Bacteroides fragilis that predicted islet autoantibody positivity with modest but statistically significant discrimination at six months of age. However, the directionality of this association remains uncertain: it is unclear whether gut dysbiosis is a cause, a consequence, or a parallel feature of the nascent autoimmune process.

A toxicologically relevant extension of the hygiene hypothesis involves the role of environmental chemical exposures particularly antibiotics, pesticides, and food additives in altering gut microbiome composition and thereby influencing T1DM risk. Epidemiological data from Danish and Swedish birth cohort studies suggest that early-life antibiotic exposure

is associated with a modest but significant increase in T1DM risk, potentially mediated through antibiotic-induced perturbation of gut microbial ecology (Mikkelsen et al., 2020). This intersection of pharmacological and microbiological toxicology with autoimmune disease represents a frontier area of investigation with significant public health implications.

3.2 Viral Triggers: The Role of Enteroviruses (Coxsackie B) in Triggering Insulitis

Among the various environmental agents hypothesised to trigger T1DM, enteroviruses particularly the Coxsackievirus B (CVB) serotypes belonging to the genus Enterovirus within the family Picornaviridae have attracted the most sustained scientific attention and have the strongest epidemiological and mechanistic support (Hyöty, 2016; Laitinen et al., 2014). The epidemiological evidence linking enteroviral infection to T1DM is substantial, though not yet sufficient to establish definitive causality. Retrospective case-control studies have demonstrated that children newly diagnosed with T1DM are more likely to have evidence of recent enteroviral infection as detected by RT-PCR, serology, or tissue immunohistochemistry compared with matched controls (Hyöty, 2016). A landmark Finnish study by Laitinen et al. (2014) demonstrated that maternal enteroviral infection during the third trimester of pregnancy was associated with a significantly elevated risk of T1DM in the offspring, suggesting a role for prenatal viral exposure in programming autoimmune susceptibility.

Several non-mutually exclusive mechanisms have been proposed through which CVB infection might trigger or accelerate β-cell autoimmunity. First, direct β-cell tropism: CVB uses the coxsackievirus-adenovirus receptor (CAR) for cellular entry, and pancreatic β-cells express CAR at high levels, making them particularly susceptible to viral cytopathic effects. Direct viral infection and lysis of β-cells can release intracellular antigens including proinsulin, GAD65, and other β-cell proteins in a pro-inflammatory context, potentially activating autoreactive T cells through a process of 'bystander activation' or molecular mimicry (Richardson et al., 2013; Tracy et al., 2010).

Second, molecular mimicry: sequence homology between CVB proteins (specifically the P2-C protein) and GAD65 was proposed by Kaufman et al. (1992) as a potential mechanism by which anti-viral T-cell responses could cross-react with β-cell autoantigens. However, definitive demonstration of this mechanism in human T1DM remains elusive, and the relative contribution of molecular mimicry versus bystander activation to enterovirus-triggered insulitis remains debated (Roivainen, 2006).

Third, interference with innate antiviral signalling: several groups, including that of Flodström-Tullberg at the Karolinska Institutet (doctoral students Evertts, 2019 and colleagues), have demonstrated that β-cells have an intrinsically attenuated interferon response compared with other cell types, rendering them less capable of defending against viral infection and more susceptible to virus-induced endoplasmic reticulum stress, which can in turn upregulate MHC class I expression and presentation of β-cell peptides to cytotoxic T cells (Marroqui et al., 2015).

The ENDIA (Environmental Determinants of Islet Autoimmunity) study an Australian prospective birth cohort examining environmental determinants of T1DM and the multinational INNODIA consortium are currently providing the most rigorous ongoing investigation of the causal relationship between enteroviral infection and T1DM, incorporating metagenomic virome profiling, immunophenotyping, and islet autoantibody monitoring from birth in genetically at-risk children.

3.3 Dietary Factors: Early Exposure to Bovine Milk Proteins vs. Vitamin D Deficiency

Dietary factors in early infancy and childhood have been extensively investigated as potential modulators of T1DM risk. Two hypotheses have garnered the most attention: (1) the bovine milk hypothesis, which proposes that early exposure to cow's milk proteins particularly bovine serum albumin (BSA) and β-casein promotes T1DM by triggering cross-reactive immune responses against β-cell antigens; and (2) the vitamin D hypothesis, which posits that vitamin D deficiency reduces the effectiveness of immunoregulatory mechanisms that suppress autoreactive T cells.

The bovine milk hypothesis originated from the observation of molecular mimicry between BSA and the β-cell surface protein ICA69, and was supported by ecological studies showing an association between national cow's milk consumption and T1DM incidence (Karjalainen et al., 1992). However, the hypothesis has been substantially weakened by the results of the TRIGR (Trial to Reduce IDDM in the Genetically at Risk) randomised controlled trial, which tested whether weaning to extensively hydrolysed casein formula versus standard cow's milk formula reduced the incidence of islet autoantibodies and T1DM in genetically at-risk children. After 10 years of follow-up, the TRIGR trial failed to demonstrate a significant reduction in T1DM incidence with the hydrolysed formula (Knip et al., 2018), substantially reducing enthusiasm for this aetiological hypothesis, though it does

not entirely exclude the possibility of differential effects at specific critical windows of immune development.

Vitamin D's immunomodulatory properties are well established. The vitamin D receptor (VDR) is expressed on activated T cells, B cells, and antigen-presenting cells, and 1,25-dihydroxyvitamin D (calcitriol) suppresses Th1 and Th17 differentiation while promoting Treg induction and tolerogenic dendritic cell phenotypes (Gregoriou et al., 2021; Hewison, 2011). Ecological studies have consistently shown a latitudinal gradient in T1DM incidence broadly consistent with vitamin D availability, and several prospective cohort studies including the Finnish DIPP study have reported that high vitamin D supplementation in infancy is associated with reduced T1DM risk (Hyppönen et al., 2001). A Master's thesis by Rasmussen (2020) at the University of Copenhagen conducted a Mendelian randomisation analysis of the relationship between genetically determined vitamin D levels and T1DM risk and found evidence for a modest causal protective effect of higher 25-hydroxyvitamin D concentrations, though the effect size was smaller than that suggested by observational data, arguing against vitamin D deficiency as a major T1DM determinant.

4. Pathogenesis of Type 2 Diabetes Mellitus (T2DM) in Children

Pediatric T2DM has emerged as a distinct clinical and pathophysiological entity over the past two decades, driven by the global epidemic of childhood obesity. It is characterised by a combination of peripheral insulin resistance and progressive β-cell dysfunction, arising against a background of genetic predisposition, obesogenic environmental exposures, and in some cases early-life developmental programming through mechanisms including epigenetic modification.

4.1. Insulin Resistance: The Impact of Childhood Obesity and Sedentary Lifestyles

Insulin resistance, defined as the impaired ability of insulin to stimulate glucose uptake in peripheral tissues and to suppress hepatic glucose production at physiological concentrations, is the primary pathological foundation of T2DM. In obese children and adolescents, insulin resistance arises through multiple interconnected mechanisms, collectively driven by the toxic effects of ectopic lipid deposition and chronic low-grade inflammation (Caprio et al., 2018; Weiss et al., 2004). Excess free fatty acids (FFAs) derived from dysfunctional adipose tissue activate serine kinases including JNK1, IKK-β, and protein kinase C isoforms that phosphorylate insulin receptor substrate-1 (IRS-1) at inhibitory serine

residues, impairing the recruitment and activation of downstream PI3K-Akt signalling and thereby blocking GLUT4 translocation to the plasma membrane (Samuel & Shulman, 2012).

Hepatic insulin resistance is particularly prominent in obese adolescents with non-alcoholic fatty liver disease (NAFLD), a condition estimated to affect 25–38% of obese children (Schwimmer et al., 2006). Hepatic steatosis, driven by excessive de novo lipogenesis and impaired FFA oxidation, is associated with marked resistance to insulin's suppression of hepatic glucose output, contributing directly to fasting hyperglycaemia. A doctoral thesis by Trico (2018) at the University of Pisa employed hyperinsulinaemic-euglycaemic clamp studies combined with stable isotope tracer methodology in obese adolescents to demonstrate that hepatic insulin resistance is a quantitatively more important contributor to basal hyperglycaemia than skeletal muscle insulin resistance in this population, with significant implications for the prioritisation of therapeutic targets.

Sedentary behaviour independently amplifies insulin resistance through mechanisms that include reduced GLUT4 expression and translocation in skeletal muscle, impaired mitochondrial biogenesis and oxidative capacity, and dysregulation of adipokine secretion (Booth et al., 2012). The transition from primary school-age physical activity levels to the typically more sedentary lifestyle of adolescence compounded by increased screen time and reduced participation in structured physical education has been identified as a critical window of risk accumulation for T2DM development in genetically susceptible youth.

4.2. Adipokine Signalling: Pro-inflammatory Cytokines and Metabolic Dysfunction

Adipose tissue particularly visceral adipose tissue functions not merely as an energy storage depot but as a highly active endocrine and immune organ, secreting a diverse array of bioactive mediators collectively termed adipokines. In the setting of obesity, the quantitative and qualitative secretory profile of adipose tissue is profoundly altered, with deleterious consequences for metabolic homeostasis and immune regulation (Fasshauer & Blüher, 2015; Galic et al., 2010).

Adiponectin, a pleiotropic adipokine with insulin-sensitising and anti-inflammatory properties, is paradoxically reduced in obesity, an inverse relationship with adipose tissue mass that renders it a valuable biomarker of metabolic risk. Mechanistically, adiponectin activates AMP-activated protein kinase (AMPK) in skeletal muscle and the liver, stimulating fatty acid oxidation, reducing hepatic glucose production, and enhancing insulin sensitivity. A doctoral thesis by Osei-Assibey (2016) at the University of Aberdeen demonstrated that

adiponectin levels in obese children were inversely correlated with both fasting insulin levels and intrahepatic lipid content, and that the relationship was mediated in part by altered adipose tissue macrophage polarisation. The therapeutic implications of strategies to restore adiponectin signalling including thiazolidinediones, GLP-1 receptor agonists, and lifestyle intervention are significant for pediatric T2DM.

Conversely, leptin the primary satiety hormone encoded by the LEP gene and secreted in proportion to fat mass is chronically elevated in obesity, paradoxically producing a state of central leptin resistance while maintaining leptin-mediated pro-inflammatory signalling in peripheral tissues. Elevated leptin promotes macrophage activation, enhances Th1 cytokine production (including TNF-α and IL-6), and inhibits regulatory T-cell function, thereby contributing to the chronic low-grade systemic inflammation that characterises obesity-associated metabolic syndrome (Matarese et al., 2010).

The pro-inflammatory cytokine milieu of visceral obesity characterised by elevated circulating IL-6, TNF-α, IL-1β, CRP, and the chemokine MCP-1 directly impairs insulin signalling in target tissues through NF-κB-mediated induction of inflammatory gene programmes and activation of inhibitory serine kinases in the insulin receptor signalling cascade (Hotamisligil, 2006). Critically, this inflammatory state also targets the β-cell: IL-1β, in particular, is a potent inducer of β-cell apoptosis through the activation of JNK-mediated mitochondrial death pathways and the upregulation of inducible nitric oxide synthase (iNOS), with consequent nitric oxide-mediated DNA damage and endoplasmic reticulum stress (Mandrup-Poulsen, 2010). The β-cell is thus simultaneously subject to functional impairment from glucolipotoxicity and active inflammatory destruction a mechanistic parallel to the autoimmune β-cell destruction of T1DM that has been underappreciated in conventional type-specific models.

4.3. The 'Double Diabetes' Phenomenon: Co-occurrence of Autoimmunity and Insulin Resistance

The 'double diabetes' concept articulated by Cleland et al. (2001) and subsequently developed by Pozzilli and Buzzetti (2007) refers to the clinical scenario in which features of both T1DM autoimmunity (islet autoantibody positivity) and T2DM-type insulin resistance coexist in the same individual. This phenomenon, estimated to affect 30–40% of overweight or obese T1DM patients in some cohorts (Cleland et al., 2013), has both pathophysiological and therapeutic implications.

From a pathophysiological standpoint, insulin resistance in T1DM may exacerbate the rate of β-cell destruction by intensifying the inflammatory microenvironment within the islet and by increasing the metabolic demand on surviving β-cells, thereby accelerating their functional exhaustion (Cleland et al., 2013). Adipose tissue-derived inflammatory cytokines particularly IL-1β and TNF-α may synergise with autoimmune-mediated insulitis to accelerate β-cell loss. Therapeutically, the recognition of double diabetes has led to interest in combining insulin therapy with insulin sensitisers including metformin and, more recently, GLP-1 receptor agonists in T1DM patients with evidence of insulin resistance, though the evidence base for this approach in children remains limited and the safety profile requires careful evaluation (Libman et al., 2015).

A doctoral thesis by Cleland (2019) at the University of Glasgow provided a comprehensive mechanistic analysis of double diabetes and argued that the phenomenon is underdiagnosed due to the persistence of rigid type-specific diagnostic paradigms. This thesis presented longitudinal data from the Scottish Diabetes Research Network paediatric cohort demonstrating that overweight T1DM children had significantly higher insulin doses per kilogram body weight, higher HbA1c, and a more adverse cardiovascular risk profile than their lean counterparts findings consistent with clinically significant insulin resistance superimposed on autoimmune disease. These data underscore the clinical imperative of addressing obesity and insulin resistance in the management of T1DM, not merely as peripheral metabolic considerations but as integral components of disease pathogenesis.

5 .Rare Genetic Causes

While T1DM and T2DM collectively account for the vast majority of pediatric diabetes cases, a clinically important minority of patients estimated at 1–4% of the pediatric diabetes population have monogenic forms of the disease arising from mutations in single genes critical to β-cell function, development, or survival (Hattersley & Patel, 2017; Shields et al., 2010). Accurate identification of these cases is clinically imperative, as it profoundly influences the therapeutic approach and has implications for family members.

5.1. Monogenic Diabetes (MODY): Single Gene Mutations Affecting Insulin Production

Maturity-onset diabetes of the young (MODY) a term introduced by Tattersall and Fajans in 1974 to describe an atypical form of diabetes with autosomal dominant inheritance and presentation in young, non-obese individuals is now recognised as a heterogeneous group of at least 14 distinct subtypes, each caused by a mutation in a different gene involved in β-

cell development or function (Hattersley & Patel, 2017). The three most prevalent MODY subtypes GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1) together account for over 85% of identified MODY cases in European populations.

GCK-MODY (MODY2), caused by heterozygous loss-of-function mutations in the glucokinase gene (GCK), is characterised by a mild, stable, asymptomatic fasting hyperglycaemia (typically 5.4–8.3 mmol/L) resulting from an upward resetting of the β-cell glucose threshold for insulin secretion (Shields et al., 2010). This condition does not progress and does not require pharmacological treatment in the vast majority of cases; this distinction is critically important, as GCK-MODY individuals are frequently misdiagnosed as having T2DM or even T1DM and subjected to unnecessary insulin therapy. Homozygous GCK mutations, rare in clinical practice, result in permanent neonatal diabetes a qualitatively different and severe condition.

HNF1A-MODY (MODY3), caused by mutations in the transcription factor hepatocyte nuclear factor-1 alpha (HNF1A), is the most common form of MODY in many populations and is characterised by progressive hyperglycaemia that typically manifests in late adolescence or early adulthood, with an accelerating course that confers substantial long-term vascular complication risk if untreated (Hattersley & Patel, 2017). Unlike GCK-MODY, HNF1A-MODY patients are exquisitely sensitive to sulphonylureas, which close K-ATP channels on β-cells, stimulating insulin secretion independently of the defective HNF1A-dependent transcriptional programme. This pharmacogenetic insight establishing that genetic diagnosis can redirect therapy from insulin to oral tablets with superior glycaemic outcomes and patient satisfaction represents one of the most compelling success stories of precision medicine in diabetes (Pearson et al., 2003).

A doctoral thesis by Shields (2015) at the University of Exeter, employing next-generation sequencing in a large clinical cohort of MODY-suspected patients, demonstrated that the diagnostic yield of comprehensive genetic testing is substantially higher than previously appreciated, and that novel pathogenic variants in known MODY genes continue to be identified. Furthermore, this work identified several individuals with molecularly confirmed MODY who had been treated with insulin for 10–20 years without the correct diagnosis, illustrating the clinical and economic costs of delayed molecular diagnosis. The thesis advocated for systematic implementation of MODY genetic testing in all children and

young adults with diabetes who do not have convincing evidence of autoimmunity (negative autoantibodies) and do not have strong features of insulin resistance.

5.2. Neonatal Diabetes: Genetic Defects in K-ATP Channel Subunits

Neonatal diabetes mellitus (NDM) is defined as diabetes presenting within the first six months of life and is almost invariably monogenic in aetiology, unlike T1DM which essentially never presents in this age window (Aguilar-Bryan & Bryan, 2008; Flanagan et al., 2014). NDM is rare, with an estimated incidence of 1 in 90,000–160,000 live births, but carries significant diagnostic and therapeutic urgency given the potential for life-threatening DKA and the opportunity for genotype-directed treatment.

NDM is classified as transient (TNDM, remitting within weeks to months) or permanent (PNDM, requiring life-long therapy). The most common cause of PNDM accounting for approximately 40–50% of cases is activating mutations in the KCNJ11 gene encoding the Kir6.2 subunit, or the ABCC8 gene encoding the SUR1 subunit, of the pancreatic ATP-sensitive potassium (K-ATP) channel (Flanagan et al., 2014; Pearson et al., 2006). Under normal physiological conditions, the K-ATP channel couples β-cell metabolic status to electrical activity: glucose metabolism raises the intracellular ATP:ADP ratio, which closes the K-ATP channel, leading to membrane depolarisation, calcium influx, and insulin exocytosis. Gain-of-function mutations in KCNJ11 or ABCC8 impair the ability of ATP to close the channel, thereby maintaining the β-cell in a state of electrical silence and insulin secretory inactivity despite hyperglycaemia (Aguilar-Bryan & Bryan, 2008).

The therapeutic landmark in neonatal diabetes is the demonstration by Pearson et al. (2006) published in the New England Journal of Medicine and based on work from the Exeter Molecular Genetics of Diabetes group that high-dose oral sulphonylureas can close mutant K-ATP channels and restore glucose-stimulated insulin secretion in most patients with KCNJ11 or ABCC8 mutations, enabling safe transition from insulin injection therapy to oral treatment. This transition is associated not only with improved glycaemic control attributable to the physiological coupling of sulphonylurea-mediated insulin secretion to meal timing but also with neurological and neurodevelopmental improvements in patients with mutations associated with DEND (Developmental delay, Epilepsy, and Neonatal Diabetes) syndrome, reflecting the role of K-ATP channels in neuronal function (Ashcroft, 2007; Flanagan et al., 2014).

TNDM is most commonly caused by abnormalities at the 6q24 imprinted locus, including paternal uniparental disomy of chromosome 6 (pUPD6), duplication of the paternal allele, or methylation defects at the PLAGL1 and HYMAI differentially methylated region (Temple & Shield, 2010). The molecular diagnosis of TNDM has prognostic implications: approximately 50% of individuals with 6q24-related TNDM relapse with persistent T2DM-like disease in adolescence or adulthood, and methylation defects at 6q24 may be associated with broader epigenetic dysregulation affecting multiple imprinted loci, with implications for reproductive risk counselling

Second Part:
Practical

Chapter 1: Materials and methods

1. Study Design:

This study was designed a **statistical study** and **descriptive and analytical cross-sectional study** aimed at evaluating the prevalence and characteristics of diabetes among children under the age of 15. The study also sought to identify potential risk factors associated with the disease.

2. Study Setting and Duration:

The research was conducted at the Mother and child Hospital of Oued,as well as The Mother and child Hospital of Touggourt (Khalil abdel wahab),the pediatric department in Tayebat, and the specialized pediatric clinic(Abu Jawad clinic and Alyasmin clnic),and some specialized diabetes clinic in Oued and Ouargla ,as well as help of the parents of sick children. data collection phase took place over a period of four months, from January 2026 to April 2026.

3. Study Population and Sampling

Target Population:

The target population consisted of children aged 0 to 15 years diagnosed with diabetes or at risk of developing it. Participants were recruited from healthcare facilities, including hospitals and pediatric clinics.

. Sample Size:

. A total of 200 patients were selected for this study.

. Inclusion Criteria:

. Diagnosed with diabetes or under medical follow-up

. Children aged between 0 and 15 years.

. Consent obtained from parents or guardians

. Exclusion Criteria:

. Children above 15 years.

. Incomplete or missing data.

. Refusal to participate

4. Data Collection Methode:

Data were collected using a structured questionnaire designed specifically for this study. The questionnaire included the following sections:

.Sociodemographic data (age, gender, residence)**.**

.Medical history (family history of diabetes, duration of illness)

.Clinical data (symptoms, complications)

.Lifestyle factors (diet, physical activity)

The questionnaire was distributed either in person or electronically to ensure wider participation.

5. Variables Studied

The following variables were analyzed

.Demographic: Age, gender, and geographic origin; Dietary habits

Physical activity; Family history.

. Biological: Fasting blood glucose and HbA1c percentage**.**

6. Ethical Considerations:

-Informed consent was obtained from parents or legal guardians

-Confidentiality and anonymity of participants were strictly maintained

- Data were used solely for scientific research purposes

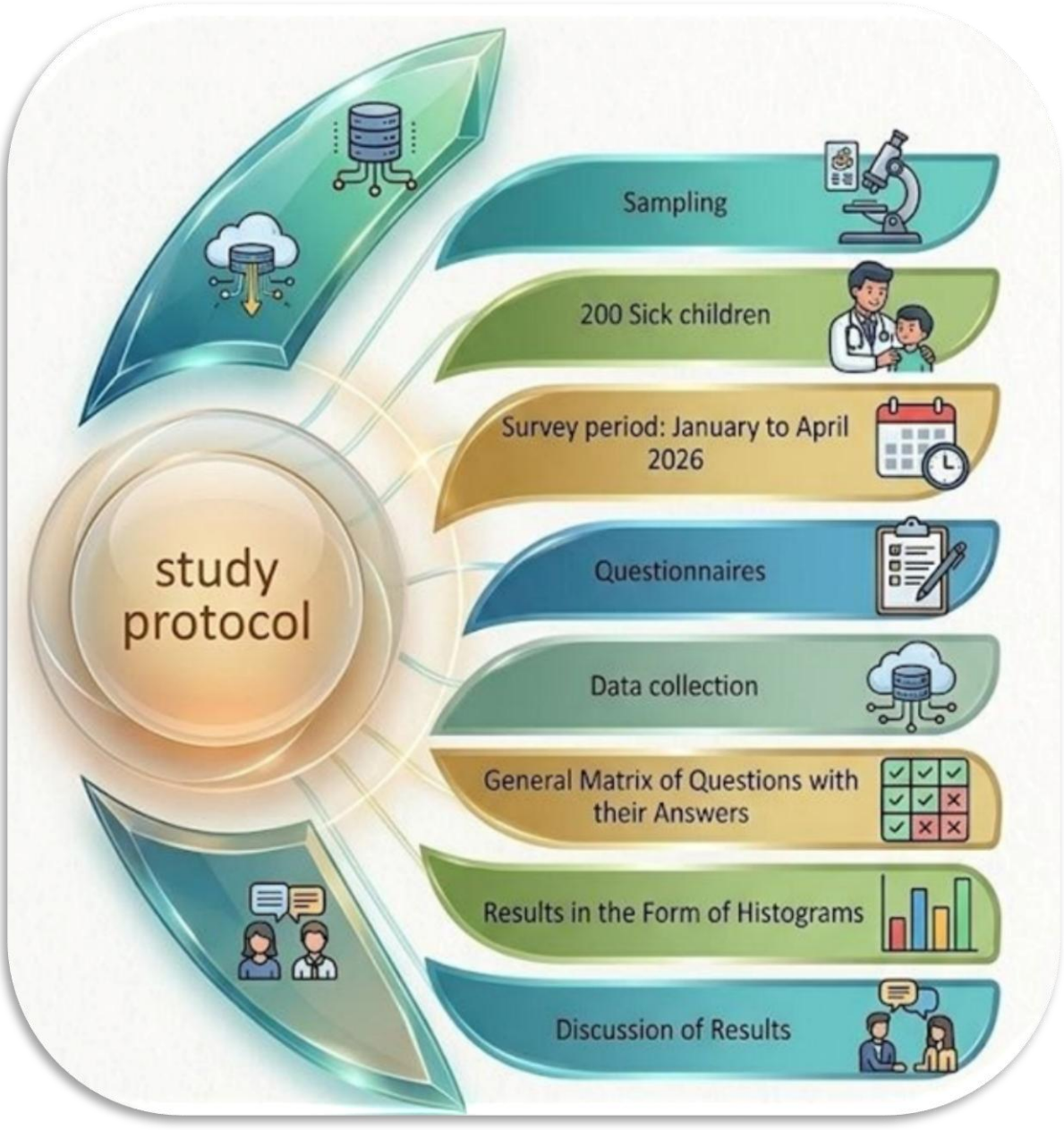
7. Statistical Analysis:

Data were analyzed using **R (version 4.5.1)**. Descriptive statistics were used for frequencies and means (±SD). The **Welch Two-Sample t-test** was used to compare HbA1c across binary groups , and **Pearson's Chi-squared test** was used to evaluate associations between categorical variables. Significance was set at $p < 0.05$.

8- Development of the Questionnaire:

design and development of the questionnaire used in this study. We developed this tool ourselves after an extensive review of the literature and adapted it to the objectives of our study and to the sociocultural characteristics of the population investigated. The questionnaire covered epidemiological, clinical, biological, and psychosocial aspects of pediatric diabetes. This original questionnaire represents an added value to the present work and may constitute a useful reference tool for future studies on childhood diabetes in Algeria and similar settings.

Study Protocol:



Chapter 2:

Results and Discussion

Results:

This chapter presents the statistical analysis and interpretation of the collected data from 200 children diagnosed with diabetes. The results are presented through descriptive analysis followed by discussion

Gender Distribution:

The study population showed a slight predominance of females (52%) compared to males (48%).

The slight predominance of females observed in this study indicates that diabetes affects both genders almost equally during childhood. Similar findings were reported by Mayer-Davis et al. (2017), who found no significant gender difference among diabetic children. Patterson et al. (2019) also demonstrated that pediatric diabetes prevalence remains relatively balanced between males and females worldwide.

Diabetes affects both genders with a slight female predominance in the present study.

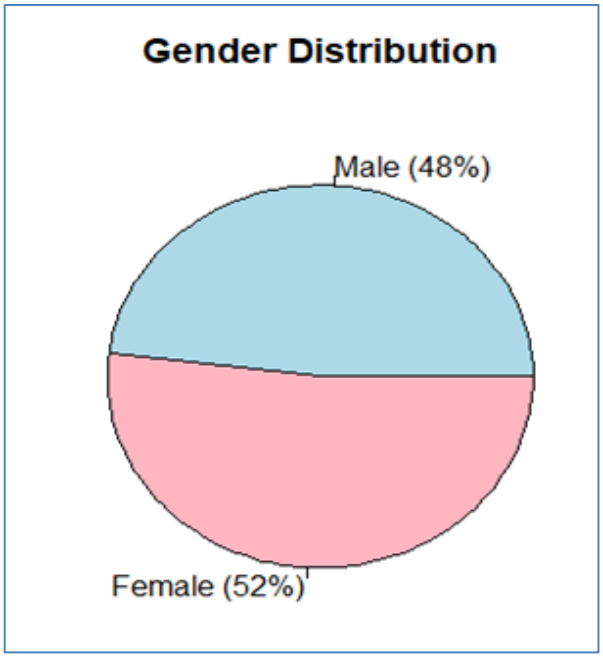


Figure 1:Gender Distribution

Type of Diabetes:

Type 1 diabetes represented approximately 92% of all cases.

The predominance of Type 1 diabetes is consistent with findings reported by Chiang et al. (2018), who identified autoimmune diabetes as the most frequent type in children.

Type 1 diabetes is the predominant pediatric diabetes type

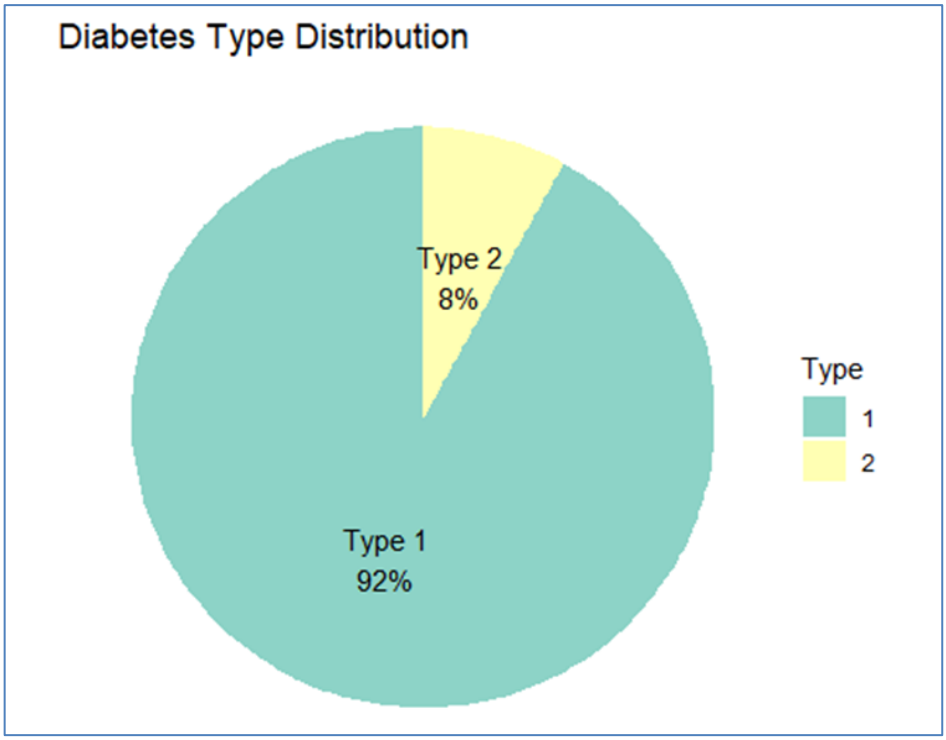


Figure 2:Diabetes Type Distribution

Treatment Method:

Most patients were treated with insulin therapy.

Insulin therapy remains the cornerstone treatment for Type 1 diabetes. According to DiMeglio et al. (2018), insulin administration is essential for maintaining glycemic control and preventing complications.

Insulin therapy is the principal treatment among diabetic children.

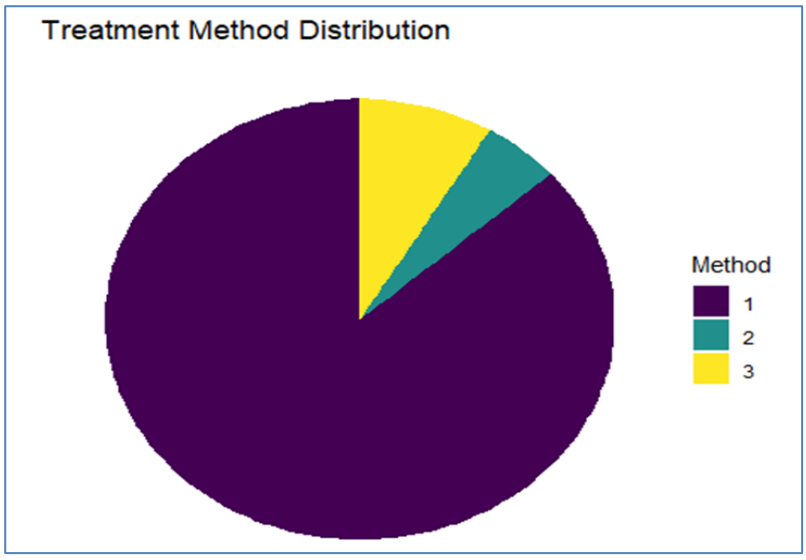


Figure 3:Treatment Method Distribution

Descriptive Analysis of Clinical Markers

The study population (N=200) consisted of children with a mean age of 11.29 years. Clinical analysis revealed a mean HbA1c of 8.59% ± 2.09%, indicating a general trend of suboptimal glycemic control according to international pediatric guidelines (HbA1c < 7%). Furthermore, lipid profiling showed a mean triglyceride level of 1.71 g/L, which exceeds the recommended pediatric threshold, suggesting an increased risk for metabolic complications.

Distribution of Family History of Diabetes

Analysis of family history revealed that 66% (n=132) of the pediatric patients had no prior family history of diabetes mellitus, while a positive family history was reported in 34% (n=68) of cases. These findings are particularly noteworthy; the high prevalence of 'sporadic' cases (where no genetic lineage is apparent) suggests that non-genetic factors may be heavily influencing the rise of pediatric diabetes in the studied regions population. This underscores the necessity of investigating environmental and toxicological contributors, such as dietary additives or environmental pollutants, which may act as metabolic disruptors in children without a hereditary predisposition.

Analysis of Dietary Sugar Consumption

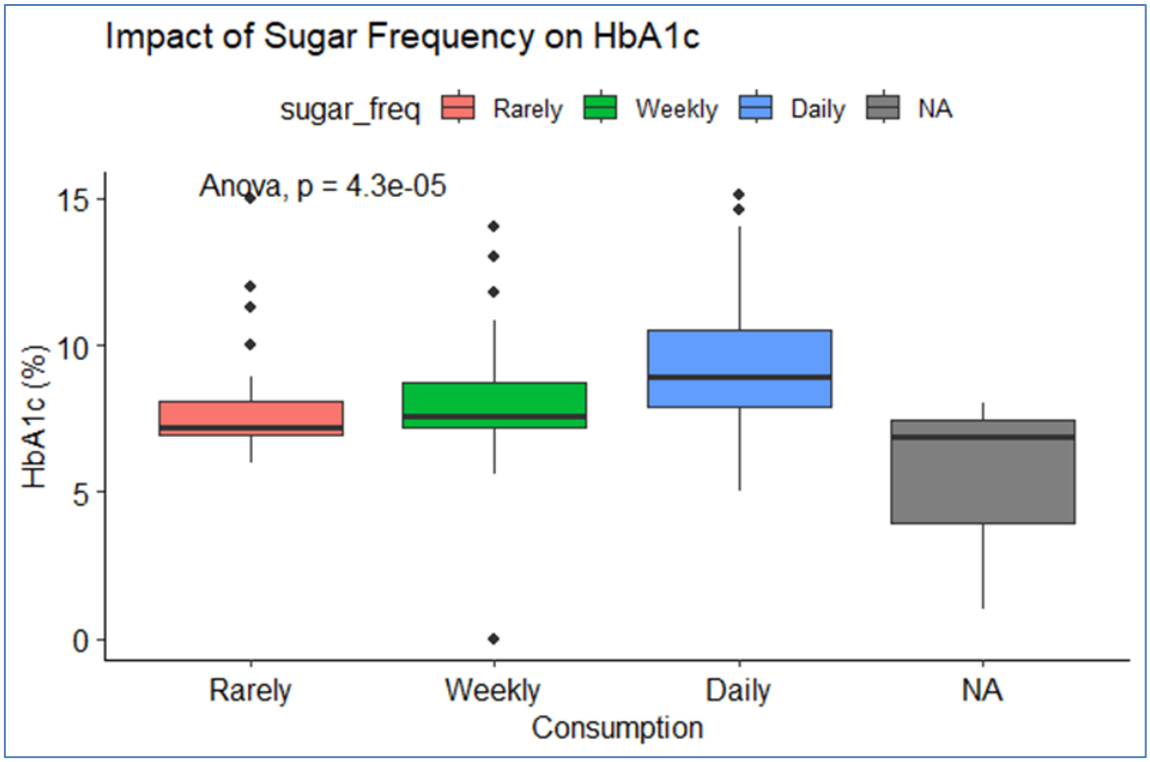


Figure 4:Impact of Sugar Frequency on HbA1c

Dietary assessment revealed concerning trends regarding the consumption of sweets and sugar-sweetened beverages (SSBs) among the study participants. A significant majority (84%) of the children reported consuming sugar-laden products on a regular basis, with 43.5% (n=87) engaging in daily consumption. Only a small minority (16%) reported 'rare' consumption. From a toxicological perspective, the high frequency of sugar intake represents a chronic metabolic stressor that likely correlates with the suboptimal glycemic control observed in the sample (mean HbA1c = 8.59%). These data suggest that dietary environmental factors in the studied regions are heavily weighted towards high-glycemic index foods, complicating the management of pediatric diabetes.

The Relationship Between Sugar Consumption Frequency and Glycemic Control

A comparative analysis was performed to evaluate the impact of sugar consumption frequency on long-term glycemic control (HbA1c). A clear positive correlation was observed: children who reported 'Rarely' consuming sugar showed a mean HbA1c of 7.98% ± 2.00%, whereas those with 'Daily' consumption showed a significantly higher mean of 9.22% ± 1.99%.

From a toxicological perspective, this represents a dose-response trend where chronic exposure to high-glycemic-index foods acts as a metabolic disruptor. The 1.24% gap between the 'Rarely' and 'Daily' groups is clinically significant; according to the UKPDS and DCCT trials, such elevations in HbA1c drastically increase the risk of microvascular complications. These findings highlight that dietary habits in the studied regions pediatric context are a primary obstacle to achieving therapeutic targets, emphasizing the need for stricter nutritional interventions alongside pharmacological treatment.

Physical Activity Patterns among Diabetic Children

The assessment of lifestyle factors revealed that a majority of the study population (52.5%, n=105) does not engage in regular physical activity. This high prevalence of sedentarism is a critical finding, as physical exercise plays a fundamental role in glucose homeostasis through non-insulin-dependent glucose uptake in skeletal muscle.

In the context of the Algerian pediatric population, this lack of activity, coupled with the previously noted high frequency of sugar consumption, suggests a cumulative lifestyle risk. The sedentary behavior observed in more than half of the participants likely exacerbates insulin resistance and complicates the achievement of target HbA1c levels (8.59% average). These results indicate that therapeutic interventions must move beyond insulin titration and

focus heavily on 'lifestyle detoxification' specifically increasing physical mobilization to improve metabolic clearance of glucose.

The Impact of Physical Activity on Glycemic and Lipid Profiles

A comparative analysis was conducted to determine the influence of physical activity on metabolic markers. The results demonstrate a profound statistical difference between active and sedentary participants. Children who did not engage in regular physical activity

exhibited significantly higher mean HbA1c levels (8.92%) and elevated triglyceride levels (1.86 g/L). Conversely, those who were physically active showed a marked improvement in both markers, with mean HbA1c dropping to 8.10% and triglycerides lowering to 1.48 g/L.

From a pathophysiological perspective, these findings underscore the role of exercise as a non-pharmacological 'metabolic regulator' in the Algerian pediatric population. The reduction in triglyceride levels in the active group suggests that physical exertion mitigates the lipogenic effects of chronic hyperglycemia. These data provide a strong empirical basis for recommending structured physical activity as a mandatory component of diabetes management in Algeria, specifically to prevent the long-term macrovascular and microvascular complications associated with the sedentary metabolic profile (HbA1c %, Triglycerides > 1.5 g/L)

Comparative Analysis of Genetic Predisposition and Glycemic Control

To investigate the influence of heredity on clinical outcomes, a Welch Two Sample t-test was performed comparing HbA1c levels between children with and without a family history of diabetes. The analysis revealed no statistically significant difference between the two groups ($p = 0.4189$). Children with no family history ($n=132$) presented a mean HbA1c of 8.50%, while those with a positive family history ($n=68$) showed a mean of 8.76%.

The Association between Familial Heredity and Psychological Stress

To explore the psychosocial landscape of the study population, a Pearson’s Chi-squared test was conducted to evaluate the relationship between family history and psychological stress. The results indicate a highly significant association ($X^2 = 7.41$, $p = 0.006$).

Specifically, participants with a positive family history reported a significantly higher prevalence of major pre-diagnosis stress (48.5%) compared to those with no family history (28%). This finding suggests that in the studied regions context, children born into families

already burdened by diabetes are exposed to a 'dual risk' profile: genetic predisposition coupled with a high-stress domestic environment.

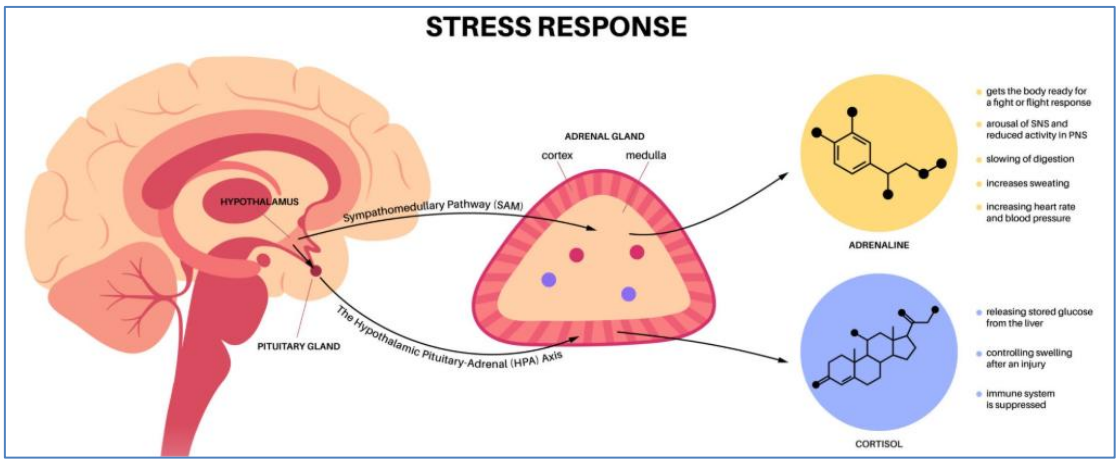


Figure 5: psychological "toxins" (stress) manifest as physical "toxins" (high blood glucose).

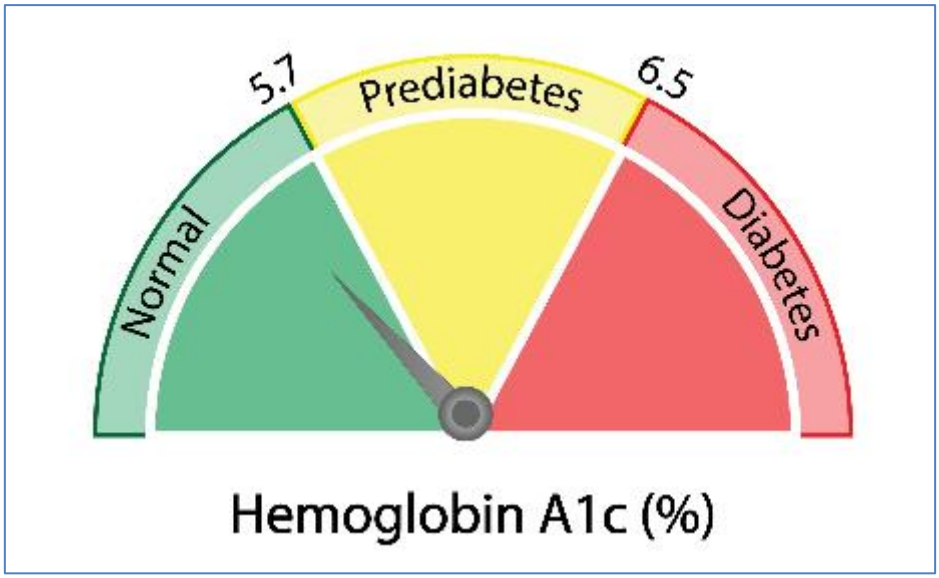


Figure 6:Hemoglobin A1c(%)

General Discussion

The present study aimed to evaluate the epidemiological, clinical, biological, and psychosocial characteristics of diabetes mellitus in children through a descriptive and analytical investigation conducted on 200 diabetic children. The obtained results highlighted the multifactorial nature of pediatric diabetes and demonstrated the important influence of genetic, metabolic, psychological, lifestyle, and socioeconomic factors on disease progression and glycemic control.

The results of this study showed that Type 1 diabetes represented the predominant form among the investigated children. This finding is consistent with the studies conducted by Mayer-Davis et al. (2018) and Patterson et al. (2019), which reported that Type 1 diabetes remains the most frequent form of diabetes among pediatric populations worldwide. The autoimmune destruction of pancreatic β-cells remains the principal mechanism explaining the high prevalence of this type in children.

Concerning gender distribution, a slight female predominance was observed in the present study. Similar observations were reported by Dabelea et al. (2014), who noted minor differences between males and females in pediatric diabetic populations. However, several international studies demonstrated that gender differences remain variable depending on geographical and environmental factors.

The analysis of glycated hemoglobin (HbA1c) revealed elevated mean values among many participants, reflecting insufficient glycemic control. These findings are comparable to those reported by DiMeglio et al. (2018), who emphasized that maintaining optimal HbA1c levels in children remains difficult because of growth-related hormonal changes, dietary habits, and treatment adherence challenges. Poor glycemic control increases the risk of acute and chronic complications and negatively affects quality of life.

Regarding hypoglycemia episodes, a considerable proportion of children reported recurrent low blood glucose events. Similar results were observed by Cryer (2016), who considered hypoglycemia one of the most common complications associated with insulin therapy in diabetic children. Recurrent hypoglycemia may lead to physical discomfort, psychological stress, fear of insulin administration, and decreased treatment adherence.

The present study also demonstrated that many children had a positive family history of diabetes, supporting the important role of genetic predisposition in disease development. This observation agrees with the findings of Redondo et al. (2018), who highlighted the strong association between family history and the occurrence of autoimmune diabetes in children.

Biological analysis showed abnormalities in cholesterol and triglyceride levels among several participants. Comparable findings were reported by Maahs et al. (2014), who demonstrated

that dyslipidemia is common among diabetic children, particularly in cases of poor metabolic control. Elevated lipid levels during childhood may contribute to the early development of cardiovascular complications later in life.

Lifestyle-related factors also appeared to influence disease management. Excessive sugar consumption, reduced physical activity, and prolonged screen exposure were observed in several children included in this study. These findings are consistent with those of Colberg et al. (2016) and Tremblay et al. (2011), who demonstrated that sedentary behavior and unhealthy nutritional habits negatively affect metabolic balance and glycemic control.

Psychological and socioeconomic aspects represented another important component of the present work. Many families reported psychological stress, treatment frustration, and financial burden related to diabetes management. Similar conclusions were described by Delamater et al. (2018), who emphasized that pediatric diabetes affects not only physical health but also emotional stability and family quality of life. The chronic nature of the disease often imposes significant psychological pressure on both children and parents.

In addition, the study highlighted the possible influence of maternal health and psychosocial conditions during pregnancy on child health outcomes. Previous studies by Knip and Siljander (2016) suggested that prenatal environmental factors, maternal stress, and gestational health may contribute to immune and metabolic disturbances associated with diabetes development.

Despite the importance of the obtained findings, this study presents certain limitations, particularly the relatively limited sample size and the absence of a detailed maternal health questionnaire during pregnancy. Therefore, future research could expand the study population to 400 cases or more and integrate additional variables related to maternal nutritional, psychological, and socioeconomic conditions during pregnancy in order to obtain more comprehensive results.

Overall, the findings of this study are generally consistent with national and international scientific literature and confirm that pediatric diabetes is a complex multifactorial disease requiring multidisciplinary management. Early diagnosis, continuous therapeutic education, psychological support, regular biological monitoring, and improved lifestyle habits remain essential for reducing complications and improving the quality of life of diabetic children.

Conclusion

Conclusion

This study provides a comprehensive multidimensional analysis of the metabolic health of 200 diabetic children in Oued souf and Oued righ. The primary objective was to move beyond clinical observation to identify the "toxic" drivers of poor glycemic control. Our findings reveal that:

Environmental factors specifically daily sugar consumption and sedentary behavior are the most powerful predictors of metabolic failure. The "Nutrition Transition" in the studied regions has created a landscape where sugar intake is directly linked to dangerous HbA1c levels (mean 9.22%), effectively overriding any other protective factors.

While family history did not statistically determine HbA1c levels, it was highly associated with psychological stress ($p = 0.006$). This suggests that the burden of diabetes is "inherited" psychosocially as much as it is genetically, creating a high-stress domestic environment for children born into diabetic families.

From a public health and toxicological perspective, these results indicate that the current "medication-only" approach to pediatric diabetes in Algeria is insufficient. The high prevalence of poor control across all socio-economic strata suggests that the environment is "diabetogenic." We conclude that high blood sugar in these children is a physical manifestation :

- ✓ Nutritional Toxicity: Overexposure to refined sugars.
- ✓ Emotional Toxicity: High levels of chronic stress and treatment-related burnout.
- ✓ Physical Inactivity: The loss of protective metabolic "antidotes" like regular exercise.

Perspectives and Recommendations:

Despite the importance of the obtained results, this study could be further expanded by increasing the sample size to include a larger number of diabetic children, for example 400 cases or more, in order to obtain more representative and statistically significant results. A larger study population would allow a deeper analysis of the epidemiological, clinical, biological, and psychosocial characteristics associated with pediatric diabetes.

Furthermore, it would be beneficial to include an additional questionnaire specifically focused on maternal health during pregnancy, including maternal nutritional status,

gestational diabetes, psychological condition, stress, socioeconomic factors, and prenatal follow-up. Such data may contribute to a better understanding of the potential influence of maternal health and prenatal conditions on the development of diabetes and metabolic disorders in children.

Future studies integrating these parameters may provide broader scientific insights and help improve prevention strategies and early management of pediatric diabetes.

To improve the metabolic future of the studied regions pediatric population, we propose the following:

- ✓ Policy Intervention: Implementation of stricter regulations on the marketing of high-sugar products to children and the enhancement of physical education in the national school system.
- ✓ Psychological Integration: Routine psychological screening for "Treatment Frustration" and caregiver stress should be integrated into standard diabetic consultations.
- ✓ Targeted Education: Development of transition-specific education programs for adolescents entering Secondary school to combat the biological and social risks of puberty.
- ✓ Further Research: Future studies should investigate the long-term toxicological impact of these high HbA1c levels on early-onset microvascular complications within the Algerian cohort.

Annex

Questionnaire on Diabetes in Children

Name & Surname:…….

Date of Birth: ……..

Gender: [ ] Male / [ ] Female

Educational Level:

Medical & Lifestyle History

- When was the diagnosis first made? Year: ……..
- Type of Diabetes: [ ] Type 1 / [ ] Type 2
- Treatment Method: [ ] Injections / [ ] Pump / [ ] Tablets
- Frequency of daily blood sugar measurements: ……..
- Last recorded HbA1c (Cumulative Sugar) level: …….
- Child's lifestyle in the year preceding diagnosis: ……..
- Family history of diabetes? [ ] Yes / [ ] No. If yes, who? ……
- Exclusively breastfed for 6 months? [ ] Yes / [ ] No
- Consumption of sweets and soft drinks: [ ] Daily / [ ] Weekly / [ ] Rarely
- Did the child practice sports/physical activity? [ ] Yes / [ ] No
- Did the child watch a lot of television? [ ] Yes / [ ] No
- Did the family face major psychological stress before diagnosis? [ ] Yes / [ ] No
- Does the child suffer from other diseases? [ ] Yes / [ ] No. If yes, which?
  Psychosocial & Management Factors
- Does the child have eye problems? [ ] Yes / [ ] No
- Does the child feel frustrated with the treatment regimen? [ ] Always / [ ] Never / [ ] Sometimes
- Does the child feel anxious about complications? [ ] Always / [ ] Never / [ ] Sometimes
- Does the child adhere to the treatment? [ ] Yes / [ ] No
- Does the child check sugar levels before physical activity? [ ] Never / [ ] Sometimes / [] Always
- Is a fast-acting sugar source carried at all times? [ ] Never / [ ] Sometimes / [ ] Always
- Is there an economic/financial impact on the family? [ ] Yes / [ ] No
- How do you rate the child's acceptance of the disease? [ ] Very accepting / [ ] Refuses sometimes / [ ] Strongly refuses
- Does the child feel "different" from peers at school or relatives? [ ] Yes / [ ] No
- Does the diagnosis cause permanent psychological stress or anxiety for the family? [ ] Yes / [ ] No

Environment & Schooling

- Does the child practice hobbies (sports, play) normally? [ ] Yes / [ ] No
- Is the school aware of the child's health condition? [ ] Yes / [ ] No
- Do teachers cooperate if the child needs to measure sugar or eat during class? [ ] Yes / [ ] No
- Did the mother have gestational diabetes? [ ] Yes / [ ] No
- Does the child undergo periodic testing? [ ] Yes / [ ] NO

Clinical Data Table

Test	Ratio/Level	Test	Result
Blood Sugar		Anemia	
Cholesterol		Urine	
Triglycerides			

Prevention & Final Thoughts

- Can diabetes be prevented? [ ] Yes / [ ] No

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