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PhD THESIS

THE METABOLIC IMPLICATIONS OF THE ASSOCIATION OF AUTOIMMUNE DISEASES IN TYPE 1 DIABETES IN CHILDREN AND ADOLESCENTS

PhD Thesis Summary

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INTRODUCTION

Type 1 diabetes (T1D) is a chronic autoimmune condition that affects the body's ability to produce insulin, a hormone essential for regulating blood glucose levels. Characterized by the destruction of the beta cells of the pancreas, this condition requires daily insulin administration and constant blood glucose monitoring.

Over time, people with T1DM have been found to be susceptible to a number of other autoimmune diseases, suggesting a common genetic and immunological predisposition. The impact of autoimmune diseases on patients with type 1 diabetes is an important area of research. particularly, due to the additional complications and complexity of medical management that these comorbidities introduce.

Autoimmune diseases associated with T1D, such as Hashimoto's thyroiditis, celiac disease, and Addison's disease, can worsen the patient's general health and complicate diabetes treatment.

This thesis aims to explore the impact of autoimmune diseases on patients with type 1 diabetes, examining both the common pathogenetic mechanisms and the clinical and therapeutic effects of this coexistence.

I will analyze the incidence and prevalence of these diseases among patients with T1D, and how they influence glycemic control, risk of acute and chronic complications, and quality of life.

The research will also focus on identifying risk factors that predispose to the simultaneous development of DM1 and other autoimmune diseases, thus providing insights into the underlying mechanisms and possible directions for future therapeutic interventions.

Understanding these complex interactions is essential for the development of more effective and personalized management strategies that improve the prognosis and quality of life of patients with type 1 diabetes and autoimmune comorbidities.

The work is structured in two parts: The general, theoretical part - The current state of knowledge and The special part - Personal contribution

The general part includes 4 chapters (71 pages):

- Chapter 1 includes notions about diabetes mellitus, reviewing data on definition, classification, current epidemiological data, the incidence of type 1 diabetes mellitus worldwide, as well as in Romania, highlighting the triggering mechanisms of autoimmunity in type 1 diabetes mellitus, starting from arguments clinical, histological, humoral and cellular mediated autoimmunity

- Chapter 2 includes notions related to autoimmune diseases associated with type 1 diabetes. The most common comorbidities associated with type I diabetes are autoimmune thyroid disease and celiac disease. Other, less frequently associated pathologies are: Addison's disease, Vitiligo, Autoimmune Gastritis, and in other situations Diabetes Mellitus can be a component of Autoimmune Polyglandular Syndrome. We made a synthesis of the main epidemiological notions related to the association of autoimmune diseases in type 1 diabetes, as well as mentioning the etiopathogenic mechanisms involved. Taking into account the importance of the association of autoimmune diseases in type 1 diabetes, in this chapter we performed a brief analysis of the mechanisms involved in their occurrence. At the same time, this chapter provides a mirror of the data related to the clinical picture of autoimmune diseases that can be associated with DM1.

- Chapter 3 includes an overview of the impact of Vitamin D, which plays an essential role in the regulation of calcium-phosphorus metabolism but also in the so-called extraskeletal actions, especially in the pediatric population. Although there is sufficient global agreement to consider 400 IU/day as the dietary reference value for vitamin D during the first year of life, recommended reference values for children and adolescents (1-18 years) differ slightly between organizations and societies,877reflecting different approaches and methods applied for their calculation. However, different dietary reference values for vitamin D are useful to guide local strategies for vitamin D supplementation, but are not directly comparable.

- **Chapter 4** includes up-to-date information on the Novelty of the 21st century - Continuous blood glucose monitoring systems. As the prevalence of diabetes is continuously increasing, better management is needed to achieve glycemic control, prevent complications and reduce the burden of this disease. Continuous glucose monitoring systems have revolutionized the management of diabetes, especially for patients with type 1 diabetes. Avoiding glycemic variability and maintaining optimal glycemic control is crucial for the evolution of patients with type 1 diabetes.

The special part includes 7 chapters (171 pages) - The personal contribution includes the observational, descriptive, longitudinal study that included 182 patients aged 0-18 enrolled from the Department of Pediatrics, Department of Diabetes, Nutrition and Metabolic Diseases, of the Hospital County Emergency Clinic, St. Apostol Andrei", Constanța, in the period 2011-2021.

In this part of the thesis, the information was structured in 7 chapters:

- **Chapter 1** – Working hypothesis and general objectives
- **Chapter 2** – General research methodology
- **Chapter 3** – Characterization of the pediatric patient diagnosed with type 1 diabetes
- **Chapter 4** – Autoimmune diseases associated with type 1 diabetes
- **Chapter 5** - The consequences of metabolic imbalance in children and adolescents with type 1 diabetes
- **Chapter 6** – Conclusions
- **Chapter 7** – Originality and innovative contributions of the thesis

1. Working hypothesis/objectives

Topic: The metabolic implications of the association of autoimmune diseases in type 1 diabetes in children and adolescents

Working hypothesis:

Associations between autoimmune diseases and type 1 diabetes in children have significant metabolic implications. Type 1 diabetes itself is the result of an autoimmune reaction in which the immune system attacks and destroys the insulin-producing beta cells in

the pancreas. If a child has other autoimmune diseases besides type 1 diabetes, such as autoimmune thyroiditis or celiac disease, this can affect glycemic control and overall metabolism in several ways:

- Complexity of management: Children with type 1 diabetes and concomitant autoimmune diseases may have a more complex therapeutic management. For example, the need to manage specific diets for celiac disease or insulin dosage adjustments for thyroid complications.
- Immune interactions: The existence of several autoimmune diseases may suggest a complex immunological predisposition. This may influence the response to type 1 diabetes-specific treatments or other therapeutic interventions.
- Risk of complications: Some autoimmune diseases may be associated with an increased risk of metabolic or vascular complications in type 1 diabetes. For example, untreated or uncompensated autoimmune thyroiditis may affect glycemic control or influence lipid metabolism.
- Monitoring and screening: Children with type 1 diabetes should be monitored and evaluated regularly for other autoimmune diseases in order to intervene early if symptoms or significant metabolic changes occur.

In the context of the discussion about the metabolic implications of the association of autoimmune diseases in type 1 diabetes in children, a working hypothesis could be: The simultaneous presence of other autoimmune diseases in children with type 1 diabetes can influence glucose metabolism and glycemic management in a way complex and variable.

The association of autoimmune diseases with type 1 diabetes in children can have profound implications for clinical and lifestyle management, requiring an integrated and coordinated approach from the medical team to ensure the best metabolic control and quality of life for affected children.

General objectives:

The purpose of this study is to investigate the metabolic implications of the coexistence of autoimmune diseases in type 1 diabetes in children. More precisely, the study aims to:

- Assessing the impact of the association of autoimmune diseases on glycemic control: Studying how the presence of other autoimmune diseases affects glucose levels and insulin requirements in type 1 diabetes.

- Evaluation of the Prevalence of Associated Autoimmune Diseases: Determining the prevalence of diseases

autoimmune diseases among children and adolescents with type 1 diabetes.

- Identifying the types of autoimmune diseases most frequently encountered in this population.

- Metabolic Impact Analysis: Investigating the metabolic effects of associated autoimmune diseases on patients with type 1 diabetes.

- Comparison of metabolic parameters (HbA1c, average blood glucose, insulin requirement, etc.) between patients with and without associated autoimmune diseases.

- Clinical Management Study: Evaluation of necessary changes in the management of type 1 diabetes in patients with associated autoimmune diseases.

- Analysis of treatment and monitoring strategies to optimize glycemic control in the presence of autoimmune diseases.

- Evaluation of Complications: Investigation of the incidence and severity of acute and chronic complications of type 1 diabetes in the presence of associated autoimmune diseases.

- Analysis of metabolic and vascular complications: Investigating the increased risk of complications associated with type 1 diabetes in the presence of other autoimmune diseases, such as thyroid dysfunction or metabolic disorders.

- Study of the impact of autoimmune diseases on the risk of complications

diabetes.

- Quality of Life Analysis: Evaluation of the impact of the combination of autoimmune diseases and type 1 diabetes on the quality of life of children and adolescents.

- Development of Clinical Recommendations: Formulation of clinical recommendations for the monitoring and treatment of children and adolescents with type 1 diabetes and related autoimmune diseases, to improve holistic health management

- Investigating risk factors that could predict the development and progression of other autoimmune diseases among children with type 1 diabetes.

- Studying the effectiveness of combined treatments and management strategies to optimize metabolic control in this particular population. Identifying predictive factors and prognostic markers

- Identification of preventive measures to reduce the negative impact of autoimmune diseases on type 1 diabetes.

By achieving these objectives, the work aims to provide a clear picture of the metabolic implications of the association of autoimmune diseases in type 1 diabetes in children and adolescents and to contribute to improving the clinical management and quality of life of these patients affected by complex conditions.

The research topic is extremely current and important. It reflects current trends and concerns in the field of pediatric and endocrinological health, considering the following reasons:

- Increasing Incidence of Autoimmune Diseases: There is a significant increase in the incidence of autoimmune diseases globally, including in children. Understanding how these conditions interact with type 1 diabetes is crucial to the holistic management of patients.

- Complexity of Management: Children with type 1 diabetes and associated autoimmune diseases require complex medical management. Studying the metabolic implications helps to optimize treatment and prevent complications.

- Improving the Quality of Life: By investigating the impact of autoimmune diseases on metabolism in type 1 diabetes, more effective strategies can be developed to improve the quality of life of these patients.

- Advances in Research: Modern technologies and recent discoveries in the field

genetics and immunology provide new insights into understanding and treating these conditions. This context makes the research topic particularly relevant and timely.

Thus, the study on the metabolic implications of the association of autoimmune diseases in type 1 diabetes in children is not only topical, but also essential for progress in the medical field.

2. General methodology

The current doctoral research has obtained the approval of the Ethics Commission of the "Sf Apostol Andrei" Emergency County Clinical Hospital, Constanta no. 8600/06.02.2023.

The present research represents a descriptive observational study. In this study we included 182 patients diagnosed with type 1 diabetes, from the Department of Pediatrics, Department of Diabetes, Nutrition and Metabolic Diseases, of the Emergency County Clinical Hospital, St. Apostol Andrei", Constanța, in the period 2011-2021

Participation in the study was voluntary.

The following criteria were applied for patient selection:

Inclusion criteria:

- Target group: Children under the age of 18 diagnosed with type 1 diabetes
- Confirmation of diagnosis: Type 1 diabetes confirmed by standard criteria, such as the presence of pancreas-specific antibodies (eg, anti-insulin, anti-GAD antibodies).
- Existence of other autoimmune diseases: Confirmed presence of other autoimmune diseases besides type 1 diabetes (eg autoimmune thyroiditis, celiac disease).
- Parents' or legal guardian's consent: Informed consent of the child's parents or legal guardian for participation in the study.

Exclusion criteria:

- Absence of confirmation of the diagnosis of type 1 diabetes: Children in whom the diagnosis of type 1 diabetes has not been confirmed.
- Inability to participate in the study: Children with health conditions or other circumstances that prevent participation in the assessments required for the study.
- Genetic syndromes/neoplastic diseases

These criteria will ensure an appropriate selection of participants and will contribute to obtaining relevant and consistent data in the descriptive observational study about the metabolic implications of the association of autoimmune diseases in type 1 diabetes in children.

Investigation protocol:

• Blood sugar (reference values: normal 60-99 mg/dL; modified basal blood sugar 100-125 mg/dL; diabetes > = 126 mg/dL);

• HbA1c (detection limit = 0.2 g/dL; reference values: normal 4.8-5.6%; increased risk of developing diabetes 5.7-6.4%; diabetes > =6.5%);

• Peptide C (detection limit = 0.05 ng/mL; reference values: 0.81 -3.85 ng/mL);

• HCO3–serum (detection limit = 1.5mmol/L; reference values: 22 -29 mmol/L);

• Anti-GAD antibodies (reference values: <10 IU/mL);

• Anti-IA2 antibodies (reference values: <10 IU/mL);

• Anti-insulin antibodies (reference values: titer <1/104);

• TSH (detection limit = 0.005 µIU/mL; reference values: 3 months-1 year -0.73-8.35 µIU/ mL; 1-6 years -0.7-5.97 µIU/mL; 6-11 years -0.6-4.84 µIU /mL; 11-18 years -0.51-4.30 µIU/mL);

• fT4 (detection limit = 0.023 ng/dL; reference values: 3 months-1 year -0.92-1.99 ng/dL; 1- 6 years -0.96-1.77 ng/dL; 6-11 years -0.97-1.67 ng /dL; 11-18 years -0.98-1.63 ngdL);

• ATPO (reference values: <34 IU/mL);

• Anti-TG IgA needle (reference values: <10 U/mL);

• HLA-DQ2, HLA-DQ8 type;

• albuminuria / 24 hours (detection limit = 3 mg/L; reference values: A1 <30 mg/g; A2 30-300 mg/g; A3 >300 mg/g);

• Serum 25 (OH)-vitamin D (detection limit = 4 ng/mL; reference values: deficiency <10 ng/mL; insufficient level 10-30 ng/mL; optimal level 30-100 ng/mL).

The data collection was carried out on the basis of the general clinic observation sheets (FOCG) from previous admissions to the Pediatric Department - Diabetes, Nutrition and Metabolic Diseases Department, made through anamnesis, clinical examination, paraclinical investigations, of the surveillance sheets that the Department of Diabetes holds them for each patient on record as well as by consulting other medical documents from other hospitalizations and specialist consultations. The following information was extracted from all these sources:

• Demographic data: age, sex, background;

• Personal physiological antecedents: type of birth (natural/caesarean section), nutrition in the first months of life (breastfeeding/artificial/mixed feeding), the timing of the diversification of the infant's nutrition;
• Personal pathological history: viral infections, autoimmune diseases
• Heredo-collateral antecedents: diabetes, autoimmune diseases;
• History of the disease: age at diagnosis of type 1 diabetes, type of onset (with/without ketoacidosis) and evolution of the disease;
• HbA1c value at the beginning and in evolution;
• Serum biochemistry analyses;
• Urinary biochemistry analyses;
• Markers for autoimmune diseases: specific antibodies anti-GAD, anti-IA2, ICA, Ac IgA/ IgG anti-TG, Ac anti endomysium, ATPO;
• Thyroid markers: TSH, fT4, ATPO;
• Molecular biology tests: HLA typing.

Statistical analysis and processing:

Data were entered electronically into a table created in Microsoft Excel, including all variables of interest. The data were validated and verified both by using automatic methods (for example, calculating some indicators based on some entered data, creating some analysis groups based on the raw values measured by using calculation formulas or manually.

To analyze the data and apply statistical tests, we used IBM SPSS Statistics and the R application. These applications allow the application of statistical tests depending on the objective pursued and the type of variables analyzed.

In the descriptive statistical analysis, we calculated essential indicators for understanding the data distribution. These indicators included the arithmetic mean, standard deviation, median, minimum and maximum values. These descriptive statistics are used to get an overview of the data and to identify any anomalies or trends. In the case of qualitative variables, we presented the data in the form of number of cases and percentages.

For data comparison, we used appropriate statistical tests depending on the type of data and their distribution.

In the case of continuous variables, if the data had a normal distribution, we applied the test to compare two categories or ANOVA test to compare more than two categories. The ANOVA test was accompanied by post hoc analyzes when the results were statistically significant, to identify specific differences between groups.

In situations where the distribution of values was not normal, we resorted to non-parametric tests, such as the Mann-Whitney U test or the Kruskal-Wallis test (depending on the number of groups compared). Nonparametric tests are useful because they do not make strict assumptions about the distribution of the data, so they are applicable in a variety of situations. To assess whether a distribution can be considered normal, we applied the Shapiro-Wilk test and performed a visual analysis of the histogram. These evaluations allowed the selection of the type of statistical tests suitable to be used in the analysis.

To test the association between the qualitative variables, we used contingency tables and the Chi-square test. The Chi-square test allowed us to assess whether there is a statistically significant association between the qualitative variables. In situations where the conditions for applying the Chi-square test were not met (for example, when the expected frequencies were too low), we used the Fisher test, which is more appropriate for 2x2 contingency tables, or the likelihood ratio (Likelihood Ratio), which provides a robust alternative when the Chi-square test is not applicable in the case of tables where at least one of the variables had more than two categories. In all analyses, we considered a result to be statistically significant at a $p < 0.05$ level.

3.Study number 1: Characterization of the pediatric patient diagnosed with type 1 diabetes

3.1 Profile of the pediatric patient diagnosed with type 1 diabetes - demographic, clinical aspects

The distribution of patients is uneven with a median of 8 years with a bimodal distribution – a peak at 9-10 years and a second peak at 7-8 years, followed by a decrease in incidence starting at the age of 4.

In the study conducted, out of the 182 children in the batch, only 6 patients were diagnosed by the age of 1 year. The male gender was represented by 99 boys (54.4%), while the female gender was represented by 83 girls (45.6%). 74.2% were born at term (38-40 gestational weeks) and developed type 1 diabetes during their lifetime. Of the patients diagnosed with diabetes, only 5.4% were born before 38 weeks of age, which demonstrates the fact that autoimmunity can be triggered regardless of the gestational age at which the child was born, without providing an additional predisposition to the patient.

The highest incidence of diabetes is recorded at a weight gain between 15-20 kg, registering a percentage of 30.8%.

Regarding the environment of origin, the large number of patients from the urban environment can be noted (75.8%, respectively 138 individuals).

There were no associations between early or late introduction of any solid foods and the development of islet autoimmunity or type 1 diabetes.

Regarding the mode of onset of the condition, at the time of diagnosis, out of the 182 patients, 110 patients had diabetic ketoacidosis, among them 103 patients (56.6%) with moderate ketoacidosis.

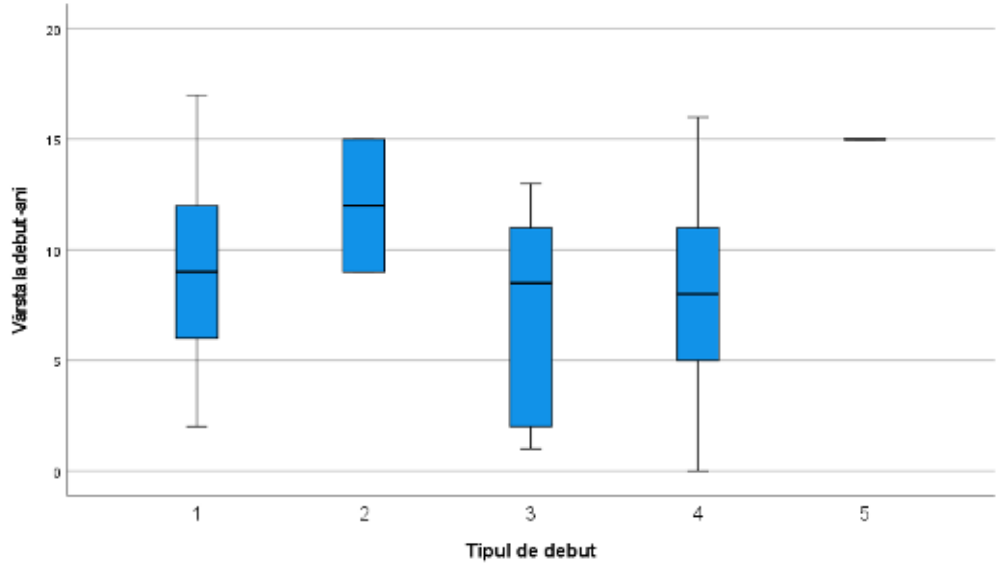

Figure 10. Correlation between age at onset and type of onset

The proportion of children with at least one relative with type 1 diabetes was high, 102 patients (45%) of which 59 patients (32%) have a relative diagnosed with autoimmune

pathology. Regarding the heredo-collateral antecedents of autoimmune diseases, it was demonstrated that in the studied group there is no relationship of this kind, the age at the onset of diabetes varies from the period of infancy and up to around the age of 16.

In all age groups, diabetic patients had a BMI at onset between 15-20kg/m2 in a percentage of 52.5%. Antibodies specific to diabetes could be determined for all patients in the study group, and they were positive, which is evidence of an autoimmune process that precedes the clinical appearance of type 1 diabetes. The average value of HbA1c at the beginning was 12.02%. Between the values of hemoglobin A1, determined at the beginning and the degree of metabolic imbalance (CAD stage) from the time of DZ1 diagnosis, it is found that the average glycosylated hemoglobin increases as the degree of metabolic imbalance worsens.

Table XXIV. The value of glycosylated hemoglobin at the beginning

N	Mean	Std. Deviation	Median	Minimum	Maximum
182	12.02%	2.66%	11.90%	6.30%	19.90%

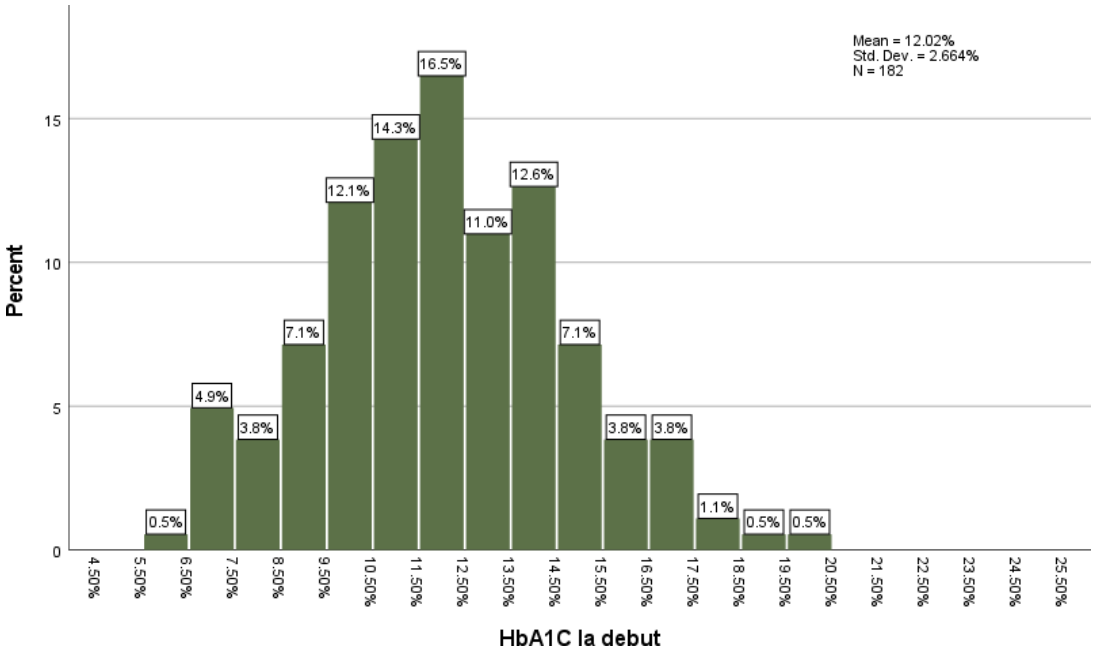

Figure 24. Glycosylated hemoglobin value at the onset of diabetes

The duration of breastfeeding did not determine significant changes between those who developed type 1 diabetes and those who did not. However, a lower risk of developing type 1 diabetes was predicted by any breastfeeding for 12 months or more compared with any breastfeeding for less than 12 months.

This analysis based on children with type 1 diabetes and their families demonstrates that type 1 diabetes and other autoimmune diseases not only occur among children's parents and siblings, but also occur more often among second- and third-degree relatives.

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This analysis based on children with type 1 diabetes and their families demonstrates that type 1 diabetes and other autoimmune diseases not only occur among children's parents and siblings, but also occur more often among second- and third-degree relatives.

Despite advances in medical management, type 1 diabetes remains a burdensome disease with daily challenges and substantial medical costs. Most young people with type 1 diabetes do not meet American Diabetes Association recommendations for glycemic control and experience excess morbidity and premature mortality.

3.2. Correlation between Vitamin D deficiency and type 1 diabetes in children

In 2012 and 2013, 2 cases of type 1 diabetes were recorded, equivalent to 5%. In 2016, 2017 and 2021, 4 cases were confirmed annually, equivalent to 10%. In 2018, 8 cases were recorded (20% cases), and in 2019, a record was set, identifying 16 subjects (40% cases) (Table 1). The number of subjects with type 1 diabetes associated with a low vitamin D level varied annually.

A significant history of autoimmune diseases, including autoimmune thyroiditis and celiac disease, was observed in the families of diagnosed patients. In 70% of cases, there were anti-GAD antibodies, anti-IA-2 antibodies, and anti-insulin antibodies, according to doses of specific antibodies. These findings confirm the autoimmune etiology of the disease and the role of genetic factors in the pathogenic mechanism.

The diagnosis was confirmed mainly in the winter and spring periods. Children frequently have low serum 25-hydroxyvitamin D values during this period, due to reduced exposure to ultraviolet radiation.

At the time type 1 diabetes was diagnosed, 83% of cases had a low serum 25-hydroxyvitamin D value below the recommended level. The values of 25-hydroxyvitamin D decreased in 79% of the cases during the course of the disease.

By measuring glycosylated hemoglobin and 25-hydroxyvitamin D, it was observed in evolution that inadequate glycemic control was associated with insufficient vitamin D level in 70% of cases and a deficit in 30% of cases. In 38% of subjects with good glycemic control, there were insufficient levels, 13% had a deficiency and 49% had an ideal level of 25-hydroxyvitamin D.

4. Study number 2: Autoimmune diseases associated with type 1 diabetes

Autoimmune polyglandular syndromes frequently have multiple endocrine damage, which affects the clinical course of diabetes in the long term. Screening programs are essential for monitoring diabetic patients, as they can intervene with substitution treatments for hypothyroidism, adrenal insufficiency, and gluten exclusion regimens in celiac disease. The male gender showed a slight prevalence compared to the female gender, with a percentage of 60%. Ketoacidosis at onset was found in 73% of cases, and the age at onset tended to be younger (<10 years).

The association between diabetes and another autoimmune disease is found in a relatively high percentage. This is of significant value for the management of type 1 diabetes. These additional conditions require specific treatment regimens, medications, or dietary changes that must be integrated into the overall diabetes management plan. Higher levels of glycosylated hemoglobin at the onset of type 1 diabetes have been associated with an increased risk of long-term complications such as retinopathy, nephropathy, and neuropathy.

At the time of onset of type 1 diabetes, 16 patients had also been diagnosed with celiac disease. Managing multiple autoimmune conditions can be challenging for both

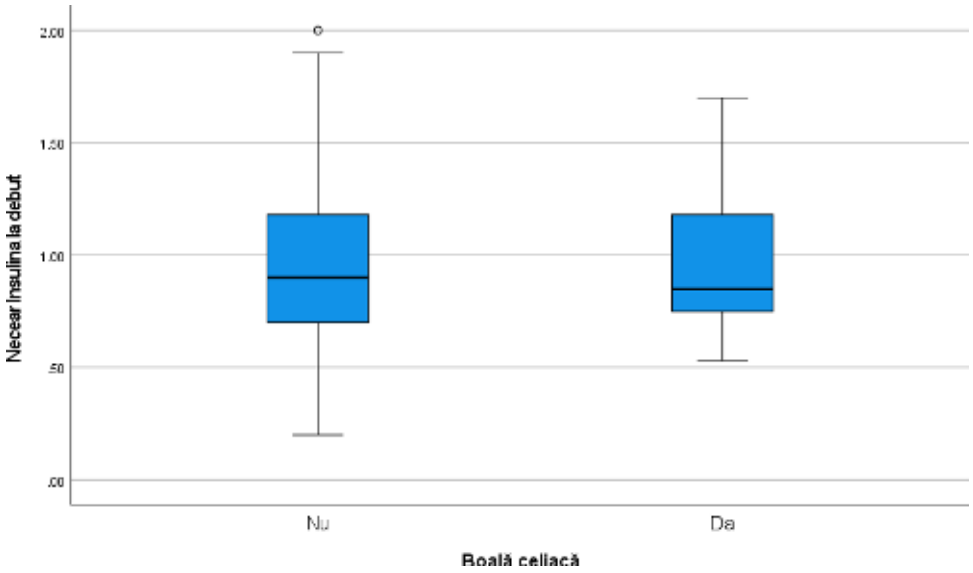
children and their families, requiring close collaboration with the medical and psychological team.

4.1 The perspective of celiac disease in the context of type 1 diabetes in children

As previously mentioned, celiac disease is the primary autoimmune disease associated with type 1 diabetes, as well as systemic lupus erythematosus. It is an enteropathy characterized by the production of antibodies, which leads to systemic and clinical manifestations. Its predisposition is influenced by both genetic and environmental factors. The main genetic contribution comes from human leukocyte antigens (HLA), particularly HLA DQ2 and DQ8, which confer the greatest susceptibility.

Studies conducted over the last decade have demonstrated an increased prevalence of celiac disease among individuals with type 1 diabetes, ranging from 3.3% to 10.6%.

Compared to healthy individuals, those with celiac disease or type 1 diabetes have a different microbiota profile, mainly characterized by a different Firmicutes/Bacteroidetes ratio and a higher abundance of the genus Bacteroides, among other species. The functionality of the microbiota in relation to human metabolism is also affected by these changes in its structure.



Autoimmune polyendocrine syndromes frequently involve multiple endocrine disorders, which can impact the long-term clinical course of diabetes. Screening programs are essential for monitoring diabetic patients, as they can intervene with substitute treatments for hypothyroidism, adrenal insufficiency, and gluten exclusion regimens in celiac disease.

4.2 The Perspective of Autoimmune Thyroiditis in Patients with Type 1 Diabetes

Autoimmune thyroiditis occurs in 17% to 30% of patients with type 1 diabetes. The close relationship between these conditions is largely explained by the sharing of a common genetic background. The antigens HLA DQ2 (DQA1 0501-DQB10201) and DQ8 (DQA10301-DQB1 0302), closely linked to DR3 and DR4, are the common predisposing factors.

Children with type 1 diabetes have a higher prevalence of autoimmune thyroiditis (AT) compared to the general population. Regular screening for AT is recommended in children with type 1 diabetes, typically through the measurement of thyroid antibodies (anti-TPO, anti-TG) and monitoring of thyroid function (TSH and FT4). Early detection is essential for the appropriate management of both conditions.

Hypothyroidism can affect glycemic control, requiring adjustments in insulin treatment. Children with both type 1 diabetes and AT are also predisposed to other autoimmune conditions, such as celiac disease. Therefore, monitoring for other autoimmune conditions is important.

With early diagnosis and appropriate treatment, children with type 1 diabetes and AT can have a good quality of life and avoid long-term complications. However, careful and continuous medical supervision is necessary.

Figure 50: Correlation between insulin requirements at onset and association with celiac disease

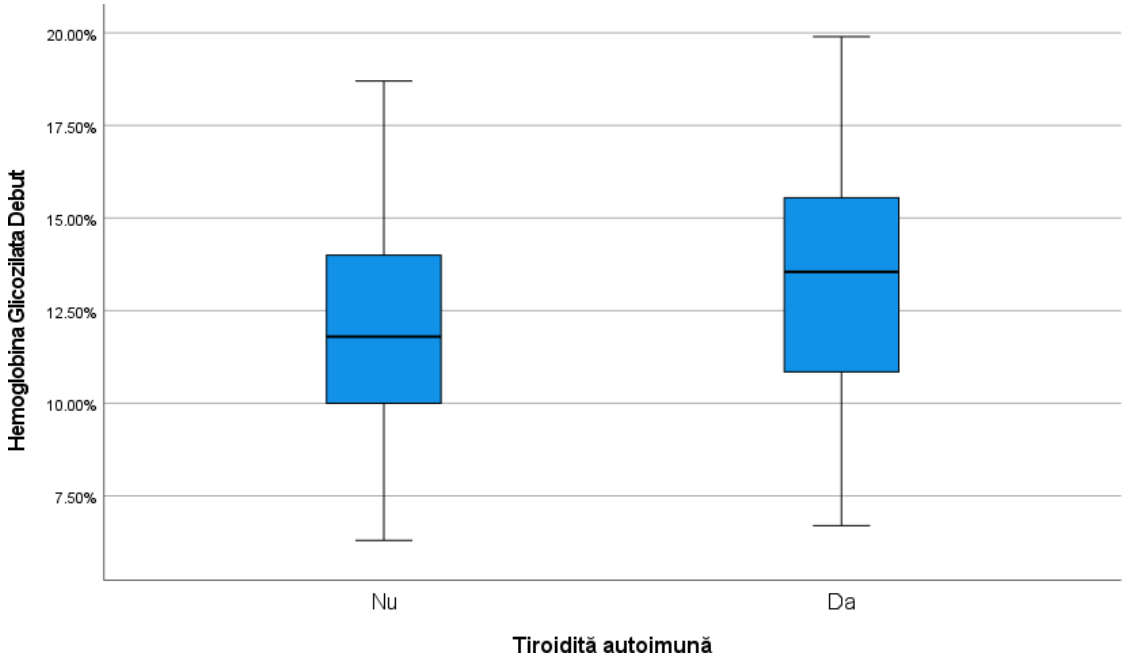


Figure 55: Association between autoimmune thyroiditis and HbA1C levels at onset.

Predictive Factors for Thyroid Dysfunction

- The HbA1c value: an increase of 1 unit is associated with a 30% increase in the likelihood of thyroid dysfunction, with the effect being statistically significant (p value < 0.05, 95% CI does not contain 1).
- The C-peptide value: an increase of 1 unit is associated with a 90% decrease in the likelihood of thyroid dysfunction, with the effect being statistically significant (although the p value is marginally non-significant – p = 0.062, 95% CI does not contain 1).
- The BMI value: an increase of 1 unit is associated with a 16% decrease in the likelihood of thyroid dysfunction, with the effect being statistically significant (although the p value is marginally non-significant – p = 0.067, 95% CI does not contain 1).
- The LDL value: an increase of 1 unit is associated with a 2% decrease in the likelihood of thyroid dysfunction, with the effect being statistically significant (although the p value is marginally non-significant – p = 0.061, 95% CI does not contain 1).

We investigated whether there is any association between TSH levels and the values characterizing diabetes (glucose, HbA1c, and C-peptide), calculating the Pearson correlation coefficients:

- For the glucose – TSH association, the Pearson correlation index = -0.12, p value = 0.226, indicating that the two variables are independent.
- For the HbA1c – TSH association, the Pearson correlation index = 0.16, p value = 0.091, indicating that the two variables are independent.
- For the C-peptide – TSH association, the Pearson correlation index = -0.06, p value = 0.650, indicating that the two variables are independent.

We investigated whether there is any association between FT4 levels and the values characterizing diabetes (glucose, HbA1c, and C-peptide), calculating the Pearson correlation coefficients:

For the glucose – FT4 association, the Pearson correlation index = -0.41, p value < 0.01, indicating a moderate, negative correlation that is statistically significant between the two variables.

For the C-peptide – FT4 association, the Pearson correlation index = 0.26, p value = 0.05, indicating a weak, positive correlation at the limit of statistical significance between the two variables.

5. Study number 3: Consequences of Metabolic Imbalance in Children and Adolescents with Type 1 Diabetes

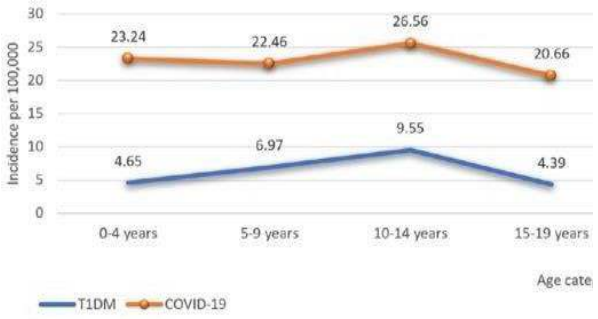
5.1 Assessment of Risk Factors for Recurrent Ketoacidosis in Children with Type 1 Diabetes

Vascular complications continue to be a key factor in premature mortality among young individuals diagnosed with diabetes during childhood. Good glycemic control, regular screenings, and patient education can delay the onset of long-term complications associated with Type 1 Diabetes (T1D).

Due to the evident increase in the incidence of T1D among the pediatric population at increasingly younger ages, there is a focus on developing new strategies to improve the quality of life and long-term prognosis for children and adolescents with T1D.

The COVID-19 pandemic has significantly altered our culture and may have had a strong impact on the epidemiology of several diseases, particularly with regard to the onset of Type 1 diabetes. After the WHO declared COVID-19 a pandemic in 2020-2021, our study reported an increase in newly diagnosed cases of Type 1 diabetes with ketoacidosis as the primary form of presentation. This was particularly pronounced among patients under 14 years of age.

Figure 80. Age-Specific Incidence of Type 1 Diabetes and COVID-19 in 2020–2021



Regarding the recurrence of ketoacidosis episodes, non-compliance with dietary guidelines has been shown to be the primary factor. During the period of 2020–2021, there were no variations in severity. This contrasts with findings from other studies in Germany, Italy, Australia, and Canada, which reported an increase in moderate and severe forms of Diabetic Ketoacidosis (DKA) in the early months following the onset of the COVID-19 pandemic [32-35].

Analysis of the incidence of repeated DKA episodes from January 2017 to July 2022 shows that the majority of cases were diagnosed in 2020. The frequency of ketoacidosis episodes was correlated with rural origin, low parental education levels, and below-average income. A family history of Type 1 diabetes was present in 64% of hospitalized patients with DKA. The classic triad of polyuria, polydipsia, and polyphagia was observed in nearly all patients (n=99).

Almost half (53%) of those diagnosed with DKA experienced moderate symptoms, 34% had severe symptoms, and 13% presented with mild symptoms at admission. Results from the Astrup method confirm this. Nearly half of the studied cases (51%) had two episodes of ketoacidosis, while one-fifth of the cases (21%) had a single episode, and only 21% experienced three or more DKA episodes.

Approximately 37% of the reasons for the recurrence of DKA episodes were due to non-compliance with dietary regimen, 28% were related to infectious pathologies, 26% were due to errors in insulin administration, 6% were associated with trauma, and only 3% were related to Mauriac syndrome. Non-compliance with treatment is the most common error in insulin administration, occurring in 40% of cases, followed by inappropriate dosing adjustments (20% of cases) and apathy (17% of cases).

Data indicate that gastroenteritis causes the most DKA episodes precipitated by an infectious factor. Pneumonias and infected wounds ranked second and third. There were correlations between random blood glucose levels ranging from 250 to 500 mg/dl, as well as HbA1c levels above 9. Lipodystrophy was present in 64% of cases, while only 36% (n=41) did not exhibit it.

5.1.1 Mauriac Syndrome

Although patients with type 1 diabetes have unrestricted access to the best types of insulin, self-monitoring tests, continuous glucose monitoring systems, and insulin pumps, we still diagnose Mauriac syndrome. Poor glycemic control is just one of the causes, as there are patients with unsatisfactory glycemic control who do not develop this complication.

Table LXXX. Mauriac Syndrome

Parameter	**C.M. (Female)**	**B.A.I. (Male)**	**T.P.N. (Male)**
Age at onset	8 years 11 months	7 years	7 years
Age at appearance of Mauriac Syndrome	11 years	14 years and 7 months	13 years and 6 months
HbA1c	**16.8%**	**15.8%**	**15.5%**
Diabetic Neuropathy	**YES**	**YES**	**YES**

Diabetic Nephropathy	NO	NO	NO
Diabetic Retinopathy	NO	NO	**YES, Stage II severe non-proliferative retinopathy**
Hypertension	**NO**	**YES**	**YES**
Short Stature	**YES**	**YES**	**YES**
Hepatomegaly	**YES, 7 cm below the costal margin**	**YES, 6 cm below the costal margin**	**Yes**
Delayed Puberty	**YES**	**YES**	**YES**
Other associated autoimmune diseases	No	**YES, AUTOIMMUNE THYROIDITIS**	No
Lipoid Necrobiosis	No	**YES**	**YES**
TGO/TGP	**505 U/L / 360 U/L**	**79 U/L / 88 U/L**	**134 U/L / 125 U/L**
GGT	**440 U/L**	55 U/L	**60 U/L**
Alkaline Phosphatase	**349 U/L**	**1262 U/L**	**480 U/L**
Total Cholesterol /Triglycerides	**380 mg/dl / 450 mg/dl**	**265 mg/dl / 323 mg/dl**	**221 mg/dl / 330 mg/dl**
hGH	1.59	7	**10**
IGF-1	**100.5**	**70**	**79.83**
Serum Lactate (Astrup)	**7.8 mmol/l**	**4.2 mmol/l**	**5.4 mmol/l**
Prothrombin Time	12.3 sec	15.1 sec	**15.9 sec**
Microalbuminuria	**60 mg**	**45 mg/l**	**40 mg/l**
Albumin / Creatinine Ratio	**34.45**	**42.2**	**26.74**
25-OH Vitamin D	**8 ng/ml**	**11.5 ng/ml**	**11.6 ng/ml**

Markers for Autoimmune Hepatitis	Negative	Negative	Negative
Markers for Viral Hepatitis	Negative	Negative	Negative
Abdominal Ultrasound	**Hepatomegaly, increased echogenicity, APLDH diameter 210 mm**	**Hepatomegaly, APLDH diameter 165 mm**	**Hepatomegaly, APLDH diameter 150 mm**
Liver Biopsy	**Hepatic glycogenosis, macrovesicular steatosis**	**Hepatic glycogenosis**	**Hepatic glycogenosis, focal steatosis**
Pituitary MRI	Normal	Normal	Normal
Wrist X-ray (VO)	**Bone age corresponds to the age of 7 years**	**Bone age corresponds to the age of 8 years**	**Bone age corresponds to the age of 10 years**
Insulin Requirement	2.1 IU/kg/day	1.5 IU/kg/day	1.9 IU/kg/day
Tanner Stage	**I – prepubertal**	**I – prepubertal**	**I – prepubertal**
Nerve Conduction Velocity	**Predominantly symmetric distal sensory diabetic polyneuropathy**	**Mild sensory axonal polyneuropathy**	**Predominantly symmetric distal sensory diabetic polyneuropathy**

5.2 The Utility of Continuous Glucose Monitoring Sensors in Transient Neonatal Diabetes

Clinically, therapeutically, and genetically, neonatal diabetes remains challenging to manage. There are no recommendations for managing diabetes in the first few months after birth; however, two points are indisputable recommendations:

- The availability of genetic results (within a few weeks) has significantly altered the short- and long-term management of these infants.
- These children require insulin with an adequate or high caloric intake to ensure satisfactory weight gain. Insulin administration can now partially mimic pancreatic physiology.

Table LXXXI. Clinical Characteristics and Laboratory Results of Patients

Patient	Case 1	Case 2
Sex	Female	Female
Age	First day of life	First day of life
Birth Weight	1480 g - 37 weeks gestation, severe IUGR	2100 g - 35 weeks gestation
IUGR	(oligohydramnios)	
Length	43 cm	44 cm
Head Circumference	29 cm	31 cm
Type of Feeding	Formula milk until 13 days of life, then natural feeding	Mixed feeding from the first day of life
Facial Dysmorphism	Facial dysmorphism. Epicanthus.	Epicanthus. Macroglossia.
Clinical Characteristics	Umbilical hernia	Pectus excavatum. Umbilical hernia. Short hallux.
Blood Glucose Level at Diagnosis	275 mg/dl	350 mg/dl
Genetic Test	Uniparental disomy at locus 6q24	Uniparental disomy at locus 6q24
Treatment	Insulin Lispro was started continuously at a rate of 0.026 units/kg/day and then gradually reduced to 0.006 units/kg/day;	Insulin Lispro was started continuously at a rate between 0.1-0.3 ml/h (0.01–0.03 units/kg/h) in the first days and then constantly at 0.1 ml/h (0.43 units/ 24h); At 2 months - insulin pump with a dose of 0.05 units/h

Patient	Case 1	Case 2
Evolution	Discharged after 2 months and 2 weeks	Discharged at 2 months when treatment with Insulin Lispro was discontinued

A molecular genetic diagnosis is recommended for all patients with Neonatal Diabetes Mellitus (NDM). These newborns with moderate or severe growth restrictions require early identification and medical therapy (continuous insulin infusion and high caloric intake) to prevent catastrophic metabolic issues and to allow for proper weight gain and brain development.

Regular follow-up is strongly recommended, especially in the early years of childhood, as common illnesses can lead to symptomatic hypoglycemia or recurrent hyperglycemia. Continuous Glucose Monitoring (CGM) has proven beneficial in this regard, as it can help avoid hypoglycemic events and reduce the rate of insulin administration.

6. Conclusions

There is a strong association between the presence of autoimmune diseases and the incidence of type 1 diabetes in children. Genetic factors play a crucial role in the development of both conditions. The distribution of patients is uneven, with a median age of 8 years and a bimodal distribution—one peak at ages 9-10 and a second peak at ages 7-8, followed by a decline in incidence starting at age 4.

In the study conducted, out of 182 children in the cohort, only 6 patients were diagnosed before the age of 1. The male population consisted of 99 boys (54.4%), while the female population consisted of 83 girls (45.6%).

74.2% were born at term (38-40 weeks gestational age) and developed type 1 diabetes throughout their lives. Among the patients diagnosed with diabetes, only 5.4% were born before 38 weeks of gestation, demonstrating that autoimmunity can be triggered regardless of

the gestational age at which the child was born, without providing any additional predisposition to the patient.

The highest incidence of diabetes is recorded at a weight gain of 15-20 kg, accounting for 30.8%. There were no associations between the early or late introduction of any solid foods and the development of insular autoimmunity or type 1 diabetes.

Regarding the onset of the condition, at the time of diagnosis, out of the 182 patients, 110 presented with diabetic ketoacidosis, of which 103 patients (56.6%) had moderate ketoacidosis. Regarding the family history of autoimmune diseases, it was demonstrated that there is no such relationship in the studied cohort, with the age of diabetes onset varying from infancy to around age 16.

Specific diabetes antibodies could be determined for all patients in the studied cohort, and they were positive, representing evidence of an autoimmune process that precedes the clinical onset of type 1 diabetes. The average HbA1c value at diagnosis was 12.02%. Between the values of A1c hemoglobin, determined at onset, and the degree of metabolic imbalance (CAD stage) at the time of type 1 diabetes diagnosis, it was observed that the average glycosylated hemoglobin increases as the degree of metabolic imbalance worsens.

The duration of breastfeeding did not result in significant changes between those who developed type 1 diabetes and those who did not. However, a lower risk of developing type 1 diabetes was predicted by any breastfeeding for 12 months or more, compared to any breastfeeding for less than 12 months.

This analysis based on children with type 1 diabetes and their families demonstrates that type 1 diabetes and other autoimmune diseases not only occur among the parents and siblings of children but also more frequently among second- and third-degree relatives.

The diagnosis of type 1 diabetes was primarily confirmed during the winter and spring periods. Children often present with low serum levels of 25-hydroxyvitamin D during this time due to reduced exposure to ultraviolet radiation.

At the time type 1 diabetes was diagnosed, 83% of cases had a low serum level of 25-hydroxyvitamin D below the recommended level. The levels of 25-hydroxyvitamin D decreased in 79% of cases throughout the course of the disease.

By measuring glycosylated hemoglobin and 25-hydroxyvitamin D, it was observed that inadequate glycemic control was associated with insufficient vitamin D levels in 70% of cases and a deficiency in 30% of cases. Among subjects with good glycemic control, 38% had insufficient levels, 13% had a deficiency, and 49% had an ideal level of 25-hydroxyvitamin D.

Children with type 1 diabetes and associated autoimmune diseases exhibit a distinct metabolic profile.

Metabolic anomalies include glycemic imbalances, variations in thyroid hormone levels, and possible nutritional deficiencies. Chronic inflammation, specific to autoimmune diseases, contributes to the deterioration of pancreatic beta cell function and exacerbates metabolic dysfunction. This underscores the importance of monitoring and managing inflammation in the treatment of type 1 diabetes.

The association between diabetes and another autoimmune disease is encountered at a relatively high percentage: celiac disease—8.79%, autoimmune thyroiditis. This has significant implications for managing type 1 diabetes. These additional conditions require specific treatment regimens, medications, or dietary modifications that need to be integrated into the overall diabetes management plan.

Therapeutic approaches that target both glycemic control and the management of autoimmune diseases are essential. Continuous monitoring of autoimmune markers and metabolic parameters is crucial for preventing long-term complications. Early interventions can improve prognosis and quality of life for pediatric patients. The results suggest the need for a multidisciplinary approach in managing children with type 1 diabetes and associated autoimmune diseases. Collaboration among endocrinologists, gastroenterologists, and dietitians is essential for providing comprehensive care.

Patients with celiac disease and type 1 diabetes in the studied cohort had a more severely affected metabolic profile than those diagnosed with type 1 diabetes alone. Regarding insulin requirements at the onset of diabetes, it was observed that a gluten-free diet led to significant improvements in growth and influenced diabetes control (patients with celiac disease required more insulin compared to the control group of patients with type 1 diabetes without celiac disease).

Weight loss was significantly more prevalent among celiac patients in our study; patients in the diabetes + celiac disease group were over four times more likely to experience weight loss. While concerns about weight gain on a gluten-free diet were raised only among celiac patients, recent data show normal growth patterns in children and adolescents with type 1 diabetes and celiac disease, with body mass index and height standard deviation scores being only marginally, but not significantly, higher in the control group (non-celiac) compared to the study group, and similar to subjects with celiac disease who adhered well to the diet.

The restriction of gluten in a diabetic diet imposes practical limitations and leads to considerable lifestyle restrictions for a child or adolescent; a proper diet is a cornerstone of management for patients with type 1 diabetes. Nutritional intervention aims to achieve and maintain normal glycemia, attain a normal lipid profile, and achieve a normal body weight.

Since the Shapiro-Wilk test result is statistically insignificant, the distribution of patients based on glycosylated hemoglobin values does not differ significantly from a normal distribution. Thus, a t-test can be used for comparison. The t-test shows a mean difference of 1.49% (with a 95% confidence interval of 0.358 – 2.62), which is statistically significant between those with and without autoimmune thyroiditis, with those without thyroiditis having lower average glycosylated hemoglobin values at onset.

It is observed that in patients with thyroid dysfunction, LDL values are lower compared to those without thyroid dysfunction, with the effect being statistically significant.

Predictive Factors for Thyroid Dysfunction

- The HbA1c value: an increase of 1 unit is associated with a 30% increase in the likelihood of thyroid dysfunction, with the effect being statistically significant (p value < 0.05, 95% CI does not contain 1).
- The C-peptide value: an increase of 1 unit is associated with a 90% decrease in the likelihood of thyroid dysfunction, with the effect being statistically significant (although the p value is marginally non-significant – p = 0.062, 95% CI does not contain 1).
- The BMI value: an increase of 1 unit is associated with a 16% decrease in the likelihood of thyroid dysfunction, with the effect being statistically significant

(although the p value is marginally non-significant – p = 0.067, 95% CI does not contain 1).

- The LDL value: an increase of 1 unit is associated with a 2% decrease in the likelihood of thyroid dysfunction, with the effect being statistically significant (although the p value is marginally non-significant – p = 0.061, 95% CI does not contain 1).

We investigated whether there is any association between TSH levels and the values characterizing diabetes (glucose, HbA1c, and C-peptide), calculating the Pearson correlation coefficients:

- For the glucose – TSH association, the Pearson correlation index = -0.12, p value = 0.226, indicating that the two variables are independent.
- For the HbA1c – TSH association, the Pearson correlation index = 0.16, p value = 0.091, indicating that the two variables are independent.
- For the C-peptide – TSH association, the Pearson correlation index = -0.06, p value = 0.650, indicating that the two variables are independent.

We investigated whether there is any association between FT4 levels and the values characterizing diabetes (glucose, HbA1c, and C-peptide), calculating the Pearson correlation coefficients:

For the glucose – FT4 association, the Pearson correlation index = -0.41, p value < 0.01, indicating a moderate, negative correlation that is statistically significant between the two variables.

For the C-peptide – FT4 association, the Pearson correlation index = 0.26, p value = 0.05, indicating a weak, positive correlation at the limit of statistical significance between the two variables.

Regular screening for thyroid dysfunction in children with type 1 diabetes is recommended, typically through the measurement of thyroid antibodies (anti-TPO, anti-TG) and monitoring of thyroid function (TSH and FT4). Early detection is essential for the appropriate management of both conditions.

Future studies should focus on identifying the molecular mechanisms linking autoimmune diseases to type 1 diabetes, as well as on developing new therapies that address these mechanisms.

Regarding the recurrence of ketoacidosis episodes, non-compliance with dietary recommendations has been shown to be the main factor. The frequency of ketoacidosis episodes was correlated with rural origin, low parental education levels, and below-average income.

A family history of type 1 diabetes was present in 64% of patients admitted with diabetic ketoacidosis (DKA). The classic triad of polyuria, polydipsia, and polyphagia was present in almost all patients (n=99). Nearly half (53%) of those diagnosed with DKA experienced an episode with moderate symptoms, 34% had severe symptoms, and 13% had mild symptoms at presentation. The results from the Astrup method confirm this. Almost half of the studied cases (51%) experienced two episodes of ketoacidosis, while one-fifth of the cases (21%) had a single episode, and only 21% had three or more episodes of DKA.

Approximately 37% of the reasons for the recurrence of DKA episodes are attributed to dietary non-compliance, 28% to infectious pathologies, 26% to errors in insulin administration, 6% to trauma, and only 3% are associated with Mauriac syndrome.

Lack of adherence to treatment is the most common error in insulin administration. This occurs in 40% of cases, followed by failure to adjust doses to the body's needs (20% of cases).

Continuous glucose monitoring (CGM) of these patients is essential, providing a benefit in achieving good metabolic control, and can be used from the first month of life.

These conclusions reflect the complexity of the interactions between autoimmune diseases and type 1 diabetes in children and highlight the need for integrated and personalized management to optimize clinical outcomes.

7. Originality and Innovative Contributions of the Thesis

The theme of the doctoral thesis on "Metabolic Implications of the Association of Autoimmune Diseases in Type 1 Diabetes in Children" is extremely interesting and relevant in the current medical context, and it has not been addressed before in Romania.

Approaching this theme could provide a significant contribution to understanding how associated autoimmune diseases can influence the evolution and management of type 1 diabetes in children. The originality of this thesis lies in the detailed exploration of the specific metabolic interactions between these diseases, their impact on treatment and prognosis, as well as potential personalized interventions based on this knowledge.

To provide an original contribution to the study of diabetes complications in children in Romania, I explored the following research directions:

- **Environmental and Socio-Economic Factors**: Analyzing the specific impact of environmental and socio-economic factors in Southeast Romania on the development and management of diabetes complications in children. This may include access to treatment, medical education, family support, and living standards.
- **Regional and Ethnic Variations**: Studying regional and ethnic variations in the prevalence and severity of diabetes complications in children across different regions of Romania, with a focus on possible genetic, cultural, and socio-economic differences.
- **Personalized Interventions and Prevention**: Evaluating the effectiveness of personalized interventions in preventing and managing diabetes complications in children in Romania, emphasizing innovative monitoring and treatment methods.
- **Quality of Life and Psychosocial Impact**: Investigating the psychosocial impact of diabetes complications in children on their quality of life and that of their families within the Romanian cultural and social context.
- **Interdisciplinary Collaboration and Education**: Promoting interdisciplinary collaboration among health and education professionals in Romania to develop integrated programs for managing diabetes complications in children, including ongoing education for health professionals and the community.
- **A Further Original Contribution**: Describing several cases of Mauriac Syndrome in the Southeast region of Romania, a complex situation with strong interdisciplinary

connections, where I performed appropriate therapeutic interventions. Some of these results were the subject of a book chapter titled “Uncontrolled diabetes complicated by glicogenic hepatopathy in Mauriac Syndrome” (pages 87-97), in *PEDIATRIC ENDOCRINOLOGY AND DIABETES 2022 UPDATE*, Iulian P. Velea, Corina Paul, Stuart Brink, Mirton Publishing, Timișoara, ISBN 978-973-52-2033-41.

These research directions not only provide an original contribution to the field of diabetes complications in children, but they could also enhance the specific understanding of the factors influencing these complications in the cultural and social context of Romania.

I have undertaken an original approach regarding vitamin D and type 1 diabetes in children for the Southeast region of Romania, utilizing a regional epidemiological study where I assessed vitamin D levels in the pediatric population and correlated them with the incidence of type 1 diabetes. This could highlight possible geographical variations and the impact of local factors on the risk of developing diabetes. I explored the immunological mechanisms and how vitamin D influences the immune system in the context of the autoimmunity specific to type 1 diabetes in children in Romania. Some of the study results were published in an article in the *Romanian Journal of Oral Rehabilitation*, an ISI-indexed journal with an impact factor of 0.6. The acceptance of this article for publication represents a confirmation of the originality and importance of the study. The article has been cited so far by authors of five other articles published in specialized, ISI-indexed journals.

New perspectives I wish to pursue include developing educational programs for parents, doctors, and teachers in Romania about the role of vitamin D in the prevention and management of type 1 diabetes in children, to promote the adoption of healthy practices in the community. These research directions could contribute to a deeper understanding of the complex interaction between vitamin D and type 1 diabetes in the specific context of the pediatric population in Romania and could offer new perspectives on prevention and treatment strategies.

The perspective of celiac disease in the context of diabetes in children in Romania has been addressed in this thesis in an original manner by exploring the following aspects:

- **Prevalence**: Studying the prevalence of celiac disease among children diagnosed with diabetes in the Southeast region of Romania and identifying specific risk factors for this association.
- **Clinical and Metabolic Impact**: Evaluating the impact of celiac disease on glycemic control and diabetes management in children in Southeast Romania, including the effects on nutrition and overall health status.
- **Early Diagnosis and Screening**: Developing and evaluating the effectiveness of screening protocols for detecting celiac disease among children with diabetes in Romania, focusing on early diagnosis and early interventions.
- **Integrated Management**: Investigating integrated management strategies for celiac disease and diabetes in children in Romania, including coordination between gastroenterology and diabetes specialists to optimize treatment.
- **Psychosocial Aspects and Quality of Life**: Assessing the impact of a dual diagnosis (diabetes and celiac disease) on the quality of life of children and their families in the specific cultural and social context of the Dobrogea region.

The impact of autoimmune diseases within the context of Polyglandular Syndrome in type 1 diabetes in children has been studied in this thesis, with some results published in the chapter "Autoimmune Polyglandular Syndrome - Type 4 – Clinical Implications in Children with Diabetes," pages 40-55, in *Current Concepts in Pediatric Practice*, Ingrith Miron, Iuliana Magdalena Stârcea, Gr T Popa Publishing House, Iași, 2023, ISBN 978-606-544-899-5.

These research directions not only provide an original perspective on the interaction between celiac disease and diabetes in children in Romania but also contribute to improving clinical management and quality of life for these vulnerable patients. Some of the study results were published in an article in the *Romanian Journal of Oral Rehabilitation*, an ISI-indexed journal with an impact factor of 0.6. The acceptance of this article for publication represents a confirmation of the originality and importance of the study.

I also made an original contribution in the field of using glucose sensors to improve metabolic control, particularly in the context of diabetes or other medical conditions requiring continuous glucose monitoring. For the first time in our country, the use of Continuous

Glucose Monitoring (CGM) in newborns has been described, showing good results in dose adaptation and achieving optimal metabolic control:

- **Technology adaptation for newborns**: Development and evaluation of glucose sensors specifically adapted for use in newborns, taking into account their small body size and specific metabolic needs.
- **Non-invasive monitoring**: Exploration and development of non-invasive or minimally invasive technologies for continuous glucose monitoring in newborns, to minimize discomfort and risks associated with traditional measurement methods.
- **Prediction algorithms and early intervention**: Utilizing artificial intelligence and advanced algorithms to predict fluctuations in glucose levels in newborns, allowing for early and personalized interventions in glycemic management.
- **Integration with existing technologies**: Integrating glucose sensors with other medical technologies or life support devices used in newborns to optimize clinical management and reduce the risk of complications.
- **Long-term impact assessment**: Studying the long-term impact of using glucose sensors on metabolic control and clinical outcomes in newborns, including effects on growth, development, and quality of life.

This innovation regarding the use of continuous glucose monitoring sensors in newborns in Romania was published in an article in the journal *Diagnostics*, which is ISI-indexed with an impact factor of 3.6, and has also been cited by authors of four other ISI-indexed articles.

These research directions can contribute to improving clinical practices and optimizing glycemic management in newborns, with the potential to reduce morbidity and improve outcomes for this vulnerable population. I aim to develop machine learning algorithms to predict glucose levels, optimize insulin dosing, and identify patterns in metabolic control that can be targeted for intervention.

Regarding telemedicine and remote monitoring, I plan to investigate the effectiveness and outcomes of telemedicine solutions and remote monitoring in managing type 1 diabetes in children, particularly in rural or disadvantaged areas.

The school-based interventions that my colleagues and I are considering involve designing and evaluating school programs aimed at improving metabolic control, including training school staff, peer support initiatives, and changes in school policies. Another future aspect would be the development of innovative educational programs to enhance health knowledge among children with type 1 diabetes and their caregivers, focusing on metabolic control and self-management.

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LIST OF PUBLICATIONS

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1. Tatiana Chisnoiu, Cristina Maria Mihai*, Adriana Luminita Bălașa, Alexandru Cosmin Pantazi1,*Antonio Andrusca, Bianca Maria Constantin, Andreea Dalila Nedelcu, Simona Claudia Cambrea - Correlation between vitamin d deficiency and type 1 diabetes in children, **Romanian Journal of Oral Rehabilitation**, Vol. 15, No.2 April-June 2023. **IF 0.6** CORRELATION-BETWEEN-VITAMIN-D-DEFICIENCY- AND-TYPE-1-DIABETES-IN-CHILDREN.pdf (rjor.ro)

2.Chisnoiu T, Balasa AL, Mihai L, Lupu A, Frecus CE, Ion I, Andrusca A, Pantazi AC, Nicolae M, Lupu VV, Ionescu C, Mihai C.M., Cambrea S.C., Continuous Glucose Monitoring in Transient Neonatal Diabetes Mellitus—2 Case Reports and Literature Review**.** ***Diagnostics***. 2023; 13(13):2271, **IF 3.6** **https://doi.org/10.3390/diagnostics13132271**

3.Chisnoiu, T (Chisnoiu, Tatiana) ; Mihai, CM (Mihai, Cristina Maria) ; Pantazi, AC (Pantazi, Alexandru Cosmin) ; Balasa, AL (Balasa, Adriana Luminita) ; Ioniuc, I (Ioniuc, Ileana) ; Constantin, BM (Constantin, Bianca Maria) ; Andrusca, A (Andrusca, Antonio) ; Marius-Daniel, R (Marius-Daniel, Radu) ; Starcea, IM (Starcea, Iuliana Magdalena) ; Pinzaru, AD (Pinzaru, Anca Daniela) ; Cambrea, SC (Cambrea, Simona Claudia), Evaluation of risk factors for recurrent diabetic ketoacidosis in children with type 1 diabetes, **Romanian Journal of oral Rehabilitation**, Volume15 Issue3, Jul-Sep 2023, Page 152-159 **IF 0.6** EVALUATION OF RISK FACTORS FOR RECURRENT DIABETIC KETOACIDOSIS IN CHILDREN WITH TYPE 1 DIABETES – Romanian Journal of Oral Rehabilitation (rjor.ro)

4. Tatiana Chisnoiu, Cristina Maria Mihai*, Alexandru Cosmin Pantazi **,** Adriana Luminița Balasa, Larisia Mihai, Corina Elena Frecus, Bianca Maria Constantin, Antonio Andrusca, Ancuta Lupu,*, Sergiu Chirila, Iuliana Magdalena Starcea, Ileana Ioniuc, Adriana Mocanu, Lorenza Forna, Simona Claudia Cambrea, An overview of celiac disease in childhood type 1 diabetes - a single center experience from south east romania, **Romanian Journal of oral Rehabilitation**, Volume16 Issue1, Jan-Mar 2024, Page 307-317 **IF 0.6**

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AN-OVERVIEW-OF-CELIAC-DISEASE-IN- CHILDHOOD-TYPE-1-DIABETES-A-SINGLE-CENTER-EXPERIENCE-FROM- SOUTH-EAST-ROMANIA.pdf (rjor.ro)

5. Pinzaru, AD (Pinzaru, Anca Daniela) ; Mihai, CM (Mihai, Cristina Maria) ; **Chisnoiu, T** (Chisnoiu, Tatiana) ; Pantazi, AC (Pantazi, Alexandru Cosmin) ; Grosan, E (Grosan, Elena) ; Cambrea, SC (Cambrea, Simona Claudia) ; Ion, I (Ion, Ileana), Correlation between metabolic control and oxidative stress in type 1 diabetes: malondialdehyde as a protective factor, Romanian Journal of oral Rehabilitation, Volume15 Issue3, Jul-Sep 2023 , Page 499-505 **IF 0.6 (autor correspondent)** CORRELATION-BETWEEN- METABOLIC-CONTROL-AND-OXIDATIVE-STRESS-IN-TYPE-1-DIABETES-MALONDIALDEHYDE-AS-A-PROTECTIVE-FACTOR.pdf (rjor.ro)

6. Silvia Fotea; Cristina Mihaela Ghiciuc; Gabriela Stefanescu; Anca Lavinia Cianga; Cristina Maria Mihai; Ancuta Lupu; Lacramioara Ionela Butnariu; Iuliana Magdalena Starcea; Delia Lidia Salaru; Adriana Mocanu; **Tatiana Chisnoiu;** Aye Aung Thet; Lucian Miron; Vasile Valeriu Lupu - Pediatric COVID-19 and Diabetes: An Investigation into the Intersection of Two Pandemics, **Diagnostics** 2023, Volume 13, Issue 14, 2436, **IF 3.992** (contributie egala cu primul autor) **https://doi.org/10.3390/diagnostics13142436**

Prize

The prize awarded by the Romanian Society of Pediatric Diabetes, Nutrition and Endocrinology (ENDOPED) within the Congress of Pediatric Diabetes, Nutrition and Endocrinology (ENDOPED 2024) - **Youth Prize - for outstanding results in scientific research carried out in the field of pediatric endocrinology and diabetology,** Timisoara 17 April 2024

Papers presented at international conferences and congresses

1. Cristina Maria Mihai, **Tatiana Chisnoiu** - Hypertrigliceridemia in children and adolescents with onset of type 1 diabetes in the pandemic COVID-19, Congresul ISPAD 13- 15 octombrie 2021 – Eposter

2. Cristina Maria Mihai, **Tatiana Chisnoiu** Concomitant presence of COVID-19 infection and inaugural diabetic ketoacidosis in children and adolescents, Congresul ISPAD 13 -15 octombrie 2021 -Eposter

3. **Tatiana Chisnoiu**, Cristina Maria Mihai - VITAMIN D DEFICIENCY AND GLYCEMIC STATUS IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES, Al 8-lea Congres International Nutrition and Growth 26-28 August 2021 - Eposter

4. **Tatiana Chisnoiu**, Cristina Maria Mihai, Adriana Luminita Balasa, Cosmin Alexandru Pantazi - Autoimmunity in type 1 diabetes, European Academy of Allergy and Clinical Immunology Congress 2022- Eposter

5. **Tatiana Chisnoiu**, Cristina Maria Mihai , Continuous glucose monitoring in the management of Transient Neonatal Diabetes Mellitus, 41st UMEMPS Congress Union of Middle Eastern and Mediterranean Pediatric Societies, 22-24 septmbrie 2022 – prezentarea orala – Prezentare orala

Papers presented at national conferences and congresses

1. Cristina Maria Mihai, Oana Laura Nicola, Georgiana Cocona, Gilda Danilov, Emanuela Nita, **Tatiana Chisnoiu**, EVALUAREA CONTROLULUI GLICEMIC LA COPIII CU DIABET ZAHARAT TIP 1 IN TIMPUL PANDEMIEI COVID-19, Al XV-lea Congres Național de Pediatrie, 15-18 septembrie 2021 – Prezentare orala

2. Cristina Maria Mihai, **Tatiana Chisnoiu,** Influența bolilor autoimume asociate diabetului zaharat insulino-dependent (tip 1) în controlul metabolic, Al XV-lea Congres Național de Pediatrie, 15-18 septembrie 2021- Prezentare orala

3. Cristina Maria Mihai, **Tatiana Chisnoiu**- Impactul infecției cu virusul SARS COV 2 asupra diabetului de tip 1 la debut la copii și adolescenți, Congresul FRDNBM 2021 online – Prezentare orala

4. Cristina Maria Mihai, **Tatiana Chisnoiu** - SINGLE ROMANIAN SOUTH EASTERN REGIONAL FINDINGS IN NEWLY ONSET TYPE 1 DIABETES IN CHILDREN DURING COVID-19 PANDEMIC, Congres ENDOPED 4-9 octombrie 2021 – Prezentare orala

5. Cristina Maria Mihai, **Tatiana Chisnoiu**, Anca Daniela Pinzaru - Vitamin D deficiency in children with type 1 diabetes, Al 47-lea Congres Natioanl al Societatii Romane de Diabet, Nutritie si Boli Metabolice, 19-25 mai 2021 - Eposter

6. Mihai Cristina Maria, **Tatiana Chisnoiu** - SINDROMUL MAURIAC O COMPLICATIE A DIABETULUI ZAHARAT LA COPIL CONSIDERATII PE BAZA UNOR CAZURI CLINICE, Conferinta Nationala Zilele Pediatriei Iesene, 15-18 iunie 2022 – Prezentare orala

7. Cristina Maria Mihai, **Tatiana Chisnoiu**, UNCONTROLLED DIABETES COMPLICATED BY GLYCOGENIC HEPATOPATHY IN MAURIAC SYNDROME, The 9 th National Congress of Diabetes, Nutrition and Pediatric Endocrinology - with international participation 2-5 noiembrie 2022 – Prezentare orala

8. **Tatiana Chisnoiu**, Cristina Maria Mihai, EVALUATION OF RISK FACTORS FOR RECURRENT EPISODES OF KETOACIDOSIS IN CHILDREN WITH TYPE 1 DIABETES, The 9 th National Congress of Diabetes, Nutrition and Pediatric Endocrinology - with international participation 2-5 noiembrie 2022 – Eposter

9. **Chisnoiu Tatiana**, Balasa Adriana, Nicolae Ana-Maria, Mihai Larisia, Cuzic Viviana, Pantazi C.A., Frecus Corina, Ion Irina, Mihai Cristina Maria, CARACTERISTICI IN BOALA CELIACA SI DIABETUL ZAHARAT DE TIP 1 LA COPIL - 10 ANI DE EXPERIENTA CLINICA, Congresul National De Gastroenterologie, Hepatologie si Nutritie Pediatrica 12-14 octombrie 2023, Cluj- Eposter

10. Cristina Maria Mihai, **Tatiana Chisnoiu** Consecintele dezechilibrului metabolic la copiii si adolescentii cu Diabet zaharat tip 1, Al XVI-lea Congres National de Pediatrie cu participare internationala, 28-30.09.2023, Sinaia – Prezentare orala

11. **Tatiana Chisnoiu**, Cristina Maria Mihai, OXIDATIVE STRESS IN CHILDREN WITH TYPE 1 DIABETES: IMPLICATIONS FOR VASCULAR AND OTHER COMPLICATIONS, Al 10-lea Congres National de Diabet, Nutritie si Endocrinologie Pediatrica cu Participare Internationala, 7-10 iunie 2023, Timisoara – Prezentare orala

12. **Tatiana Chisnoiu**, Mihaela Pistalu, Oana Nicola, Gilda Elena Danilov, Adriana Luminita Balasa, Cristina Maria Mihai, IMPACT OF METABOLIC CONTROL OF DIABETES DURING PREGNACNY AND HYPERTROPHIC CARDIOMYOPATHY IN INFANTS, Al 10-lea Congres National de Diabet, Nutritie si Endocrinologie Pediatrica cu Participare Internationala, 7-10 iunie 2023, Timisoara- Eposter

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Iasi – Prezentare orala

15. **Tatiana Chisnoiu**, Bianca Constantin, Georgiana Cocona, Gilda Elena Danilov, Cristina Maria Mihai, The utility of genetic tests in the diagnosis of neonatal diabetes, Al 10-lea Congres National de Diabet, Nutritie si Endocrinologie Pediatrica cu Participare Internationala, 7-10 iunie 2023, Timisoara – E-poster – comunicari scurte

16. **Tatiana Chisnoiu**, Mihaela Pistalu, Oana Nicola, Gilda Elena Danilov, Adriana Luminita Balasa, Cristina Maria Mihai, Impact Of Metabolic Control Of Diabetes During Pregnacny And Hypertrophic Cardiomyopathy In Infants Al 10-lea Congres National de Diabet, Nutritie si Endocrinologie Pediatrica cu Participare Internationala, 7 -10 iunie 2023, Timisoara – E-poster – comunicari scurte

17. **Tatiana Chisnoiu**, Cristina Maria Mihai, SEVERE ACUTE RENAL FAILURE IN DIABETIC KETOACIDOSIS AT ONSET IN A PATIENT WITH X FRAGILE CHROMOSOME SYNDROME, The 9 th National Congress of Diabetes, Nutrition and Pediatric Endocrinology - with international participation 2-5 noiembrie 2022– Prezentare orala

Sub-investigator in international multicenter clinical studies:

- **NN9924-4437-902 Pioneer** Efficacy and safety of oral semaglutide versus placebo both in combination with metformin and/or basal insulin in children and adolescents with type 2 diabetes (PI Mihai Cristina Maria, **SI Chisnoiu Tatiana)**

- **Studiul MSD MK0341-083**: Phase III, multicenter, double-blind, randomized, placebo- and metformin-controlled clinical trial to evaluate the safety and efficacy of sitagliptin in pediatric patients with poorly controlled type 2 diabetes mellitus (2013-2018); (PI Mihai Cristina Maria, **SI Chisnoiu Tatiana)**

- **Studiul MSD MK0341-170**: Phase III, Multicenter, Double-Blind, Randomized,

Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-0341A (Fixed-Dose Combination of Sitagliptin and Metformin) in Pediatric Patients with Type 2 Diabetes Mellitus (2013-2018); (PI Mihai Cristina Maria, **SI Chisnoiu Tatiana)**

- **Studiul Novonordisk NN2211-3659:** Efficacy and safety of liraglutide in combination with metformin compared to metformin alone on glycemic control in children and adolescents with type 2 diabetes (2015-2019); Multicenter study (PI Mihai Cristina Maria, **SI Chisnoiu Tatiana)**

- **Studiul Sanofi Edition Junior EFC13957**: Multicenter, randomized, open-label, two-arm, parallel-group, 6-month study comparing the efficacy and safety of a new formulation of insulin glargine and once-daily Lantus in children and adolescents aged 6 -17 years with type 1 diabetes, with a safety extension period of 6 months (2017-2019); (PI Mihai Cristina Maria, **SI Chisnoiu Tatiana)**

➢ **Completed courses:**

International Diabetes Center Time in Range Academy: Using Continous Glucose Monitoring to improve Type 2 Diabetes Managament, University of Minnesota Medical School, March-October 2023, Certificate No 5007004

➢ **Ongoing programs**

Resident doctor in the second specialty: Diabetes, Nutrition, and Metabolic Diseases, year 3

Certificate in pediatric diabetology – Module 1