Doctoral School of Medical Sciences

Manuscript title:

C.Z.U.: 616.379-008.64-06:616.12-07-053.2(043.2)

EȘANU Valeriu

INFLAMMATORY AND MORPHO-FUNCTIONAL CARDIAC STATUS IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

322.01 – PAEDIATRICS AND NEONATOLOGY

Summary of Ph.D. thesis in medical sciences

CHIȘINĂU, 2026

The thesis was developed in the Paediatric Department of the „Nicolae Testemitanu" State University of Medicine and Pharmacy from the Republic o f Moldova.

Scientific adviser:
Palii Ina, MD PHD, universitary professor
Cotutelle scientific adviser:
Vudu Lorina, MD, associate professor
Members of the steering committee:
Revenco Ninel, MD PHD, universitary professor

Cobeț Valeriu, MD PHD, universitary professor

Golovin Boris, MD, associate professor

The presentation will take place on 16.09.2026, at 14:00, in the premises of "Nicolae Testemitanu" SUMPh, bd. Ștefan cel Mare și Sfânt, 165, office 205 in the meeting of the Commission for the public defense of the PhD thesis, approved by the decision of the Scientific Council of the Consortium of 05.05.2026 (issued document nr. 6).

The composition o f the Commission for the public presentation of the doctoral thesis:
Chairperson:
Nelea Mătrăgună, MD, PhD, Associate Professor
Specialty 321.03 Cardiology, "Nicolae Testemițanu" SUMPh

Members:
Ina Palii, MD, PhD, University Professor
Specialty 322.01 Pediatrics and Neonatology,
321.03 Cardiology, "Nicolae Testemițanu" SUMPh
Lorina Vudu, MD, Associate Professor
Specialty 321.02 Endocrinology, "Nicolae Testemițanu" SUMPh

Official Reviewers:
Ninel Revenco, MD, PhD., University Professor
Specialty 322.01 Pediatrics and Neonatology,
321.04 Rheumatology, "Nicolae Testemițanu" SUMPh
Veronica Mocanu, MD, PhD,
University Professor Department of Pathophysiology,
"Grigore T. Popa" UMP, Iași, Romania
Victoria Ivanov, MD, PhD, Research Professor
Specialty 321.03 Cardiology, "Institute of Cardiology" PHI

Autor:

Eșanu Valeriu

TABLE OF CONTENTS

TYPE 1 DIABETES MELLITUS IN THE PEDIATRIC POPULATION – SCIENTIFIC RATIONALE OF THE RESEARCH

Topicality of the research. Type 1 diabetes mellitus is recognized as a clinical entity characterized by the autoimmune destruction of pancreatic beta cells, ultimately leading to insufficient insulin production and the onset of hyperglycemia, with a lifelong dependence on exogenous insulin. It also carries a major risk for the development of complications, including cardiovascular disorders, comorbidities, and premature mortality.

Regarding the global burden, type 1 diabetes accounts for 5–10% of all diabetes cases, while constituting over 90% of pediatric cases [1], making it the most common form of childhood diabetes and one of the most frequent chronic endocrine diseases of childhood [2]. Estimated data from the International Diabetes Federation Atlas confirm a rising global incidence with significant geographic variations, which are more pronounced among populations of European descent [3]. The geographic variability in the incidence and prevalence of type 1 diabetes mellitus, with higher rates reported in children of European origin, suggests the involvement of a complex interaction between genetic predisposition and environmental factors [4].

Under physiological conditions, pancreatic -cells respond promptly to blood glucose fluctuations through the adequate secretion of insulin, thereby contributing to the maintenance of euglycemia. However, their functional and structural particularities—intensive metabolic activity, high demands associated with insulin synthesis and secretion, rich vascularization, intrinsically low antioxidant capacity, and sensitivity to proinflammatory mediators—render them highly vulnerable in the context of autoimmune aggression.

In type 1 diabetes mellitus, the exposure of -cells to proinflammatory cytokines, such as tumor necrosis factor-alpha, interferon-gamma, and interleukin-1 beta, progressively disrupts cellular function. These molecules interfere with energy metabolism, reduce adenosine triphosphate production, induce deoxyribonucleic acid damage, and activate apoptotic pathways, thereby compromising insulin secretory capacity. A major role in this process is played by the activation of nuclear factor κB, which stimulates the expression of inducible nitric oxide synthase, leading to increased nitric oxide production. In the initial phases, this response may have an adaptive character, participating in DNA damage repair and limiting apoptosis. However, persistent inflammatory stimulation transforms this mechanism into a factor of cellular aggression, associated with the exacerbation of DNA lesions, activation of the protein stress response, reduction of mitochondrial oxidation, and decreased ATP synthesis.

At the national level, epidemiological data indicate an upward trend in the incidence of type 1 diabetes mellitus in children [5]. Nevertheless, in the Republic of Moldova, no studies have been identified to date that comprehensively and integratedly evaluate the inflammatory status, redox imbalance, lipid profile, and cardiac morpho-functional alterations in children with this condition. This insufficiently explored direction justifies the need for the present research and provides the scientific foundation for this study.

In this context, the research endeavor underlying this study was based on the premise that the integrated evaluation of inflammatory status, oxidative stress, lipid profile, and echocardiographic parameters can contribute to the early identification of cardiometabolic changes in children with type 1 diabetes mellitus. A better understanding of these mechanisms and their impact on left ventricular remodeling can support the development of strategies for pediatric cardiovascular risk stratification and the optimization of clinical management, aiming to delay or prevent disease-associated complications.

General Objective of the Study: To evaluate markers of inflammation, oxidative stress, lipid profile, and cardiac remodeling in children with type 1 diabetes mellitus and a disease duration of 5 years, in order to identify early predictors of cardiovascular impairment.

To achieve this goal, the research pursued the following **specific objectives**:

1. To determine the systemic inflammatory status in children with type 1 diabetes mellitus by evaluating serum levels of interleukin-1beta, interleukin-6, tumor necrosis factor-alpha, and C-reactive protein in relation to the severity of poor glycemic control.
2. To assess the oxidative-antioxidant imbalance in children with type 1 diabetes mellitus by quantifying pro-oxidant markers alongside enzymatic and non-enzymatic antioxidant components relevant to the mechanisms of cardiometabolic impairment.
3. To analyze the characteristics of lipid metabolism in children with type 1 diabetes mellitus by investigating standard lipid profile components—total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides—and to highlight disease-associated dyslipidemic changes.
4. To evaluate left ventricular remodeling in children with type 1 diabetes mellitus and to determine the interrelationships with parameters of inflammatory status, oxidative-antioxidant imbalance, lipid profile, and glycemic control.

Scientific Research Methodology. This observational, analytical, case-control study was conducted between 2019 and 2023 within the Department of Pediatrics of the "Nicolae Testemițanu" State University of Medicine and Pharmacy, at the clinical site of the Mother and Child Institute, Department of Pediatric Endocrinology. The study group comprised 44 children with type 1 diabetes mellitus and a disease duration of 5 years, while the control group included 46 conditionally healthy, demographically comparable children, with ages ranging from 10 to 18 years. The evaluation focused on the inflammatory profile, redox status, lipid profile, and echocardiographic parameters of left ventricular remodeling. Statistical analysis was performed using the R software environment. The study was approved by the Research Ethics Committee of the "Nicolae Testemițanu" State University of Medicine and Pharmacy, under minutes no. 42 dated June 17, 2019.

Scientific Novelty and Originality of the Results. This study represents the first integrated local evaluation within the pediatric population of the Republic of Moldova to analyze the clinical and paraclinical profiles of children with type 1 diabetes mellitus. It achieves this by simultaneously assessing oxidative stress and antioxidant activity markers, inflammatory and lipid profile indicators, and echocardiographic parameters of left ventricular remodeling. Furthermore, the interrelationship between these independent yet interconnected cardiovascular risk factors is thoroughly analyzed. The results highlight the presence of pathological left ventricular remodeling, which is tightly linked to oxidative-antioxidant imbalance, altered lipid profiles, and the activation of proinflammatory processes under conditions of suboptimal glycemic control.

Approval of Scientific Results. The research findings have been disseminated through 10 published scientific papers (1 article in a journal indexed in international databases, 6 articles in accredited Category B national scientific journals, and 2 in peer-reviewed international collective volumes). These results were presented as oral presentations or abstracts at 16 international scientific events (Romania, the Russian Federation, Switzerland, Portugal) and 7 national scientific events. Additionally, 7 innovator certificates were obtained, attesting to the originality and applicability of the results.

Keywords: type 1 diabetes mellitus; pediatric population; early cardiovascular risk; inflammation; proinflammatory cytokines; oxidative stress; antioxidant status; dyslipidemia; lipid profile; left ventricular remodeling; echocardiography.

1. MATERIALS AND RESEARCH METHODS

General Characteristics of the Research and Sample Size Design

Study Period, Setting, and Subjects. The research project was conducted between 2019 and 2023 within the Department of Pediatrics of the Mother and Child Institute, specifically in the Pediatric Endocrinology Section. Recruitment, investigation, and monitoring activities were carried out in a single-center setting, enrolling a total of 90 children aged between 10 years and 17 years, 11 months, and 29 days, from both urban and rural areas. The study sample consisted of 44 subjects diagnosed with type 1 diabetes mellitus, presenting a disease duration of more than 5 years and undergoing continuous insulin therapy initiated within the first year of diagnosis. Conversely, the control group comprised 46 children without type 1 diabetes mellitus, selected to match the demographic characteristics of the study cohort. To achieve the established aim and objectives, an analytical, observational cohort study design was planned.

Research Timeline. The research process consisted of a staged prospective evaluation structured into four consecutive phases (see Figure 1).

Phase I. Participant Selection. Application of inclusion/exclusion criteria to electively referred patients establishment of the study group (children with type 1 diabetes mellitus) and the control group (conditionally healthy children). Obtaining informed consent.

Phase II. Clinical and Paraclinical Evaluation. Standardized medical history, physical examination, and anthropometric parameters; collection of biological samples for metabolic profiling (blood glucose, HbA1c, lipid profile), oxidative stress and antioxidant system markers, and inflammatory markers (CRP, IL-1beta, IL-6, TNF-); echocardiographic evaluation (structural and functional parameters of the left ventricle).

Phase III. Data Processing. Construction of the database, followed by descriptive and inferential statistical analysis (R software environment).

Phase IV. Data Interpretation and Formulation of Conclusions. Drafting of final conclusions and practical clinical recommendations.

Statistical Analysis. Data management was performed using *Microsoft Excel* for database construction and cleaning, while the *R Programming Language* (updated version) was utilized for advanced data processing, application of statistical tests, and generation of automated graphs, tables, and reports. This combination of tools ensured efficient database management alongside a rigorous, reproducible statistical analysis tailored to the research requirements. The statistical methodology was validated through consultation with a specialist in medical statistics, ensuring the appropriate selection of statistical tests and accurate interpretation of the results.

Ethical Considerations. The study was approved by the Research Ethics Committee of the "Nicolae Testemițanu" State University of Medicine and Pharmacy (Approval No. 42 dated June 17, 2019).

Reference Management. Bibliographic references were managed automatically using the integrated citation function of Microsoft Word 2007 and the Zotero application (version 6.0.18) [available at: www.zotero.org], along with its corresponding extension for Google Chrome.

STAGE I - Participant selection, PMSI Institute of Mother and Child · 2019-2023

Children electively referred to the Pediatric Endocrinology Department (10-18 years)

MAIN GROUP (n=44)	CONTROL GROUP (n=46)
Children with: type 1 DM, disease duration ≥ 5 years, continuous insulin therapy, age 10-18 years	Conditionally healthy children (health groups I and II; demographic similarity with the main group)

Written informed consent (parents + assent ≥ 14 years)

STAGE II - Clinical and paraclinical assessment

Clinical assessment	Biochemical spectrum
▪ Standardized history (questionnaire) ▪ Anthropometric parameters (W, H, BMI, Z-score - WHO) ▪ Hemodynamic parameters (BP; HR)	▪ Lipid profile (TC, LDL-C, HDL-C, TG) ▪ Inflammatory markers (CRP, IL-1β, IL-6, TNF-α) ▪ Redox status: prooxidant markers and the antioxidant system ▪ Color Doppler echocardiography

Color Doppler echocardiography

- Dimensions of the cardiac chambers and great vessels (aortic diameter, left atrial size, right ventricular size, LV end-diastolic diameter, LV end-systolic diameter)
- LV parietal parameters (interventricular septal thickness, LV posterior wall thickness)
- LV volumetric parameters (LV end-diastolic volume, LV end-systolic volume)
- LV functional parameters (LV ejection fraction, LV fractional shortening)
- LV myocardial mass - calculated according to the Devereux formula
- Left ventricular geometry - assessed by the association between left ventricular mass index and relative wall thickness, classified into four types: normal geometry, concentric remodeling, eccentric hypertrophy, concentric hypertrophy.

STAGE III - Statistical data processing

- Database: Microsoft Excel; variable coding; consistency check; missing/extreme values.
- Variables analyzed: clinical-demographic, metabolic, inflammatory, oxidative-antioxidant, lipid and echocardiographic.
- Descriptive statistics: Mean ± SD; Median [IQR]; n (%).
- Between-group comparisons: Student t-test; Fisher exact test; 95% CI.
- Correlations: Pearson / Spearman.
- Regressions: univariate linear and logistic regression.
- Software: Microsoft Excel for the database; R for statistical analysis.
- Statistical significance: $p < 0.05$.

STAGE IV - Interpretation of results and formulation of conclusions

- Integration of results with the literature (comparative reporting)
- Formulation of conclusions and development of practical recommendations

Figure 11. Conceptual diagram of the study

2. SYNTHESIS OF CHAPTERS

2.1. Demographic, Anthropometric, and Clinico-Metabolic Characteristics of the Study Cohorts

Descriptive Analysis of the Study Cohort. The descriptive assessment indicated a balanced structure of the groups, with no significant differences by sex or age groups at study inclusion. In the group of children with diabetes, 24 (54.5%) boys and 20 (45.5%) girls were recorded, while the control group included 17 (37.0%) boys and 29 (63.0%) girls ($p = 0.072$). The distribution by age groups was also comparable: the mean age was 13.6 ± 2.2 years in the diabetes group and 14.0 ± 2.4 years in the non-diabetes group, without statistically significant differences (95% CI: −0.63 to 1.3; $p = 0.5$). This homogeneity of demographic characteristics between the groups ensured the valid comparability of the results obtained in the subsequent stages of the research.

Anthropometric characteristics of the study groups. In accordance with the analytical structure of the study, assessment of anthropometric indices included measurement of body weight and height and calculation of body mass index. Comparative analysis between the main group and the control group did not reveal statistically significant differences, confirming the comparability of the two groups from a somatometric perspective. Specifically, mean height (cm) was 158.4 ± 15.7 versus 159.1 ± 14.0 (95% CI: −5.5 to 7.0; $p = 0.8$), mean weight (kg) was 50.9 ± 14.9 versus 51.4 ± 12.2 (95% CI: −13 to 12; $p = 0.9$), and body mass index (kg/m²) was 19.8 ± 2.9 versus 20.1 ± 3.3 (95% CI: −0.96 to 1.6; $p = 0.6$). The ancillary analysis confirmed comparable anthropometric distributions between the two groups, with no relevant differences, based on reporting to the standard deviation from the median and to the corresponding percentiles.

Descriptive statistical analysis of clinical-metabolic characteristics and the insulin-therapy profile in children from the main group. In the cohort of children with diabetes, the mean duration of disease was 7.5 ± 3.0 years (range: 5-14 years), highlighting prolonged exposure to metabolic stress secondary to persistent hyperglycemia. Earlier onset was also associated with longer disease duration and a subsequently higher insulin requirement, suggesting a cumulative impact of metabolic exposure. In addition, mean plasma glucose values were 10.0 ± 2.1 mmol/L / 180 ± 38 mg/dL (range: 5.8-15.7 mmol/L / 104-283 mg/dL), indicating suboptimal glycemic control in the analyzed group. The mean glycated hemoglobin level was 9.8 ± 1.5% (range: 5.8-15.7%), confirming poor glycemic control in most cases and correlating strongly with plasma glucose values ($r \approx 0.9$, $p < 0.001$). Regarding the insulin-therapy profile, the mean total insulin dose adjusted for body weight was 1.0 ± 0.3 U/kg (range: 0.54-1.57 U/kg). Higher values were recorded in children with early onset and long disease evolution, emphasizing a combination of physiological pubertal changes, disease progression and the possible emergence of insulin resistance. The total daily insulin dose was 50 ± 15 U/day (range: 18-87 U/day), directly correlated with body weight ($r \approx 0.65$, $p < 0.01$) and pubertal stage. Of the total dose, basal insulin accounted for a mean of 25 ± 10 U/day (range: 0-48 U/day), varying according to individual metabolic needs, while prandial insulin averaged 24 ± 9 U/day (range: 9-60 U/day), increasing with preprandial glucose values and carbohydrate intake. From a correlational perspective, the almost perfect interdependence ($r \approx 1.00$) between glucose and glycated hemoglobin confirms the coherence of the data and the quality of laboratory determinations; clinically, it accurately reflects mean glycemia and confirms suboptimal glycemic control.

2.2. Assessment of oxidative stress parameters and quantification of antioxidant capacity

Markers of carbohydrate peroxidation.

Advanced glycation end products (μg/L, AGEs pentosidine-like and vesperlysines-like, formed in hyperglycemic environments and mediators of cardiovascular pathology in diabetes) [6,7]. Serum levels of AGEs pentosidine-like and AGEs vesperlysines-like showed a statistically relevant variation, with significantly increased values in the diabetes group compared with the control group. AGEs pentosidine-like: diabetic subjects - 533.5 ± 77.5 μg/L vs non-diabetic subjects - 315.2 ± 56.2 μg/L; difference = −218 (95% CI −247 to −190, $p < 0.001$); overall group - 422.0 ± 128.6 (95% CI 395-449). AGEs vesperlysines-like: diabetic subjects - 741.9 ± 165.9 μg/L vs non-diabetic subjects - 340.1 ± 48.4 μg/L; difference = −402 (95% CI −454 to −350, $p < 0.001$); overall group - 536.6 ± 235.1 (95% CI 487-586).

Markers of protein peroxidation.

Advanced oxidation protein products (μmol/L, biomarkers of oxidative protein injury, formed under the action of oxidizing agents and also able to contribute to amplification of oxidative stress through feed-forward mechanisms) [8]. A statistically significant difference between groups was found, with higher values recorded in the study group versus the control group (9.4 ± 4.0 μmol/L vs 6.0 ± 1.8 μmol/L; difference = −3.4, 95% CI −4.7 to −2.1, $p < 0.001$), overall group 7.7 ± 3.5 μmol/L (95% CI 6.9-8.4).

Ischemia-modified albumin [μM/L, an early biomarker of hypoxia-induced oxidative stress, recognized as an unfavorable prognostic factor for acute cardiac complications (within the first 72 hours) and as a long-term predictor [8], as well as an indicator of glycemic control]. It was significantly increased in diabetic subjects compared with non-diabetic subjects [469.8 ± 53.6 μM/L vs 229.4 ± 50.0 μM/L; difference = −240, 95% CI −262 to −219, $p < 0.001$), overall group - 349.2 ± 127.5 μM/L (95% CI 333-365)].

Markers of lipid peroxidation.

Malondialdehyde (μM/L, one of the universal molecular markers of stress status, the most mutagenic product of lipid peroxidation, and a prognostic indicator of cardiovascular diseases [8,9]). Values were 17.5 ± 1.8 μM/L among those with diabetes, compared with 13.0 ± 1.2 μM/L in potentially healthy subjects (difference = −4.5, 95% CI −5.2 to −3.9, $p < 0.001$), overall group - 15.2 ± 2.7 μM/L (95% CI 14.8-15.6). The differences were statistically confirmed ($p < 0.001$).

Markers of endothelial dysfunction.

Nitric oxide (μmol/L, an endogenous modulator of respiratory function, with a role as a proinflammatory and immunomodulatory mediator in various physiological and pathological conditions [10,11]; it influences central hemodynamics and microcirculation [12], regulates vascular permeability and contributes to maintaining antiplatelet protection). Values were comparable between groups (59.8 ± 6.2 μmol/L vs 62.1 ± 5.1 μmol/L; difference = 2.3, 95% CI −0.11 to 4.7, $p = 0.061$), overall group - 61.0 ± 5.8 μmol/L (95% CI 60-62).

On the other hand, **antioxidant protection** in the study, assessed through antioxidant reserves, showed that superoxide dismutase (u/c) - considered the most effective antioxidant enzyme and a central element of antioxidant defense - was significantly inhibited in diabetic subjects (46.6 ± 5.9 vs 80.4 ± 10.6; difference = 34, 95% CI 30-37; $p < 0.001$; overall group = 63.9 ± 19.1; 95% CI 60-68), suggesting depletion of antioxidant mechanisms and possible uncontrolled activation of peroxidation processes. A similar tendency was recorded for catalase (μM/L) - an enzyme with high substrate specificity that acts synergistically with SOD, together forming the most effective system for neutralizing free radicals [13] - which was also significantly reduced in children with diabetes (19.4 ± 5.1 vs 34.5 ± 6.7; difference = 15, 95% CI 13-18; $p < 0.001$; overall group = 27.1 ± 9.6; 95% CI 25-29), confirming decompensation of redox balance. Total antioxidant activity (mmol/L), expressed as free-radical neutralization capacity, was also

statistically significantly decreased in participants from the main group by both methods used: ABTS (mmol/L): 93.7 ± 20.6 vs 177.3 ± 29.0; difference = 84, 95% CI 73-94; p < 0.001; overall group = 136.5 ± 48.9; 95% CI 126-147; CUPRAC (mmol/L): 2.1 ± 0.7 vs 6.6 ± 3.2; difference = 4.5, 95% CI 3.5-5.5; p < 0.001; overall group = 4.4 ± 3.3; 95% CI 3.7-5.1.

Table 1. Distribution trends of values of selected oxidative stress parameters in the studied groups1

Variabile	nonDZ, N = 46[1]	95% CI[2]	DZ, N = 44[1]	95% CI[2]	Diff.[3]	95% CI[2]3	p[3]
Carbohydrate peroxidation							
AGEs pentosidine-like (µg/L)	315.2 (56.2) 322.6 (89.6) 164.8 397.1	299, 332	533.5 (77.5) 521.7 (67.8) 425.0 809.3	510, 557	-218	-247, -190	<0.001
AGEs vesperlysines-like (µg/L)	340.1 (48.4) 339.1 (66.7) 254.0 505.8	326, 354	741.9 (165.9) 720.3 (142.7) 465.5 1,253.8	691, 792	-402	-454, -350	<0.001
Peroxidare proteine							
PPOA (µmol/l)	6.0 (1.8) 6.1 (1.7) 2.3 9.8	5.5, 6.6	9.4 (4.0) 8.4 (3.0) 5.3 27.6	8.2, 11	-3.4	-4.7, -2.1	<0.001
AIM (µM/L)	229.4 (50.0) 226.3 (69.6) 106.0 361.5	215, 244	469.8 (53.6) 467.4 (87.9) 349.1 611.2	454, 486	-240	-262, -219	<0.001
Peroxidare lipide							
DAM (µM/L)	13.0 (1.2) 12.9 (1.3) 10.3 15.7	13, 13	17.5 (1.8) 17.1 (2.4) 14.1 22.7	17, 18	-4.5	-5.2, -3.9	<0.001
Endothelial dysfunction							
NO (µmol/L)	62.1 (5.1) 61.2 (7.4) 51.9 76.7	61, 64	59.8 (6.2) 60.5 (7.8) 47.3 73.6	58, 62	2.3	-0.11, 4.7	0.061

[1]Mean (SD); Median (IQR); Minimum-Maximum

[2]CI - 95% confidence interval.

[3]t-test for independent samples (Welch Two Sample t-test).

Note: *Values are expressed as mean ± standard deviation (Mean ± SD) and 95% confidence interval (95% CI). The difference represents the mean value in T1D minus the mean value in non-T1D. p < 0.05 was considered statistically significant. Abbreviations: AGEs - advanced glycation end products; AOPP - advanced oxidation protein products; IMA - ischemia-modified albumin; MDA - malondialdehyde; NO - nitric oxide.*

In contrast, the indicators of *thiol-disulfide homeostasis* (µM/L) were higher in diabetic subjects: *free SH thiol group*s (µM/L): 97.8 ± 21.5 vs 81.3 ± 13.7; difference = −17, 95% CI −24 to −8.9; p < 0.001; overall group = 89.4 ± 19.7; 95% CI 85-93; *total SH thiol groups* (µM/L): 104.6 ± 20.3 vs 89.8 ± 12.9; difference = −15, 95% CI −22 to −7.7; p < 0.001; overall group = 97.0 ± 18.4; 95% CI 93-101. A similar behavior was also noted for *ceruloplasmin* (mg/L) - an acute-phase protein with antioxidant properties (379.6 ± 52.7 vs 266.0 ± 44.2; difference = −114, 95% CI −134 to −93), overall group = 322.8 ± 75.3 (95% CI 317-329), with statistically confirmed differences (p < 0.001). *Total serum protein* (g/L) did not show significant differences between the studied groups, with mean values of 59.6 ± 8.2 g in children with diabetes compared with 58.7

± 3.2 in non-diabetic children, difference = −0.91 (95% CI −3.6 to 1.8; p = 0.5), overall group = 59.1 ± 6.3 (95% CI 58.6-59.7).

Assessment of the relationship between chronic glycemic control, evaluated by HbA1c, and redox-status markers generally revealed weak and statistically non-significant correlations. HbA1c was not significantly associated with markers of lipid and protein peroxidation: malondialdehyde (r = −0.042; p = 0.788) and advanced oxidation protein products (r = −0.043; p = 0.784). The correlation with AGEs pentosidine-like was also positive but statistically non-significant (r = 0.156; p = 0.312). In contrast, AGEs vesperlysines-like showed a positive correlation of low-to-moderate intensity, statistically significant, with HbA1c (r = 0.314; p = 0.038), suggesting a possible association between chronic glycemic exposure and accumulation of some advanced glycation products. Antioxidant capacity parameters had weak and non-significant correlations with HbA1c: superoxide dismutase (r = −0.017; p = 0.911), catalase (r = 0.078; p = 0.592) and total antioxidant activity ABTS (r = −0.171; p = 0.240), indicating the absence of a direct relationship between chronic glycemic control and antioxidant-system activity in the analyzed group.

Table 2. Distribution trends of values of selected antioxidant protection indicators in the studied groups2

Variable	nonDZ, N = 46[1]	95% CI[2]	DZ, N = 44[1]	95% CI[2]	Diff.[3]	95% CI[2,3]	p[3]
AAT-ABTS (mmol/l	177.3 (29.0) 168.5 (51.2) 119.5 241.2	169, 186	93.7 (20.6) 91.0 (17.5) 57.6 145.6	87, 100	84	73, 94	**<0.001**
Cuprac (mmol/l)	6.6 (3.2) 5.9 (2.6) 3.0 17.6	5.6, 7.6	2.1 (0.7) 2.0 (1.0) 1.0 3.5	1.9, 2.3	4.5	3.5, 5.5	**<0.001**
SOD (u/c)	80.4 (10.6) 79.4 (15.7) 60.8 99.8	77, 84	46.6 (5.9) 47.0 (6.7) 29.9 56.3	45, 48	34	30, 37	**<0.001**
Catalaza (µM/L)	34.5 (6.7) 33.8 (11.0) 22.6 46.2	33, 37	19.4 (5.1) 20.3 (7.5) 12.4 32.8	18, 21	15	13, 18	**<0.001**
CP (mg/l)	266.0 (44.2) 257.4 (49.5) 192.6 385.3	253, 279	379.6 (52.7) 377.4 (64.9) 276.9 477.8	364, 396	-114	-134, -93	**<0.001**
SH-grupe tiolice (µM/L)	4.6 (0.9) 4.4 (1.2) 2.9 7.1	4.3, 4.8	5.2 (1.3) 5.0 (1.7) 2.8 8.0	4.8, 5.6	-0.62	-1.1, -0.15	0.011
SH-grupe tiolice totale (µM/L)	89.8 (12.9) 90.0 (17.9) 66.5 125.9	86, 94	104.6 (20.3) 99.6 (22.9) 77.8 153.0	98, 111	-15	-22, -7.7	**<0.001**
SH-grupe tiolice libere (µM/L)	81.3 (13.7) 80.5 (20.9) 51.4 121.4	77, 85	97.8 (21.5) 93.2 (22.9) 63.5 148.4	91, 104	-17	-24, -8.9	**<0.001**

[1]Mean (SD); Median (IQR); Minimum-Maximum

[2]CI - 95% confidence interval.

[3]t-test for independent samples (Welch Two Sample t-test).

Note: *Values are expressed as mean ± standard deviation (Mean ± SD) and 95% confidence interval (95% CI). The difference represents the mean value for the T1D group minus the mean value for the non-T1D group. A p value <*

0.05 was considered statistically significant. Abbreviations: SOD - superoxide dismutase; SH - thiol groups (total/free); CP - ceruloplasmin; AAT-ABTS - total antioxidant capacity determined by the ABTS method; CUPRAC - total antioxidant capacity determined by the CUPRAC method; Catalase - serum catalase activity.

2.3. Estimation of the serum expression of reference inflammatory markers in pediatric diabetes mellitus

C-reactive protein, recognized as a marker of acute-phase inflammation and chronic metabolic stress [14], recorded a mean value of 11.4 ± 2.8 mg/L in the diabetic group, significantly higher than in the control group (4.1 ± 1.4 mg/L), with a difference of −7.3 (95% CI −8.3 to −6.3, $p < 0.001$; boys: 12.2 mg/L vs 4.2 mg/L -> difference: 8.02 mg/L, 95% CI: [6.85-9.19], $p < 0.001$; girls: 10.4 mg/L vs 3.9 mg/L -> difference: 6.44 mg/L, 95% CI: [5.08-7.80], $p < 0.001$), reflecting the presence of persistent chronic subclinical inflammation associated with immunometabolic dysfunction.

Similarly, *IL-1β*, a proinflammatory cytokine involved in amplification of the autoimmune response, activation of oxidative stress and deterioration of pancreatic β cells [15], showed significantly increased values in children with diabetes (15.2 ± 1.5 pg/mL) compared with non-diabetic subjects (8.2 ± 0.5 pg/mL), with a mean difference of −6.9 (95% CI −7.4 to −6.5, $p < 0.001$; boys: 14.9 pg/mL vs 8.3 pg/mL -> difference: 6.62 pg/mL, 95% CI: [6.19-7.05], $p < 0.001$; girls: 15.5 pg/mL vs 8.2 pg/mL -> difference: 7.22 pg/mL, 95% CI: [6.36-8.08], $p < 0.001$).

At the same time, *IL-6* - a pleiotropic cytokine considered a central mediator of the inflammatory cascade and a promoter of autoimmune and apoptotic processes in β cells [16] - showed a significantly increased mean value among those with diabetes (83.6 ± 35.2 pg/mL), compared with 13.9 ± 3.6 pg/mL in the control group, with a difference of −70.0 (95% CI −81 to −59, $p < 0.001$; boys: 85.1 pg/mL vs 14.2 pg/mL -> difference: 71.0 pg/mL, 95% CI: [56.91-85.05], $p < 0.001$; girls: 81.8 pg/mL vs 13.7 pg/mL -> difference: 68.2 pg/mL, 95% CI: [52.95-83.39], $p < 0.001$).

Likewise, *TNF-α,* a major cytokine in the initiation of systemic inflammation, with a role in inducing β-cell apoptosis and disrupting immune tolerance [16], recorded a mean value of 50.2 ± 39.9 pg/mL in the main group compared with 26.5 ± 10.0 pg/mL in the control group, with a difference of −24.0 (95% CI −36 to −11, $p < 0.001$; boys: 52.1 pg/mL vs 27.1 pg/mL -> difference: 24.99 pg/mL, 95% CI: [7.33-42.65], $p = 0.010$; 48.0 pg/mL vs 26.2 pg/mL -> difference: 21.77 pg/mL, 95% CI: [5.71-37.83], $p = 0.014$).

The correlation matrix analysis between glycated hemoglobin and the inflammatory markers analyzed in the main group showed the following: CRP - a very weak positive correlation ($r = 0.04$; $p = 0.814$), indicating that higher HbA1c values are not consistently associated with increases in C-reactive protein; IL-1β and IL-6 - inverse but low-intensity interdependences ($r = −0.09$; $p = 0.573$ and $r = −0.15$; $p = 0.345$), suggesting a slight tendency for these cytokines to decrease as HbA1c increases, but without statistical relevance; TNF-α - a weak-to-moderate negative correlation ($r = −0.259$), practically at the limit of significance ($p \approx 0.09$), indicating a particular inflammatory response in the context of chronic hyperglycemia.

Table 3. Variation in serum TNF-α, IL-1β, IL-6 and CRP content in study participants3

Variabile	nonDZ, N = 46[1]	95% CI[2]	DZ, N = 44[1]	95% CI[2]	Diff.[3]	95% CI[2,3]	p[3]
PCR	4.1 (1.4) 3.9 (1.8) 2.3 7.1	3.6, 4.5	11.4 (2.8) 10.7 (5.7) 6.7 15.3	11, 12	-7.3	-8.3, -6.3	**<0.001**
IL-1β	8.2 (0.5) 8.2 (0.6) 6.7 9.7	8.1, 8.4	15.2 (1.5) 14.6 (0.9) 14.0 21.1	15, 16	-6.9	-7.4, -6.5	**<0.001**
IL-6	13.9 (3.6) 13.0 (4.5) 10.1 31.1	13, 15	83.6 (35.2) 63.3 (72.8) 49.7 153.4	73, 94	-70	-81, -59	**<0.001**
TNF -α	26.5 (10.0) 28.3 (15.9) 11.0 50.5	24, 30	50.2 (39.9) 42.2 (18.3) 22.9 202.1	38, 62	-24	-36, -11	**<0.001**
[1]Mean (SD); Median (IQR); Minimum-Maximum							
[2]CI - 95% confidence interval.							
[3]t-test for independent samples (Welch Two Sample t-test).							

Note: *Values are expressed as mean ± standard deviation (Mean ± SD) and 95% confidence interval (95% CI). The difference represents the mean value in the T1D group minus the mean value in the non-T1D group. p values below 0.05 (p < 0.05) were considered statistically significant. Abbreviations: CRP - C-reactive protein; IL-1β - interleukin 1 beta; IL-6 - interleukin 6; TNF-α - tumor necrosis factor alpha; T1D - type 1 diabetes mellitus; 95% CI - 95% confidence interval.*

2.4. Lipid pattern in the pediatric subjects included in the research

Analyzing the study results through the lipidogram approach (see Table 4) in accordance with the recommendations issued by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents for the pediatric population [acceptable values (75th percentile), borderline values (75th-95th percentiles), and abnormal values (>95th percentile; and <10th percentile for HDL-C)] for TC, LDL-C, TG and HDL-C, the following data were recorded: total cholesterol (mmol/L) showed a statistically relevant difference between participants in the main group versus the control group (5.7 ± 0.2; 100% above the 95th percentile vs 4.7 ± 0.3; 0% above the 95th percentile), with a difference of −0.94 (95% CI: −1.10 to −0.82; $p < 0.001$); LDL-C (mmol/L) also showed increased values in the type 1 diabetes group (1.7 ± 0.5; 1 case above the 95th percentile, 2 cases between the 75th-95th percentiles) compared with controls (1.0 ± 0.1), with a difference of −0.73 (95% CI: −0.89 to −0.57), a contrast statistically validated by $p < 0.001$; HDL-C (mmol/L) in both groups similarly showed subthreshold values (<10th percentile, 0.8 ± 0.1 mmol/L vs 0.7 ± 0.2, respectively), with a difference of −0.04 (95% CI: −0.10 to 0.03; $p = 0.30$), but with statistically non-significant findings; TG (mmol/L) showed a statistically significant difference between participants in the main group (2.0 ± 0.2 mmol/L; 100% above the 95th percentile) and controls (1.7 ± 0.3; 52.2% above the 95th percentile), with a difference of −0.50 (95% CI: −0.57 to −0.42; $p < 0.001$); and non-HDL-C (mmol/L) values were significantly higher in the diabetes group (4.89 ± 0.29 mmol/L) compared with the control group (3.99 ± 0.37 mmol/L), with a difference of −0.90 mmol/L (95% CI: −1.04 to −0.77; $p < 0.001$).

Analysis of lipid clusters showed the predominance of the TC+TG+HDL-C combination, identified in 42 children, including 23 boys and 19 girls, followed by TC+TG and TC+TG+LDL-C+HDL-C, with one case each. The sex distribution in the major cluster was relatively balanced,

confirming an atherogenic pattern dominated by total hypercholesterolemia, hypertriglyceridemia and low HDL-C.

Table 4. Variation in lipid-pattern values in the pediatric subjects included in the research

Variable	nonDZ, N = 46[1]	95% CI[2]	DZ, N = 44[1]	95% CI[2]	Diff.[3]	95% CI[2],[3]	p
CT	4.7 (0.3) 4.7 (0.4) 3.9 5.2	4.6, 4.8	5.7 (0.2) 5.6 (0.3) 5.3 6.3	5.6, 5.7	-0.94	-1.1, -0.82	**<0.001**
HDL-C	0.7 (0.2) 0.7 (0.2) 0.3 1.3	0.67, 0.78	0.8 (0.1) 0.8 (0.2) 0.5 1.1	0.72, 0.80	-0.04	-0.10, 0.03	0.3
LDL-C	1.0 (0.1) 1.0 (0.2) 0.6 1.3	0.95, 1.0	1.7 (0.5) 1.6 (0.4) 1.1 3.4	1.6, 1.9	-0.73	-0.89, -0.57	**<0.001**
Non HDL-C	3.99 (0.37) 4.00 (0.58) 3.2 4.8	3.88–4.10	4.89 (0.29) 4.84 (0.14); 4.3 5.6	4.81, 4.98	-0.90	-1.04, -0.77	**<0.001**
TG	1.5 (0.1) 1.5 (0.2) 1.2 1.7	1.5, 1.5	2.0 (0.2) 2.0 (0.3) 1.6 2.4	1.9, 2.1	-0.50	-0.57, -0.42	**<0.001**
[1]Mean (SD); Median (IQR); Minimum-Maximum							
[2]CI - 95% confidence interval.							
[3]t-test for independent samples (Welch Two Sample t-test).							

Note: *Values are expressed as mean ± standard deviation (Mean ± SD) and 95% confidence interval (95% CI). The difference represents the mean value in the T1D group minus the mean value in the non-T1D group. p values below 0.05 ($p < 0.05$) were considered statistically significant. Abbreviations: TC - total cholesterol; LDL-C - low-density lipoprotein cholesterol; HDL-C - high-density lipoprotein cholesterol; non-HDL-C - non-HDL cholesterol; TG - triglycerides; T1D - type 1 diabetes mellitus.*

According to the ISPAD 2022 target for optimal glycemic control, HbA1c < 7%, the lipid profile was more favorable in children with optimal glycemic control; however, lipid changes were also present in this group, supporting the need for periodic lipid monitoring regardless of HbA1c level. In the correlation analysis, HbA1c showed moderate negative, statistically significant correlations with total cholesterol ($r = -0.346$; $p = 0.021$), non-HDL-C ($r = -0.337$; $p = 0.025$) and triglycerides ($r = -0.389$; $p = 0.009$). Correlations with LDL-C ($r = -0.195$; $p = 0.205$) and HDL-C ($r = 0.094$; $p = 0.545$) were weak and statistically non-significant.

2.5. Analysis of echocardiographic changes associated with type 1 diabetes mellitus: comparison with the control population

Echocardiographic parameters were evaluated based on analysis of the entire patient cohort, with acceptable threshold values objectified and 95% confidence intervals (CI) estimated as follows: aorta: 25.7 ± 2.9 mm (95% CI: 25-26 mm), left atrium: 27.6 ± 2.9 mm (95% CI: 27-28 mm), right atrium: 3.0 ± 0.4 cm (95% CI: 3.0-3.1 cm) and 3.1 ± 0.4 cm (95% CI: 3.1-3.2 cm), right ventricle: 14.8 ± 3.4 mm (95% CI: 14-16 mm), left ventricular (LV) end-diastolic diameter: 42.8 ± 4.1 mm (95% CI: 42-44 mm), LV end-systolic diameter: 25.8 ± 3.0 mm (95% CI: 25-28 mm), interventricular septum: 7.6 ± 1.1 mm (95% CI: 7.4-7.8 mm), LV posterior wall: 7.4 ± 1.0 mm (95% CI: 7.2-7.6 mm), LV myocardial mass: absolute values 98.3 ± 27.9 g (95% CI: 92-104 g), percentile: 39.1 ± 30.9 (95% CI: 33-46), LV myocardial mass index: 28.3 ± 6.6 mm (95% CI: 26-30 mm), percentile: 41.0 ± 33.3 (95% CI: 34-48), relative thickness of the LV posterior wall: 0.35

± 0.02 mm (95% CI: 0.34-0.36 mm), percentile: 78.5 ± 26.6 (95% CI: 73-84), LV end-diastolic volume: 83.0 ± 20.1 mL (95% CI: 79-87 mL), LV end-systolic volume: 24.7 ± 7.2 mL (95% CI: 23-26 mL), LV ejection fraction: 70.2 ± 4.0% (95% CI: 69-71%), LV fractional shortening: 40.1 ± 4.9% (95% CI: 39-41%).

Comparative analysis demonstrated statistically significant differences between groups regarding echocardiographic parameters involved in the assessment of left ventricular remodeling. Thus, left ventricular end-diastolic diameter was 41.6 ± 4.0 mm vs 44.0 ± 3.9 mm, with a difference of 2.4 mm (95% CI: 0.70-4.0; p = 0.006), and end-systolic diameter was 25.0 ± 2.9 mm vs 26.5 ± 2.8 mm, a difference of 1.6 mm (95% CI: 0.36-2.8; p = 0.011). Left ventricular end-diastolic volume was 76.5 ± 19.7 mL vs 89.3 ± 18.6 mL, difference 13 mL (95% CI: 4.8-21; p = 0.002), and end-systolic volume was 23.0 ± 7.2 mL vs 26.3 ± 6.9 mL, difference 3.3 mL (95% CI: 0.40-6.3; p = 0.027). In addition, the left ventricular myocardial mass index adjusted for body surface area was 62.6 ± 12.9 vs 68.2 ± 12.1, with a difference of 5.6 units (95% CI: 0.34-10.9; p = 0.036). For the other echocardiographic variables, differences between groups did not reach the threshold for statistical significance (p > 0.05).

Assessment of the pattern of left ventricular myocardial remodeling.

Distribution of left ventricular remodeling types was performed according to left ventricular myocardial mass index and relative thickness of the left ventricular posterior wall, defining the following forms: normal geometry, concentric remodeling, eccentric hypertrophy and concentric hypertrophy. In the group of children with type 1 diabetes mellitus, normal left ventricular geometry was identified in 36 subjects, representing 81.8%, while concentric left ventricular hypertrophy was identified in 8 children, representing 18.2% of the main group. No cases of concentric remodeling or eccentric hypertrophy were recorded. In the control group, all participants had normal left ventricular geometry.

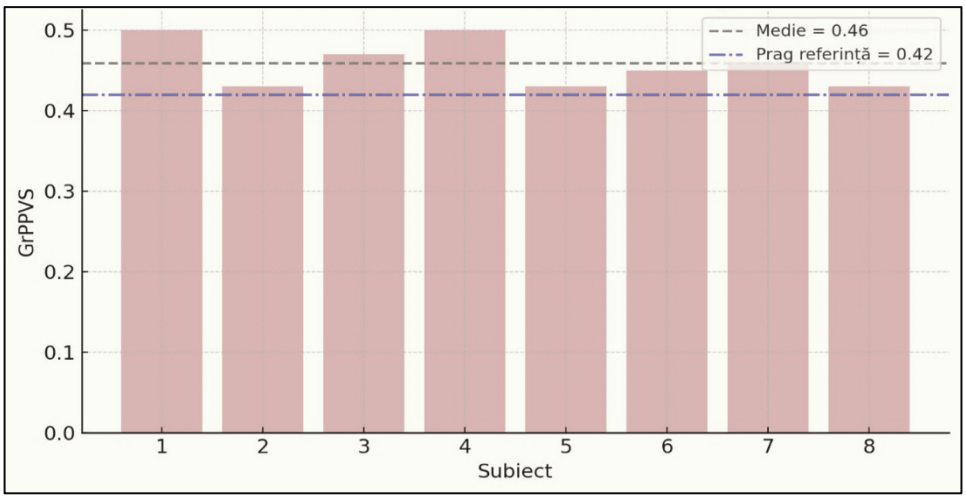

Figure 2. RWT-LVPW values for subjects with concentric hypertrophy compared with the reference threshold of 0.42 (blue dotted line)

Risk analysis demonstrated the exclusive presence of concentric hypertrophy in children with type 1 diabetes mellitus, with 100% specificity of the association. Owing to the absence of cases in the control group, the relative risk could not be estimated numerically by conventional methods, with a theoretical tendency toward infinity. The association was statistically significant according to Fisher's exact test (p = 0.002), supporting the value of concentric hypertrophy as an early marker of structural cardiac remodeling in pediatric type 1 diabetes mellitus.

2.6. Redox, lipid and inflammatory interdependences in cardiac remodeling in children with type 1 diabetes mellitus

Correlation analysis revealed significant interdependences among lipid profile, low-grade chronic inflammation, oxidative stress, antioxidant capacity and echocardiographic parameters of the left ventricle in children with type 1 diabetes mellitus.

Total cholesterol correlated positively with inflammatory markers IL-1β ($r = 0.82$), IL-6 ($r = 0.75$), CRP ($r = 0.75$) and TNF-α ($r = 0.39$), as well as with oxidative stress markers: AGE pentosidine-like ($r = 0.70$), AGE vesperlysine-like ($r = 0.75$), ischemia-modified albumin ($r = 0.76$), malondialdehyde ($r = 0.75$) and AOPP ($r = 0.36$), $p < 0.05$. At the same time, inverse correlations were observed with SOD ($r = -0.73$), catalase ($r = -0.68$), CUPRAC ($r = -0.50$) and AAT-ABTS ($r = -0.71$), $p < 0.05$. LDL-C showed positive associations with IL-1β ($r = 0.66$), CRP and IL-6 ($r = 0.61$), as well as with AGE vesperlysine-like and IMA ($r = 0.68$), while triglycerides correlated with CRP and IL-1β ($r = 0.75$), IL-6 ($r = 0.65$), IMA ($r = 0.80$) and MDA ($r = 0.67$), $p < 0.05$. HDL-C did not show significant correlations with the analyzed markers.

Inflammatory markers showed a convergent correlation profile with oxidative stress. IL-1β was positively associated with AGE pentosidine-like ($r = 0.81$), AGE vesperlysines-like ($r = 0.83$), IMA ($r = 0.86$), MDA ($r = 0.74$) and AOPP ($r = 0.40$), while CRP correlated with AGE pentosidine-like ($r = 0.72$), AGE vesperlysines-like ($r = 0.73$), IMA ($r = 0.81$), MDA ($r = 0.74$) and AOPP ($r = 0.40$), $p < 0.05$. IL-6 correlated with AGE pentosidine-like ($r = 0.72$), AGE vesperlysines-like ($r = 0.66$), IMA and MDA ($r = 0.78$), while TNF-α had more moderate associations with AGE pentosidine-like ($r = 0.39$), IMA ($r = 0.36$) and MDA ($r = 0.52$), $p < 0.05$. In relation to the antioxidant system, the most important inverse correlations were observed for IL-1β with SOD ($r = -0.78$), catalase ($r = -0.77$) and AAT-ABTS ($r = -0.83$), for CRP with SOD ($r = -0.78$), catalase ($r = -0.68$) and AAT-ABTS ($r = -0.73$), and for IL-6 with SOD ($r = -0.74$) and AAT-ABTS ($r = -0.72$), $p < 0.05$.

From an echocardiographic perspective, the atherogenic lipid profile was predominantly inversely associated with morphological and volumetric parameters of the left ventricle. Total cholesterol correlated with LVEDD and LVESD ($r = -0.23$), LVEDV ($r = -0.26$) and LVESV ($r = -0.22$); LDL-C with LVEDD ($r = -0.34$), LVESD ($r = -0.24$), LVEDV ($r = -0.33$) and LVESV ($r = -0.24$); and triglycerides with LVEDD ($r = -0.31$), LVESD ($r = -0.29$) and LVEDV ($r = -0.41$), $p < 0.05$. Among the inflammatory markers, only IL-1β showed a significant inverse correlation with LVEDV ($r = -0.31$; $p < 0.05$).

Oxidative stress markers were also associated with structural changes of the left ventricle. AGE pentosidine-like correlated inversely with LVEDD ($r = -0.28$), LVESD ($r = -0.23$), LVMI ($r = -0.22$), LVEDV ($r = -0.28$) and LVESV ($r = -0.24$), while AGE vesperlysines-like correlated with LVEDD ($r = -0.31$), LVESD ($r = -0.29$), LVEDV ($r = -0.32$) and LVESV ($r = -0.26$), $p < 0.001$. Ischemia-modified albumin was inversely associated with LVEDD ($r = -0.26$), LVESD ($r = -0.27$), LVEDV ($r = -0.29$) and LVESV ($r = -0.25$), while MDA correlated with LVEDD ($r = -0.21$), $p < 0.001$. Indicators of thiol-disulfide homeostasis showed inverse correlations with LVEDD, LVESD, LVPW, LVMM, LVEDV and LVESV, with r values between −0.22 and −0.31, $p < 0.001$.

Conversely, antioxidant capacity markers showed favorable relationships with echocardiographic parameters. SOD correlated positively with LVEDD ($r = 0.27$) and LVEDV ($r = 0.29$), while total antioxidant capacity determined by the CUPRAC method correlated with LVEDD ($r = 0.28$), LVESD ($r = 0.22$), LVEDV ($r = 0.30$) and LVESV ($r = 0.21$), $p < 0.001$. SOD,

catalase and CUPRAC also correlated inversely with RWT-LVPW ($r = -0.22$; $r = -0.27$; and $r = -0.22$, respectively), $p < 0.001$.

Overall, the results support the existence of an interconnected biological phenotype characterized by atherogenic dyslipidemia, low-grade chronic inflammation, intensified oxidative stress and reduced antioxidant capacity, associated with subclinical structural changes of the left ventricle in children with type 1 diabetes mellitus. The correlational nature of the analysis does not allow a direct causal relationship to be established, but it indicates relevant biological associations that require confirmation in longitudinal studies.

2.7. Determination of biomarkers associated with type 1 diabetes mellitus and echocardiographic parameters using regression models

To identify biomarkers with discriminatory value in type 1 diabetes mellitus in children, univariate logistic regression was applied to a sample of 88 participants after excluding extreme values below the 1st percentile and above the 99th percentile. Membership in the type 1 diabetes group was considered the dependent variable, and metabolic, inflammatory, redox and lipid biomarkers were analyzed separately as predictive variables.

The logistic regression model highlighted significant positive associations between membership in the diabetes group and markers of prooxidant status. The strongest relationships were observed for malondialdehyde, OR = 7.564; 95% CI: 2.945-19.427; $p < 0.001$, and advanced oxidation protein products, OR = 2.039; 95% CI: 1.469-2.830; $p < 0.001$. AGE vesperlysines-like also showed a significant positive association, OR = 1.048; 95% CI: 1.009-1.088; $p = 0.016$.

Among inflammatory markers, TNF-α emerged as a significant predictor of membership in the diabetes group, OR = 1.145; 95% CI: 1.078-1.217; $p < 0.001$, supporting the involvement of low-grade chronic inflammation in the biological profile of children with this pathology. In contrast, antioxidant capacity markers showed negative associations with the main group: catalase OR = 0.584; 95% CI: 0.457-0.747; $p < 0.001$, AAT-ABTS OR = 0.848; 95% CI: 0.765-0.939; $p = 0.002$ and CUPRAC OR = 0.007; 95% CI: 0-0.197; $p = 0.004$. These results reflect the reduction of enzymatic and global antioxidant mechanisms. Ceruloplasmin was positively associated with diabetes, OR = 1.044; 95% CI: 1.027-1.062; $p < 0.001$, suggesting a possible acute-phase response.

Atherogenic lipid parameters also showed positive associations: LDL-C OR = 1.5×10^{9}; 95% CI: 1.3×10^{4}-1.8×10^{14}; $p < 0.001$ and triglycerides OR = 5.9×10^{16}; 95% CI: 2.4×10^{6}-1.4×10^{27}; $p = 0.002$, although the very wide confidence intervals require cautious interpretation of these results. The increase in thiol groups in the diabetes group - free SH groups OR = 1.057; 95% CI: 1.023-1.091; $p < 0.001$, total SH groups OR = 1.057; 95% CI: 1.022-1.092; $p = 0.001$ and protein thiol SH groups OR = 1.752; 95% CI: 1.135-2.706; $p = 0.011$ - may reflect a compensatory redox phase rather than preserved global antioxidant capacity. This interpretation is supported by the concomitant decrease in catalase and total antioxidant capacity assessed by CUPRAC and AAT-ABTS.

Univariate linear regression in the total group identified significant associations between the analyzed biomarkers and echocardiographic parameters of the left ventricle. TNF-α was positively associated with LVEF, $\beta = +0.038$; $p = 0.019$, and LVFS, $\beta = +0.026$; $p = 0.048$, suggesting a possible early myocardial hyperdynamic response of low amplitude. For LVESD, inverse associations were observed with total cholesterol, $\beta = -1.431$; $p = 0.015$, triglycerides, $\beta = -2.316$; $p = 0.028$, LDL-C, $\beta = -1.414$; $p = 0.029$, IMA, $\beta = -0.006$; $p = 0.009$, AGE vesperlysines-like, $\beta = -0.003$; $p = 0.015$, IL-1β, $\beta = -0.179$; $p = 0.043$, and TNF-α, $\beta = -0.023$; $p = 0.049$. These

relationships support the predominance of a remodeling profile that is more concentric than dilatative.

In the total group, relative thickness of the left ventricular posterior wall was inversely associated with catalase, $\beta = -0.0011$; $p = 0.023$, and CUPRAC, $\beta = -0.003$; $p = 0.041$, suggesting that reduced antioxidant defense may correlate with concentric ventricular geometry. IL-6 was inversely associated with LVMI_BSA, $\beta = -0.074$; $p = 0.014$, a relationship that should be interpreted cautiously given the complex relationship between inflammation, disease duration, metabolic status and myocardial remodeling.

The analysis restricted to the group of children with diabetes highlighted the central role of antioxidant capacity in morpho-functional changes of the left ventricle. SOD activity was positively associated with LVEF, $\beta = +0.293$; $p = 0.017$, and LVFS, $\beta = +0.262$; $p = 0.011$, suggesting that maintenance of residual enzymatic antioxidant activity may contribute to preservation of global systolic function. In contrast, AAT-ABTS was inversely associated with LVESD, $\beta = -0.047$; $p = 0.047$.

CUPRAC showed important inverse associations with structural parameters of the left ventricle in the T1D group: LVMI_BSA, $\beta = -7.40$; $p = 0.007$, IVS, $\beta = -0.70$; $p = 0.015$, and LVPW, $\beta = -0.49$; $p = 0.030$. A tendency toward an inverse association with RWT-LVPW was also observed, $\beta = -0.018$; $p = 0.064$. These results indicate that reduced total antioxidant capacity is associated with increased ventricular mass, thickening of the interventricular septum and posterior wall, and a tendency toward concentric geometry. Free SH groups were inversely associated with LVMI_BSA, $\beta = -0.187$; $p = 0.040$, suggesting the involvement of thiol homeostasis in ventricular remodeling.

Overall, the regression models confirm the existence of a biological profile characteristic of children with type 1 diabetes mellitus, defined by intensified oxidative stress, subclinical inflammation, atherogenic dyslipidemia and decreased antioxidant capacity. These changes are associated with echocardiographic parameters suggestive of subclinical left ventricular remodeling, particularly of the concentric type.

Research limitations. Interpretation of the results should be performed in the context of methodological limitations inherent to the research design. The study was single-center, conducted in a tertiary pediatric referral center, which may limit extrapolation of the results to other pediatric populations. Nevertheless, this feature allowed application of a standardized clinical and paraclinical protocol, rigorous participant selection and better homogeneity of the analyzed groups.

The relatively modest sample size was adequate for the proposed objectives and allowed significant differences between groups to be identified for metabolic, inflammatory, lipid, oxidative-antioxidant and echocardiographic parameters. However, the number of participants limited the possibility of detailed stratified analyses by sex, disease duration, degree of glycemic control or left ventricular remodeling patterns.

The exclusive inclusion of children with type 1 diabetes mellitus with disease duration of at least 5 years does not allow direct extrapolation of the results to the very early stages of the disease. This approach was, however, justified by the research objective, which focused on assessing the cumulative impact of chronic hyperglycemia, persistent inflammation and oxidative-antioxidant imbalance on subclinical cardiac changes.

The strict inclusion and exclusion criteria reduced the influence of major confounding factors but may limit the applicability of the results to the entire pediatric population with type 1 diabetes mellitus. In addition, most included children had suboptimal glycemic control, which

limited comparison between subgroups with different degrees of metabolic balance, but reflects a frequently encountered clinical reality and gives the results practical relevance.

Cardiac assessment was performed by conventional echocardiography, a clinically validated method widely used in pediatric practice. The absence of advanced imaging techniques such as speckle-tracking echocardiography or cardiac magnetic resonance may limit the identification of very subtle myocardial dysfunction. However, the demonstration of structural and geometric changes by standard echocardiography supports the usefulness of this method in routine cardiac monitoring of children with type 1 diabetes mellitus.

Despite these limitations, the study makes relevant contributions regarding the interaction between low-grade chronic inflammation, oxidative stress, dyslipidemia and subclinical cardiovascular remodeling in children with type 1 diabetes mellitus. The results obtained may provide a basis for future multicenter research and for the development of integrated cardiovascular monitoring and prevention strategies in this vulnerable population.

GENERAL CONCLUSIONS

1. The study conducted on 90 children, including 44 with type 1 diabetes mellitus and 46 conditionally healthy children, demonstrated that pediatric type 1 diabetes mellitus with disease duration ≥5 years is associated with an altered cardiometabolic profile. In children with diabetes, the mean disease duration of 7.5 ± 3.0 years and mean HbA1c value of 9.8 ± 1.5% reflected chronic metabolic exposure and suboptimal glycemic control, associated with systemic inflammation, oxidative-antioxidant imbalance, an atherogenic lipid profile and subclinical echocardiographic changes.
2. Children with type 1 diabetes mellitus had an active systemic inflammatory status, expressed by significantly increased IL-1β, IL-6, TNF-α and C-reactive protein values compared with the control group. TNF-α showed significant differences between groups ($p < 0.001$), supporting the involvement of low-grade chronic inflammation in mechanisms of pediatric cardiometabolic impairment.
3. Redox-status assessment demonstrated intensification of oxidative processes and reduction of antioxidant capacity in children with type 1 diabetes mellitus. Advanced oxidation protein products were significantly increased compared with the control group (9.4 vs 6.0 μmol/L; $p < 0.001$), and lipid peroxidation was accentuated, expressed by higher malondialdehyde values (17.5 vs 13.0 μM/L; $p < 0.001$). At the same time, superoxide dismutase activity was significantly reduced (46.6 vs 80.4 u.c.; $p < 0.001$), along with decreased catalase and total antioxidant capacity assessed by the ABTS and CUPRAC methods, confirming the existence of a persistent oxidative-antioxidant imbalance.
4. The lipid profile of children with type 1 diabetes mellitus had an atherogenic character, with significantly higher values of total cholesterol, LDL-C, triglycerides and non-HDL-C compared with the control group ($p < 0.001$), while HDL-C did not show statistically significant differences ($p = 0.30$). These results confirm the early establishment of atherogenic dyslipidemia in pediatric type 1 diabetes mellitus and support the need to monitor the lipid profile as part of cardiometabolic risk assessment.
5. Echocardiographic assessment revealed subclinical morpho-functional changes of the left ventricle in children with type 1 diabetes mellitus, expressed by lower left ventricular diameters and volumes, without cavitary dilatation or overt systolic dysfunction ($p < 0.05$). Concentric left ventricular hypertrophy was identified exclusively in the diabetic group, in 18.2% of children (8/44), in the absence of this change in the control group, suggesting a particular pattern of concentric geometric remodeling. Correlation analysis and univariate linear regression models supported the existence of a redox-cardiac relationship: SOD activity was positively associated with LVEF ($\beta = +0.293$; $p = 0.017$) and LVFS ($\beta = +0.262$; $p = 0.011$), while total antioxidant capacity assessed by CUPRAC was a negative predictor for left ventricular myocardial mass index adjusted to body surface area ($\beta = -7.40$; $p = 0.007$), IVS ($\beta = -0.70$; $p = 0.015$) and LVPW ($\beta = -0.49$; $p = 0.030$). These results indicate that reduced antioxidant defense is associated with structural changes of the left ventricle and may contribute to concentric-type remodeling.

PRACTICAL RECOMMENDATIONS

1. For clinical practice

1.1. Rigorous monitoring of glycemic control and achievement of individualized HbA1c targets are recommended in children with type 1 diabetes mellitus, considering the association between metabolic imbalance and reduced antioxidant activity, including SOD ($r = -0.339$; $p < 0.01$).

1.2. Periodic assessment of the extended lipid profile - total cholesterol, LDL-C, HDL-C, triglycerides and non-HDL-C - is recommended, because children with type 1 diabetes mellitus showed an atherogenic lipid profile, with hypertriglyceridemia in 50% of cases.

1.3. Annual echocardiography is recommended in children with type 1 diabetes mellitus with disease duration ≥5 years, for early identification of left ventricular remodeling. In the conducted study, concentric left ventricular hypertrophy was present in 18.18% of patients, with a relative risk 17.8 times higher than in the control group.

1.4. The use of oxidative stress and inflammation markers - AOPP, IMA, MDA, IL-1β, IL-6 and TNF-α - is recommended as complementary indicators for stratifying subclinical cardiovascular risk in children with type 1 diabetes mellitus.

2. For monitoring organization and health policies

2.1. Inclusion of the extended lipid profile and assessment of left ventricular geometry in the annual evaluation of the child with type 1 diabetes mellitus is recommended.

2.2. Facilitating access to the determination of oxidative stress and inflammation markers in tertiary pediatric diabetology centers is recommended.

2.3. A multidisciplinary approach is recommended for children with type 1 diabetes mellitus and increased cardiovascular risk, through collaboration among the pediatric endocrinologist, pediatric cardiologist, laboratory physician and family physician.

3. For future research

3.1. Multicenter and longitudinal studies with larger samples are recommended to validate the role of inflammatory, oxidative-antioxidant, lipid and echocardiographic markers in predicting subclinical cardiovascular impairment in children with type 1 diabetes mellitus.

SELECTIVE BIBLIOGRAPHY

1. Bolu S, Aşık A, Bucak İH. An evaluation of clinical and epidemiological characteristics and autoantibody status of children with type 1 diabetes mellitus at presentation. Northwestern Medical Journal. 2024 Jul 12;4(3):148–56. doi:10.54307/2024.NWMJ.136
2. Ogrotis I, Koufakis T, Kotsa K. Changes in the Global Epidemiology of Type 1 Diabetes in an Evolving Landscape of Environmental Factors: Causes, Challenges, and Opportunities. Medicina (B Aires). 2023 Mar 28;59(4):668. doi:10.3390/medicina59040668
3. Magliano DJ, Boyko EJ. IDF Diabetes Atlas 10th edition scientific committee. IDF DIABETES ATLAS [Internet] 10th ed Brussels: International Diabetes Federation. 2021;35914061.
4. Hertiš Petek T, Petek T, Močnik M, Marčun Varda N. Systemic Inflammation, Oxidative Stress and Cardiovascular Health in Children and Adolescents: A Systematic Review. Antioxidants. 2022 Apr 30;11(5):894. doi:10.3390/antiox11050894
5. Șeremet A, Casian V, Alexa Z, Harea D. Epidemiologia diabetului zaharat în Republica Moldova: realitate și perspective. Общественное здоровье, экономика и менеджмент в медицине. 2019;(3 (81)):79–82.
6. Perrone A, others. GLAP, such as pentosidine and other AGE compounds, is a biomarker involved in metabolic diseases such as diabetic and vascular complications. Aging Dis. 2020;11(5):1257–69. doi:10.14336/AD.2020.0104
7. Kosmopoulos M, others. Impact of advanced glycation end products (AGEs) on cardiovascular events in diabetic patients: evidence from recent clinical studies. Atherosclerosis. 2019;289:1–8. doi:10.1016/j.atherosclerosis.2019.07.032
8. TIMERCAN T. Current markers of myocardial ischemia: review article. Moldovan Journal of Health Sciences Revista de Ştiinţe ale Sănătăţii din Moldova MJHS. 2018;16(2):62–72.
9. Cepoi L, Rudi L, Chiriac T, Miscu V, Rudic V. Dialdehida malonică–un potențial marcher al toxicității nanoparticulelor în mediul acvatic. One Health & Risk Management. 2020;1(1):64–71.
10. Cyr AR, Huckaby L V, Shiva SS, Zuckerbraun BS. Nitric oxide and endothelial dysfunction. Crit Care Clin. 2020;36(2):307–21.
11. Janaszak-Jasiecka A, Płoska A, Wierońska JM, Dobrucki LW, Kalinowski L. Endothelial dysfunction due to eNOS uncoupling: molecular mechanisms as potential therapeutic targets. Cell Mol Biol Lett. 2023;28(1):21.
12. Gonzalez M, Clayton S, Wauson E, Christian D, Tran QK. Promotion of nitric oxide production: mechanisms, strategies, and possibilities. Front Physiol. 2025;16:1545044.
13. Chetruș O. Optimizarea metabolismului cardiac prin terapie citoprotectorie la pacienții cu insuficiență coronariană cronică. Teză de doctor în științe medicale. Specialitatea 321.03 – Cardiologie. [Chișinău]; 2024.
14. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. Front Immunol. 2018;9:586. doi:10.3389/fimmu.2018.00586 PubMed PMID: 29686666.
15. Cano-Cano F, Gómez-Jaramillo L, Ramos-García P, Arroba AI, Aguilar-Diosdado M. IL-1β Implications in Type 1 Diabetes Mellitus Progression: Systematic Review and Meta-Analysis. J Clin Med. 2022 Feb 27;11(5):1303. doi:10.3390/jcm11051303
16. Tylutka A, Walas Ł, Zembron-Lacny A. Level of IL-6, TNF, and IL-1β and age-related diseases: A systematic review and meta-analysis. Front Immunol. 2024;15:1330386.

LIST OF SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

of Mr. EȘANU Valeriu, PhD student, Department of Pediatrics, made for his doctoral thesis in medical sciences on the theme "Inflammatory and cardiac morpho-functional status in children with type 1 diabetes mellitus"**,**
doctoral program 322.01 Pediatrics and Neonatology,
"Nicolae Testemițanu" State University of Medicine and Pharmacy of the Republic of Moldova

SCIENTIFIC PUBLICATIONS

- **Articles in international scientific journals:**

✓ **articles published in ISI-, Scopus-indexed, and other international scientific journals**

1. **Esanu V**, Palii I. Correlation between echocardiographic parameters of left ventricle and glycosylated hemoglobin in children with type 1 diabetes mellitus. One Health Risk Manag. 2022;3(1):44-52. ISSN 2587-3458. doi:10.38045/ohrm.2022.1.06. https://doi.org/10.38045/ohrm.2022.1.06
2. Esanu V, Palii I, Mocanu V, Vudu L, **Esanu V.** Left ventricular remodeling patterns in children with metabolic syndrome. One Health Risk Manag. 2020;1(2):41-49. ISSN 2587-3458. doi:10.38045/ohrm.2020.1.15. https://doi.org/10.38045/ohrm.2020.1.15

- **Articles in accredited national scientific journals:**

✓ **Articles published in category B journals**

3. **Eșanu V**, Palii I, Revenco N, et al. Afectarea cardiacă în diabetul zaharat. Buletin de Perinatologie. 2020;2(87):62–70. ISSN: 1810-5289. https://repository.usmf.md/xmlui/handle/20.500.12710/17055
4. **Eșanu V**, Eșanu V, Pîrțu L, et al. Corelația dintre hemoglobina glicată și profilul lipidic seric în diabetul zaharat de tip 1. Buletin de Perinatologie. 2022;1(93):123–128. ISSN: 1810-5289. https://repository.usmf.md/handle/20.500.12710/24418

✓ **Articles in international scientific proceedings**

5. **Eșanu V**, Vudu L, Cobeț V, et al. Markeri ai inflamației sistemice în diabetul de tip 1 la copii. In: Concepte actuale în practica pediatrică. Iași: Editura Gr. T. Popa; 2023. p. 93-100. ISBN: 978-606-544-899-5.
6. **Eșanu V**, Eșanu V, Vudu L, Golovin B, Lozovanu S, Palii I. Pattern-ul inflamator la copii cu diabet zaharat tip 1. În: Sinteza cunoașterii în Pediatrie. Iași: Editura „Gr. T. Popa"; 2025. p. 179–186. ISBN: 973-630-345-083-4.

▪ **natinal**

7. **Eșanu V**, Vudu L, Gudumac V, Cobeț V, Revenco N, Palii I. Markerii circulanți ai stresului oxidativ și sistemului antioxidant în diabetul zaharat de tip 1 la copii. În: Ziua bolilor rare; 2023 feb 28; Chișinău, Republica Moldova. Chișinău: Editura Taicom (Ridgeone Group); 2023. p. 26–30. ISBN: 978-9975-58-297-1.

https://conferinte.stiu.md/sites/default/files/evenimente/Ziua%20bolilor%20rare%202023%20(ebook).pdf

- **Abstracts/theses in scientific conference proceedings:**

8. **Esanu V**, Palii I. Correlation between echocardiographic parameters of left ventricular and glycosylated hemoglobin in children with type 1 diabetes mellitus. One Health & Risk Management. 2021;2(suppl 4):39. ISSN: 2587-3466. https://repository.usmf.md/handle/20.500.12710/18254
9. Rodoman I, **Eșanu V**, Eșanu V, et al. Investigating the relation between hemoglobin A1c with left ventricular remodeling patterns in children with type 1 diabetes mellitus (P-145/Moderated Poster). *Cardiol Young.* 2022;32(Suppl 2):S121. ISSN: 1047-9511. https://www.cambridge.org/core/services/aop-cambridge-core/content/view/E1038CE40CA35DD2E4FDBFF5BD7FE62D/S1047951122001950a.pdf/55th-annual-meeting-of-the-association-for-european-paediatric-and-congenital-cardiology-aepc-geneva-switzerland-or-25-28-may-2
10. Rodoman I, **Esanu V**, Esanu V, Palii I. Association between glycated hemoglobin and left ventricular remodeling in children with type 1 diabetes. *Cardiol Young.* 2024;34(Suppl S2):S1944. ISSN: 1047-9511. https://www.cambridge.org/core/services/aop-cambridge-core/content/view/CA4F69124DA52AF282ACE7E25AD8570E/S1047951124034103a.pdf/57th-annual-meeting-of-the-association-for-european-paediatric-and-congenital-cardiology-aepc-wednesday-may-8-2024-saturday-may

✓ **Abstracts published in volumes of international conferences**

11. **Ешану ВФ**, Палий ИИ, Ешану ВГ. Формы геометрии левого желудочка у детей с диабетом 1-го типа. В: Сборнике материалов XXIII Конгресса педиатров России с международным участием «Актуальные проблемы педиатрии»; 2021 Март 5-7; Москва, Россия. 2021. с. 57. DOI: 10.15690/rpj.v2i1.2248 https://www.pediatr-russia.ru/information/kongressy-i-sezdy-pediatrov/2021/Tezisi_VSP_2021.pdf
12. **Ешану ВФ**, Палий ИИ, Ешану ВГ. The relationship between left ventricular mass and other cardiovascular risk factors in children with type 1 diabetes. В: Abstract Book. VIII Global Educational Forum «Russian Cardiovascular Days»; 2021 Апр. 22–24; **Санкт-Петербург, Россия.** 2021. с. 43. https://old.scardio.ru/content/activities/2021/RCD/event_13768_thesises-2.pdf
13. **Esanu V**, Vudu L, Palii I. The effect of glycated hemoglobin on left ventricular structure and function in children with type 1 diabetes mellitus. In: *Abstracts of The 8th National Congress of Diabetes, Nutrition and Pediatric Endocrinology – with international participation*; 2021 Oct 4–9; Timișoara, Romania. Organized by: Societatea Română de Diabet, Nutriție și Endocrinologie Pediatrică. 2021. p. 49. ISSN: 2810-3076 https://endoped.ro/wp-content/uploads/2023/10/ENDOPED-2021-Abstract-Book.pdf
14. **Esanu V**, Belii O, Tiron L, et al. Traiectoria relației remodelării ventriculare stângi cu valoarea HbA1c la copii cu diabet de tip 1. In: Volum de rezumate. Conferința Națională Zilele Pediatriei Ieșene „N.N. Trifan”; 2022 Jun 15–18; Iași, România. 2022. p. 90–91. ISBN: 978-606-685-871-7.

https://zilelepediatriei.ro/wp-content/uploads/2022/06/Pediatrie2022_VolumRezumate.pdf

15. **Ешану ВФ**, Ешану ВГ, Палий ИИ. The complex reciprocal relation of subclinical myocardial changes, oxidative stress, inflammation, and dyslipidemia in type 1 diabetes mellitus. В: *Сборник тезисов II Международного конгресса «Ожирение и метаболические нарушения: осознанная перезагрузка»*; 2024 Окт. 10–12; Москва, Россия. 2024. с. 16. doi:10.14341/ozhirenie-conf-2024-oct10-12-2024-8 https://www.endocrincentr.ru/sites/default/files/all/EVENTS_2024/10-12.10_2_mezhdunarodnyj_kongress_ozhirenie_perezagruzka/10-12.10_2_mezhdunarodnyy_kongress_ozhirenie_perezagruzka_tezisy.pdf
16. **Ешану ВФ**, Ешану ВГ, Палий ИИ. Type 1 diabetes in a child with COVID-19 – case report. В: *Сборник тезисов II Международного конгресса «Ожирение и метаболические нарушения: осознанная перезагрузка»*; 2024 Oct 10–12; Москва, Россия. 2024. с. 16. doi:10.14341/ozhirenie-conf-2024-oct10-12-2024-8. https://www.endocrincentr.ru/sites/default/files/all/EVENTS_2024/10-12.10_2_mezhdunarodnyj_kongress_ozhirenie_perezagruzka/10-12.10_2_mezhdunarodnyy_kongress_ozhirenie_perezagruzka_tezisy.pdf

- **national with international participation:**

17. **Eșanu V**, Palii I, Golovin B, Chiriac A. Impactul metodelor de reabilitare la copiii cu diabet zaharat de tipul 1 – reactualizare. În: Congresul consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină și Farmacie „Nicolae Testemițanu”; 2020 Oct 21–23; Chișinău, Republica Moldova. Chișinău: USMF; 2020. p. 544. ISBN: 978-9975-82-198-8. https://ibn.idsi.md/vizualizare_articol/126577
18. **Eșanu V**, Palii I. Impact of the glycated hemoglobin on the left ventricular mass index in children with type 1 diabetes mellitus. În: Cercetarea în biomedicină și sănătate: calitate, excelență și performanță; 2021 oct 20–22; Chișinău, Republica Moldova. Chișinău: 2021. p. 366. ISBN: 978-9975-82-223-7. https://ibn.idsi.md/vizualizare_articol/144800
19. **Eșanu V**, Palii I. Impact of the glycated hemoglobin on the left ventricular mass index in children with type 1 diabetes mellitus. În: Cercetarea în biomedicină și sănătate: calitate, excelență și performanță; 2021 Oct 20–22; Chișinău, Republica Moldova. Chișinău; 2021. p. 366. ISBN: 978-9975-82-223-7. https://ibn.idsi.md/vizualizare_articol/144800

- **Invention patents, patents, registration certificates, materials presented at invention salons**

20. **Eșanu Valeriu**, Palii Ina, Vudu Lorina, Revenco Ninel, Golovin Boris, Cobeț Valeriu. *Evaluarea markerilor de peroxidare carbohidrată age pentosidines-like și age verpelysines-like ca indicatori ai decompensării diabetului zaharat tip 1 la copii.* Certificat de inovator Nr. 6341 din 18.03.2025 (USMF „Nicolae Testemițanu”) și Certificat de inovator Nr. 571 din 17.03.2025 (IMSP Institutul Mamei și Copilului).
21. **Eșanu Valeriu**, Palii Ina, Vudu Lorina, Revenco Ninel, Golovin Boris, Cobeț Valeriu. *Evaluarea markerului de peroxidare a proteinelor - produse proteice avansat oxidate, ca indicator al decompensării diabetului zaharat tip 1 la copii.* Certificat de inovator Nr. 6342

din 18.03.2025 (USMF „Nicolae Testemițanu”) și Certificat de inovator Nr. 571 din 17.03.2025 (IMSP Institutul Mamei și Copilului).

22. **Eșanu Valeriu**, Palii Ina, Vudu Lorina, Revenco Ninel, Golovin Boris, Cobeț Valeriu. *Evaluarea markerilor de peroxidare a lipidelor - dialdehida malonică și albumina ischemic-modificată ca indicatori ai decompensării diabetului zaharat tip 1 la copii.* Certificat de inovator Nr. 6343 din 18.03.2025 (USMF „Nicolae Testemițanu”) și Certificat de inovator Nr. 573 din 17.03.2025 (IMSP Institutul Mamei și Copilului).
23. **Eșanu Valeriu**, Palii Ina, Vudu Lorina, Revenco Ninel, Golovin Boris, Cobeț Valeriu. *Evaluarea markerilor antioxidanți: superoxid dismutaza, catalaza, activitatatea antioxidantă totală prin metoda cuprac și aat-abts și ceruloplasmina ca indicatori ai decompensării diabetului zaharat tip 1 la copii.* Certificat de inovator Nr. 6344 din 18.03.2025 (USMF „Nicolae Testemițanu”) și Certificat de inovator Nr. 574 din 17.03.2025 (IMSP Institutul Mamei și Copilului).
24. **Eșanu Valeriu**, Palii Ina, Vudu Lorina, Revenco Ninel, Golovin Boris, Cobeț Valeriu. *Evaluarea markerilor inflamatori: pcr, tnf, il-6 și il-1β ca indicatori ai stratificării riscului cardiovascular la copiii cu diabet zaharat tip 1.* Certificat de inovator Nr. 6345 din 18.03.2025 (USMF „Nicolae Testemițanu”) și Certificat de inovator Nr. 575 din 17.03.2025 (IMSP Institutul Mamei și Copilului).
25. **Eșanu Valeriu**, Palii Ina, Vudu Lorina, Revenco Ninel, Golovin Boris, Cobeț Valeriu. *Evaluarea markerilor profilului lipidic: colesterolul total, trigliceridele și ldl - colesterol ca indicatori ai stratificării riscului cardiovascular la copiii cu diabet zaharat tip 1.* Certificat de inovator Nr. 6346 din 18.03.2025 (USMF „Nicolae Testemițanu”) și Certificat de inovator Nr. 576 din 17.03.2025 (IMSP Institutul Mamei și Copilului).
26. **Eșanu Valeriu**, Palii Ina, Vudu Lorina, Revenco Ninel, Golovin Boris, Cobeț Valeriu. *Evaluarea remodelării ventriculare stângi la copiii cu diabet zaharat tip 1 cu intervalul de vîrsta 10-18 ani.* Certificat de inovator Nr. 6347 din 18.03.2025 (USMF „Nicolae Testemițanu”) și Certificat de inovator Nr. 577 din 17.03.2025 (IMSP Institutul Mamei și Copilului).

- **Participation with oral communications at scientific forums:**

✓ **international**

27. **Eșanu V.** Rehabilitation methods – determinants of daily insulin dose in type 1 diabetes. Al 46-lea Congres Național al Societății Române de Diabet, Nutriție și Boli Metabolice. Timișoara, România, 2–8 septembrie 2020.
28. **Eșanu V.** The effect of glycated hemoglobin on left ventricular structure and function in children with type 1 diabetes mellitus. Al 8-lea Congres Național de Diabet, Nutriție și Endocrinologie Pediatrică. Timișoara, România, 4–9 octombrie 2021.
29. **Eșanu V.** Traiectoria relației remodelării ventriculare stângi cu valoarea HbA1c la copii cu diabet de tip 1. Conferința Națională Zilele Pediatriei Ieșene „N.N. Trifan”. Iași, România, 15–18 iunie 2022.
30. **Eșanu V.** Corelații între hemoglobina glicată și indicatorii stresului oxidativ și activitatea antioxidantă la copiii cu diabet zaharat de tip 1. Conferința Națională Zilele Pediatriei Ieșene „N.N. Trifan”, ediția a XXXV-a. Iași, România, 22–24 iunie 2023.
31. **Eșanu V.** Correlation between hemoglobin A1c and serum lipid profile in children with type 1 diabetes: hemoglobin A1c prognosticates dyslipidemia. Al 10-lea Congres Național

de Diabet, Nutriție și Endocrinologie Pediatrică – cu participare internațională. Timișoara, România, 7–10 iunie 2023.

32. **Eșanu V.** The complex interplay of subclinical myocardial changes, oxidative stress, inflammation, and dyslipidemia in type 1 diabetes mellitus. Al 11-lea Congres Național de Diabet, Nutriție și Endocrinologie Pediatrică – cu participare internațională. Timișoara, România, 17–20 aprilie 2024.
33. **Eșanu V.** Pattern-ul inflamator la copii cu diabet zaharat tip 1. Conferința Națională Zilele Pediatriei Ieșene „N.N. Trifan", ediția a XXXVII-a. Iași, România, 18–21 iunie 2025.

✓ **national**

34. **Eșanu V.** Impactul hemoglobinei glicate asupra indicelui de masă ventriculară stângă la copiii cu diabet zaharat de tip 1. Conferința științifică anuală „Cercetarea în biomedicină și sănătate: calitate, excelență și performanță". Chișinău, Republica Moldova, 20–22 octombrie 2021.
35. **Eșanu V.** Interrelația modificărilor stresului oxidativ, inflamației, dislipidemiei și miocardice subclinice în diabetul zaharat de tip 1 la copii. Al 3-lea Congres Național al Societății Medicilor Endocrinologi din Republica Moldova, cu participare internațională. Chișinău, Republica Moldova, 10–12 octombrie 2024.
36. **Eșanu V.** Lipid profile in children with insulin-dependent diabetes mellitus. Congresul Internațional al Societății de Pediatrie din Republica Moldova, ediția a VIII-a „Pediatria – specialitate multidisciplinară". Chișinău, Republica Moldova, 6–8 iunie 2024.

- **Participation with posters at scientific forums:**

✓ **international**

37. **Eșanu V.** Modele de geometrie ventriculară stângă la copiii cu diabet zaharat tip 1. Conferința Națională de Pediatrie „Ghiduri și protocoale în Pediatrie". București, România: 7–10 aprilie 2021.
38. **Eșanu V.** Investigating the relation between HbA1c with left ventricular remodeling patterns in children with type 1 diabetes mellitus. The 47th National Congress of the Romanian Society of Diabetes, Nutrition and Metabolic Diseases. România: 19–25 mai 2021.
39. **Eșanu V.** Investigating the relation between hemoglobin A1c with left ventricular remodeling patterns in children with type 1 diabetes mellitus (P-145/Moderated Poster). 55th Annual Meeting of the Association for European Paediatric and Congenital Cardiology (AEPC). Geneva, Switzerland: 25–28 mai 2022.
40. **Eșanu V.** Left ventricular remodeling in children with type 1 diabetes (P-12). The 62nd National Congress of Cardiology. Sinaia, România: 20–23 septembrie 2023.
41. **Eșanu V.** Markeri ai inflamației sistemice în diabetul de tip 1 la copii. Conferința Națională Zilele Pediatriei Ieșene „N.N. Trifan", ediția a XXXV-a. Iași, România: 22–24 iunie 2023.
42. **Eșanu V.** Association between glycated hemoglobin and left ventricular remodeling in children with type 1 diabetes. 57th Annual Meeting of the Association for European Paediatric and Congenital Cardiology (AEPC). Porto, Portugalia: 8–11 mai 2024.