CD95 (Fas Receptor) As A Biomarker Of B-Cell Apoptosis In Children With Type 1 Diabetes Mellitus Following COVID-19 Infection

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Abstract

Background: The COVID-19 pandemic has been associated with increased incidence and severity of type 1 diabetes mellitus (T1DM) in children, but pathogenic mechanisms remain unclear.

Objective: To investigate CD95 (Fas receptor) as a biomarker of β-cell apoptosis in children with T1DM following COVID-19 and assess its prognostic value.

Methods: Prospective cohort study of 100 children (6-17 years) with newly diagnosed T1DM: 50 with confirmed prior SARS-CoV-2 infection and 50 controls. Serum CD95, autoantibodies (anti-GAD, anti-IAA, anti-ICA), inflammatory markers (IL-6), and endothelial dysfunction markers (ICAM-1, VCAM-1) were measured at diagnosis, 6, and 24 months.

Results: Post-COVID-19 patients showed markedly elevated CD95 (249.5±72.3 vs. 4.87 pg/mL in controls, $p<0.001$), representing >50-fold increase. CD95 correlated significantly with autoantibody titers ($r=0.58$, $p<0.001$), IL-6 ($r=0.67$, $p<0.001$), and disease severity. The post-COVID-19 group had higher diabetic ketoacidosis frequency (38% vs. 16%, $p<0.05$), greater metabolic decompensation (HbA1c 10.6±2.5% vs. 9.12±0.46%, $p<0.05$), and no remission phase. A combined risk score incorporating CD95 >100 pg/mL, IL-6 >5 pg/mL, VCAM-1 >150 ng/mL, and ≥2 autoantibodies predicted severe disease (sensitivity 92.1%, specificity 90.0%, AUC 0.94).

Conclusions: CD95 is a valuable biomarker of accelerated β-cell apoptosis in post-COVID-19 T1DM, enabling risk stratification and personalized management.

Keywords: Type 1 diabetes mellitus, COVID-19, CD95, Fas receptor, apoptosis, biomarker.

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1. Introduction

Type 1 diabetes mellitus (T1DM) results from autoimmune destruction of pancreatic β-cells, with viral infections recognized as environmental triggers. The COVID-19 pandemic has revealed concerning increases in pediatric T1DM incidence, with more severe

presentations including frequent diabetic ketoacidosis (DKA) and accelerated complications [1-3]. Studies from the US, UK, and Germany report 30-50% increases in new T1DM cases during pandemic periods [4-6].

SARS-CoV-2 can directly infect β-cells via ACE2 receptors, causing cellular damage and reduced insulin secretion [7,8]. Simultaneously, massive cytokine production (IL-6, TNF-α) exacerbates metabolic dysfunction and may trigger autoimmune responses through molecular mimicry and epitope spreading [9,10].

CD95 (Fas/APO-1), a death receptor of the TNF superfamily, mediates apoptosis when bound by FasL [11]. β-cells express CD95, and their apoptosis can be induced by activated T cells [12,13]. Soluble CD95 (sFas) in serum reflects ongoing apoptotic activity [14]. While modest sFas elevation has been reported in classical T1DM, comprehensive data in post-COVID-19 pediatric diabetes are lacking [15,16].

This study investigated CD95 as a biomarker of β-cell apoptosis in children with post-COVID-19 T1DM, evaluating its relationship to disease severity and prognostic utility.

2. Methods

Study Design

Prospective cohort study at the Republican Specialized Scientific and Practical Medical Center of Endocrinology, Tashkent, Uzbekistan (February 2021-December 2023). Ethics approval obtained; informed consent provided by parents/guardians.

Participants

From 120 children hospitalized with newly diagnosed T1DM in 2021, 100 meeting criteria were enrolled:

- Study group (n=50): T1DM with confirmed prior SARS-CoV-2 infection (PCR/IgG positive)
- Control group (n=50): T1DM without COVID-19 history

Inclusion criteria: Age 6-17 years; newly diagnosed T1DM (WHO/ISPAD criteria); complete documentation.

Exclusion criteria: Type 2/monogenic diabetes; severe comorbidities; incomplete data.

Measurements

Clinical assessment: Anthropometry, vital signs, DKA severity (ISPAD guidelines), symptoms.

Laboratory parameters:

- Glucose metabolism: fasting/postprandial glucose, HbA1c, C-peptide
- CD95 measurement: ELISA (Human FAS/CD95 Kit, Elabscience, sensitivity 15.6 pg/mL, intra-assay CV <10%, reference <100 pg/mL)
- Autoantibodies: anti-GAD, anti-IAA, anti-ICA (ELISA)
- Inflammatory markers: IL-6, CRP (reference IL-6: 1.5-7.0 pg/mL)
- Endothelial markers: ICAM-1 (reference 0.84-8.45 ng/mL), VCAM-1 (reference 5.08-47.72 ng/mL)
- Additional: lipids, liver/renal function, TSH, vitamin D, coagulation profile

Timing: Baseline (diagnosis), 6 months, 24 months.

Statistical Analysis

SPSS 26.0. Continuous variables: mean±SD or median (IQR). Comparisons: t-test, Mann-Whitney U, χ^2. Correlations: Pearson/Spearman. ROC analysis for prognostic value. Significance: $p<0.05$.

3. Results

Baseline Characteristics

Groups were matched for age (10.55±4.41 vs. 10.70±2.50 years, p=0.832), sex (52% vs. 46% male, p=0.549), and BMI (15.69±0.59 vs. 15.8±1.0 kg/m², p=0.503). In the post-COVID-19 group, mean interval from COVID-19 to T1DM was 1.92±4.03 months (range 0-15); 70% developed T1DM within 1-3 months post-infection.

Clinical Severity at Diagnosis

Post-COVID-19 patients had significantly more severe presentation (Table 1).

Table 1. Clinical Presentation at T1DM Diagnosis

Parameter	Post-COVID-19 (n=50)	Control (n=50)	p-value
DKA (any), n (%)	19 (38.0)	8 (16.0)	0.011*
Severe DKA (ICU), n (%)	13 (26.0)	5 (10.0)	0.035*
Postprandial glucose, mmol/L	12.68±2.16	10.7±1.76	<0.001*
HbA1c, %	10.6±2.5	9.12±0.46	<0.001*
Insulin dose, units/kg/day	1.15±0.12	1.02±0.18	0.089

*p<0.05. DKA: diabetic ketoacidosis; ICU: intensive care unit

CD95 and Immunological Markers

Post-COVID-19 patients showed dramatic CD95 elevation and enhanced autoimmune activation (Table 2).

Table 2. CD95 and Immunological Markers at Diagnosis

Marker	Post-COVID-19	Control	Fold Change	p-value
CD95, pg/mL	249.5±72.3	4.87±1.2	51.2×	<0.001*
Anti-GAD, U/mL	222.9±497.6	63.4±85.2	3.5×	<0.001*
Anti-IAA, U/mL	7.83±9.27	4.04±2.93	1.9×	0.014*
≥2 autoantibodies, n (%)	44 (89.3)	34 (68.0)	-	0.007*
IL-6, pg/mL	8.33±3.10	1.24±0.90	6.7×	<0.001*
ICAM-1, ng/mL	42.53±12.4	2.7±1.3	15.8×	<0.001*
VCAM-1, ng/mL	376.85±85.2	24.3±2.7	15.5×	<0.001*
Vitamin D <20 ng/mL, n (%)	36 (72.0)	34 (68.0)	-	0.664

*p<0.05

Mean CD95 was 249.5±72.3 pg/mL (range 95.2-412.8) in post-COVID-19 group versus 4.87±1.2 pg/mL in controls—a 51.2-fold increase (p<0.001). All post-COVID-19 patients exceeded the reference limit of 100 pg/mL.

Correlations

CD95 correlated significantly with multiple severity markers (Table 3).

Table 3. Correlations Between CD95 and Disease Parameters

Parameter	Correlation (r)	95% CI	p-value
Anti-GAD titer	0.58	0.41-0.72	<0.001*
IL-6	0.67	0.52-0.78	<0.001*
ICAM-1	0.59	0.42-0.72	<0.001*
VCAM-1	0.54	0.36-0.68	<0.001*
HbA1c at diagnosis	0.63	0.47-0.75	<0.001*
C-peptide	-0.44	-0.61 to -0.24	<0.001*
DKA severity score	0.56	0.38-0.70	<0.001*

*p<0.05. r: Spearman correlation coefficient

The strongest correlations were with IL-6 (r=0.67) and HbA1c (r=0.63), indicating CD95 reflects both inflammatory activity and metabolic severity.

Temporal Dynamics

CD95 showed distinct temporal pattern: dramatic initial elevation (249.5 pg/mL), partial decline at 6 months (157.6±55.8 pg/mL), and near-normalization by 24 months (3.65±1.9 pg/mL, p<0.001). In contrast, IL-6 showed biphasic pattern with rebound elevation at 24 months (25.88±8.70 pg/mL, p=0.01), while control group markers remained stable (all p>0.05).

HbA1c in post-COVID-19 group worsened progressively (10.6%→10.1%→12.0%, p=0.021), indicating deteriorating control despite apoptosis resolution.

Prognostic Value

ROC analysis demonstrated excellent discriminative ability for CD95 predicting severe disease course (Table 4).

Table 4. Prognostic Performance of Biomarkers

Biomarker	AUC (95% CI)	Optimal Cut-off	Sensitivity (%)	Specificity (%)
CD95 alone	0.89 (0.82-0.95)	>180 pg/mL	84.2	86.7
IL-6 alone	0.82 (0.74-0.90)	>6.5 pg/mL	78.9	80.0
Combined Score*	**0.94 (0.89-0.98)**	**≥3 criteria**	**92.1**	**90.0**

* Combined: CD95 >100 pg/mL, IL-6 >5 pg/mL, VCAM-1 >150 ng/mL, ≥2 autoantibodies (1 point each)

COVID-19 T1D RISK SCORE

Based on prognostic analysis, we developed a practical risk stratification tool:

Scoring Criteria (1 point each):

- CD95 >100 pg/mL
- IL-6 >5 pg/mL
- VCAM-1 >150 ng/mL
- ≥2 autoantibody types positive

Risk Categories:

- Score 0-1 (Low, 22%): 8% severe disease rate
- Score 2-3 (Moderate, 44%): 42% severe disease rate
- Score 4 (High, 34%): 87% severe disease rate

High-risk patients (score 4) had dramatically worse outcomes: 87% severe course vs. 8% in low-risk (OR 78.5, p<0.001), HbA1c 13.8±1.9% vs. 8.9±1.2% at 24 months (p<0.001), and 43% early microvascular complications vs. 0% (p<0.001).

4. Discussion

This study provides the first comprehensive evaluation of CD95 as a biomarker in pediatric post-COVID-19 T1DM. The >50-fold CD95 elevation far exceeds levels in classical T1DM, indicating a distinct, aggressive phenotype with accelerated apoptotic β-cell destruction.

Mechanisms of CD95 Elevation

Several pathways likely contribute: (1) Direct viral effects—SARS-CoV-2 infects β-cells via ACE2, activating stress pathways that upregulate CD95 [7,8]; (2) Cytokine-mediated induction—the 6.7-fold IL-6 elevation drives Fas expression on β-cells [17,18]; (3) Autoimmune activation—89.3% had multiple autoantibodies, with autoreactive T cells expressing FasL inducing β-cell apoptosis; (4) Endothelial dysfunction—15-fold ICAM-1/VCAM-1 elevation impairs pancreatic microcirculation, creating hypoxic conditions enhancing apoptosis.

The strong CD95-IL-6 correlation (r=0.67) and CD95-autoantibody correlation (r=0.58) support interconnected inflammatory, autoimmune, and apoptotic mechanisms.

Temporal Dynamics and Clinical Implications

The biphasic pattern—acute apoptotic crisis (0-6 months) followed by chronic inflammation (6-24 months)—explains why post-COVID-19 T1DM lacks remission: by the time acute apoptosis resolves, β-cell mass is irreversibly depleted. The secondary IL-6 surge at 24 months suggests transition to chronic inflammatory state perpetuating poor glycemic control (HbA1c 12.0%).

Clinical Utility

CD95 >180 pg/mL predicts 84% probability of severe course, warranting intensive management. The combined risk score (AUC 0.94) enables practical risk stratification without specialized immunology expertise. High-risk patients (score 4) require monthly monitoring, aggressive insulin optimization, and early complication screening.

Comparison with Literature

Our findings extend previous observations. The ASK/Fr1da studies showed accelerated T1DM progression after COVID-19 (IRR 1.9) but didn't measure CD95 [19,20]. Adult T1DM studies report modest sFas elevation (~50-80 pg/mL) [15,16], far lower than our 249.5 pg/mL, confirming post-COVID-19 pediatric T1DM as a distinct, severe phenotype. Müller et al. demonstrated direct β-cell infection and apoptosis experimentally [8]; we provide first clinical evidence linking this to measurable biomarker elevation and outcomes.

Therapeutic Implications

Findings suggest several strategies: (1) Early intervention—high-risk patients may benefit from immunomodulation (e.g., teplizumab) if detected early; (2) Vitamin D supplementation—given 72% deficiency and immune dysfunction links, all patients should receive 2000-4000 IU daily; (3) Enhanced monitoring—extreme endothelial dysfunction mandates complication screening from diagnosis rather than waiting traditional 5 years; (4) Personalized insulin regimens—anticipate sustained high requirements (1.2 U/kg at 24 months vs. 0.82 U/kg controls).

Limitations

Single-center design limits generalizability. Observational nature precludes causality determination. We didn't assess SARS-CoV-2 variants, HLA genotypes, or perform direct mechanistic studies (pancreatic imaging, T-cell subsets). Sample size adequate for primary objectives but limits subgroup analyses. Future multicenter studies with mechanistic investigations and interventional trials are needed.

5. Conclusions

CD95 serves as a valuable biomarker of accelerated β-cell apoptosis in post-COVID-19 pediatric T1DM. The >50-fold elevation reflects massive Fas-mediated β-cell destruction, correlating strongly with autoantibody titers, inflammatory cytokines, endothelial dysfunction, and clinical severity. CD95 demonstrates excellent prognostic value (AUC 0.89), with the combined COVID-19 T1D RISK SCORE enabling accurate risk stratification (92% sensitivity, 90% specificity, AUC 0.94).

Clinically, CD95 >180 pg/mL or risk score ≥3 warrants aggressive management including intensified insulin therapy, frequent monitoring, early complication screening, vitamin D supplementation, and potentially immunomodulation. The temporal dynamics—acute apoptotic crisis resolving by 24 months—explain absence of remission phase due to irreversible β-cell depletion.

These findings establish CD95 as a clinically useful biomarker for a growing population of children with severe post-viral T1DM, providing mechanistic insights and practical guidance for personalized care in the post-pandemic era.

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