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Original Article

Adenosine deaminase isoenzyme activity in blood plasma of young patients with type 1 diabetes: a correlative analysis

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Abstract

The global incidence of T1D is increasing, particularly among children, adolescents, and young adults. Adenosine deaminase (ADA) isoenzymes, specifically ADA1 and ADA2, are key regulators of the immune system and are potential biomarkers for autoimmune conditions such as T1D. This study investigated ADA isoenzyme activity in the plasma of young Armenian T1D patients to determine whether these enzymes could serve as biomarkers of immune status and disease progression. We analyzed ADA isoenzyme activity in young Armenian T1D patients and compared it to that of healthy controls. We also established normal ADA2 reference values for healthy children, noting age- and sex-dependent variations. Healthy children showed age- and sex-dependent variations in ADA2 activity, with levels correlating positively with age in adults but showing no significant change up to 20 years of age. T1D patients had significantly higher total ADA, ADA1, and especially ADA2 levels than the controls. ROC analysis confirmed ADA2's strong diagnostic potential for T1D (AUC up to 0.822). Notably, ADA isoenzyme activities did not correlate with long-term glycemic control (HbA1c). In patients with T1D, ADA isoenzyme levels, particularly ADA2, are significantly elevated compared with healthy controls, suggesting heightened immune and inflammatory responses. The statistically significant AUC values across all comparisons underscore ADA2's potential as a valuable diagnostic or monitoring biomarker, independent of blood sugar levels, particularly in the young population.

Keywords: adenosine deaminase isoenzymes, blood plasma, glycated hemoglobin, type 1 diabetes mellitus

Introduction

Diabetes mellitus (DM), which includes both type 1 (T1D) and type 2 (T2D), is a profound and growing global health concern with staggering prevalence. In 2021, an estimated 537 million adults aged 20–79 were living with diabetes. The number of people with T1D exceeded 9.5 million in 2021, including 1.2 million children and adolescents under 20. The total number of people with diabetes is projected to reach 853 million by 2050 [1, 2].

DM is a metabolic disorder characterized by dysregulation of glucose metabolism, resulting from defects in insulin secretion, decreased insulin sensitivity, or both [3, 4]. T1D is a chronic autoimmune condition in which the body's immune system mistakenly attacks and destroys the insulin-producing pancreatic β-cells in the islets of Langerhans, leading to an absolute insulin deficiency. This makes it one of the most prevalent and serious non-communicable diseases affecting children and adolescents [5–10]. Recent research has increasingly highlighted the critical role of the adenosine signaling system in regulating glucose homeostasis and in the pathophysiology of DM and its complications [11, 12]. Adenosine levels are tightly regulated

in the body by two main enzymes: adenosine kinase, which converts it to AMP, and adenosine deaminase, which deaminates it to inosine [13].

Adenosine deaminase (ADA, EC 3.5.4.4) is a key enzyme in the purine salvage pathway. It catalyzes the deamination of (deoxy)adenosine to (deoxy)inosine. By modulating adenosine concentrations, ADA plays a crucial role in immune function and development [14]. A classic example of ADA's immunological importance is that its deficiency leads to profound lymphopenia and severe combined immunodeficiency (SCID), due to impaired T- and B-cell development and function. ADA is also involved in the proliferation and differentiation of lymphocytes and cells of the monocyte/macrophage lineage [15].

In mammals, there are two distinct ADA isoenzymes: ADA1 and ADA2. These isoenzymes are genetically and functionally different. ADA1 isoenzyme is encoded by a gene on chromosome 20q13.12 and is the more extensively studied of the two. It has a high substrate affinity (Km=0.02 mM). ADA1 exists as either a 35–40 kDa monomer or in a high-molecular-weight complex (280–300 kDa) with ADA-binding protein, which is identical to CD26/dipeptidyl peptidase IV. ADA2 is a less-characterized isoenzyme, encoded by the CECR1 gene (Cat Eye Syndrome Chromosome Region 1) on chromosome 22q11.21. It is a dimer with a molecular mass of approximately 110–120 kDa and has a lower substrate affinity (Km=2 mM). Both isoenzymes are widely expressed and have been proposed as useful biomarkers for cell-mediated immunity in various immunological disorders [13, 15]. ADA2 is secreted predominantly by monocytes and macrophages, which is why it has been proposed as a biomarker for macrophage-driven inflammation [16].

Most research on ADA in diabetes has focused on T2D [17, 18]. Despite significant research efforts, our understanding of the immunopathogenesis of T1D, particularly in its early stages, remains limited. The exact role of adenosine metabolism and its influence on T-cell function at the onset of T1D remains unclear. Furthermore, data on ADA activity in pediatric T1D patients are sparse and often contradictory.

Genetic factors also contribute to the initiation of β-cell autoimmunity and disease progression in T1D. Variations in the ADA1 gene alleles have been studied in relation to T1D susceptibility, showing polymorphic diversity across different populations [19]. In other pediatric autoimmune and inflammatory conditions, such as systemic juvenile idiopathic arthritis, significant increases in ADA2 activity have been observed, especially in patients with macrophage activation syndrome [20].

The primary goal of this study was to investigate the activity of ADA isoenzymes in the blood plasma of a young Armenian population, including both healthy children and those with T1D. We aimed to identify age- and sex-dependent correlations with ADA isoenzyme activity and explore its relationship with long-term glycemic control. Our ultimate goal was to determine if these isoenzymes could serve as biomarkers for immune status and disease progression in T1D.

Material and methods

Reagents

Adenosine and erythro-9-(2-hydroxy-3-nonyl)-adenine (EHNA) were purchased from Sigma-Aldrich (St. Louis, MO, USA). All reagents were of high purity.

Participants

The young subjects with T1D and healthy subjects were patients at the "Muratsan" Center of the Yerevan State Medical University (YSMU) after Mkhitar Heratsi, Department of Endocrinology. All subjects or their legal representatives gave their informed consent to participate in the study in accordance with Good Clinical Practice (GCP) standards and the WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects [21]. Patients with T1D were diagnosed according to the American Diabetes Association (ADA) guidelines [22]. The study was reviewed and approved by the Independent Bioethics Committee for Scientific Research of Yerevan State Medical University after Mkhitar Heratsi, RA, under license number #N7-1/2023.

Study criteria and procedures

The study involved 130 patients (64 girls and 66 boys) aged 5 to 26 years with T1D of varying duration. Sex- and age-matched healthy subjects (108 individuals, 52 girls and 56 boys) were enrolled as controls. Individuals with any infection or inflammatory disease known to increase ADA levels were excluded. At the time of T1D diagnosis, at least two types of antibodies associated with the development of T1D, including islet cell autoantibodies to insulin (ICA) and glutamic acid decarboxylase (GADA), were positive. Patients with

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T1D were further categorized into two groups based on disease duration: newly diagnosed diabetes (T1D/NO): n=45. These patients were either newly diagnosed or had received insulin for up to one year (average of 0.5–0.6 years). Long-term diabetes (T1D/LT): n=85. These patients had received insulin for more than one year (average of 5.3–5.9 years).

Patients were also distributed into two groups by sex: girls (G) and boys (B), and into subgroups by age: 5–9, 10–13, 14–19, and ≥20 years old. Healthy controls (HC) were divided into corresponding groups. Procedures were performed at the Department of Endocrinology of "Muratsan" University Hospital (Yerevan, Armenia).

Isolation of peripheral blood plasma

Venous blood was drawn into tubes containing 3.2% sodium citrate anticoagulant. After centrifugation at 3400 × g for 20 min, the supernatant (platelet-free plasma) was collected and used immediately in the assay.

Plasma HbA1c was measured at the "Muratsan" Hospital clinical laboratory by a latex turbidimetric assay and estimated as a percentage (%) [23].

Adenosine deaminase activity in plasma was assessed by measuring the ammonia produced during the enzymatic deamination of adenosine. The assay mixture (0.5 mL) contained 0.04 M potassium phosphate buffer (pH 7.0), 6 mM adenosine, and a 20 µL aliquot of the sample. This mixture was incubated at 37°C for 40 minutes. The enzymatic reaction was stopped by adding 1 mL each of phenol-nitroprusside and hypochlorite reagents [24]. The samples were then incubated for an additional 30 minutes at 42–45°C to allow for color development. Absorbance was measured at 630 nm against a blank containing all reagents except the substrate. Ammonia content was determined using ammonium sulfate as a standard. ADA activity was expressed as micromoles of ammonia produced per liter of plasma per minute (U/L). ADA2 activity was measured using the same protocol but with the addition of 0.04 mM EHNA, a selective ADA1 inhibitor. ADA1 activity was calculated by subtracting ADA2 activity from the total ADA activity. All samples were analyzed in duplicate or triplicate.

Spectral measurements were performed using a Cary 60 spectrophotometer (Agilent, USA) and a Spekol-211 (Carl Zeiss, Iena, Germany).

Statistical analysis was performed using GraphPad Prism 8, Version 8.0.2. All results are expressed as the mean±standard error of the mean (SEM). To compare groups, we used nonparametric tests: the Mann–Whitney test for two groups and the Kruskal-Wallis test for three or more groups. One-way analysis of variance (ANOVA) was also performed to compare differences in plasma ADA and clinical parameters across various groups. Spearman's (r) correlation coefficients were used for correlation analysis. Receiver operating characteristic (ROC) curve analysis was conducted to determine the sensitivity, specificity, and optimal cut-off values for the parameters. The control group was adjusted to match the patient groups for number, age, and sex. A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Age-dependent variations in ADA isoenzyme activities in healthy controls

The age- and sex-dependent activities of ADA isoenzymes (ADA1 and ADA2) and their respective activity values in healthy controls (HC) are shown in Figure 1 A–C.

A significant increase in ADA2 activity was observed exclusively in individuals older than 20 years ($p<0.001$), accompanied by a slight decrease in ADA1 activity (Figure 2 A–C).

As shown in Figure 2A, significant increases in total ADA, ADA1, and ADA2 activity were observed in patients with T1D compared with controls ($p<0.0001$). This suggests that ADA activity is markedly elevated in individuals with T1D. Furthermore, the strong correlations between ADAt and ADA2 in the T1D group imply that ADA2 activity is a major contributor to total ADA activity in these patients. As illustrated in panels A, B, and C, both isoenzymes (ADA1 and ADA2) are notably elevated in T1D, highlighting their potential roles in the disease.

These analyses provide insight into how sex and age may influence the activity of these immunologically important enzymes in both healthy adolescents and those with T1D. A comparison of ADA activity in HC revealed differences only in ADA1 activity within the 14–19 year age group (Figure 3A). As shown in Figure 1A, the average ADA1 activity values in HC are very similar across the two age groups under 14 years (5–9 and 10–13), so we combined these groups. Consequently, all patients with T1D were divided into two age groups: under 14 years and 14 years and older (up to 20 years). A decrease in ADA1 and ADA2 activities was evident in T1D

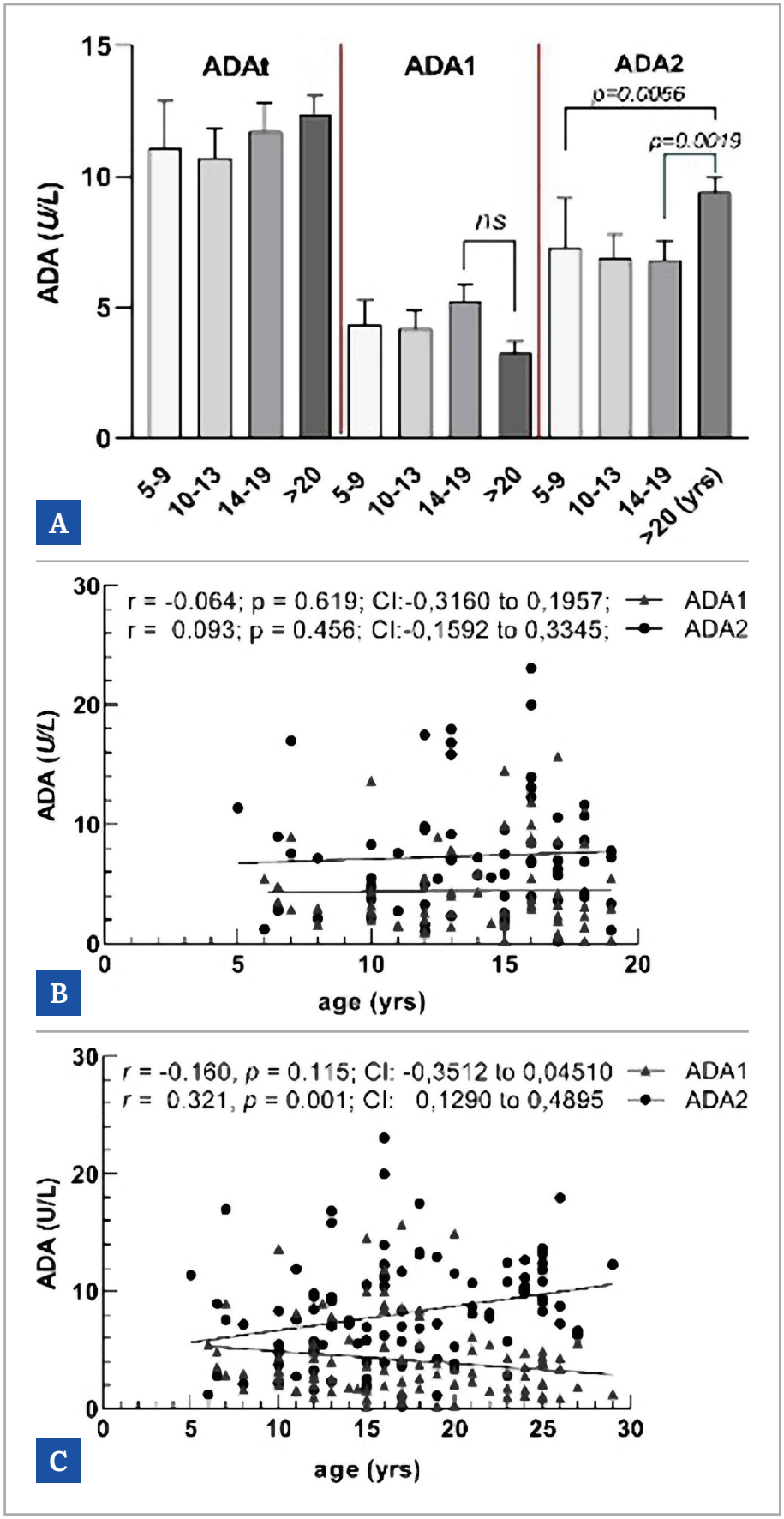

Figure 1: Plasma ADA isoenzyme activities and their correlation with age in HC. A – Comparison of plasma total ADA (ADAt), ADA1, and ADA2 isoenzyme activities across different age groups. B – Correlation between plasma ADA isoenzyme activities and age in the HC group, including subgroups of young (<20 years. and (C – older (≥20 years) participants. r=Spearman's correlation coefficient. Data are presented as mean±SEM.

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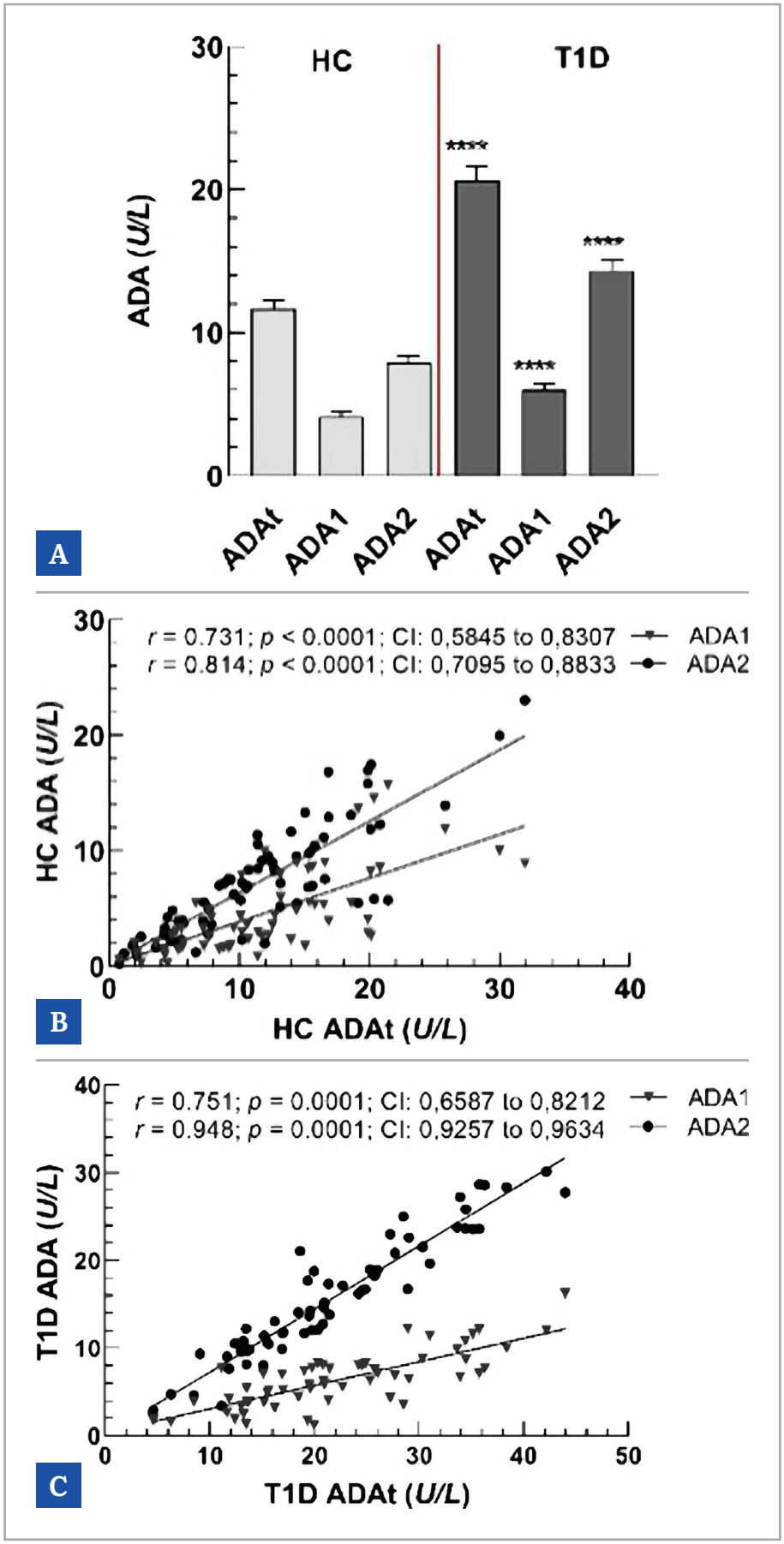

Figure 2: ADA activity in T1D patients *vs*. HC. A – Comparison of total ADA and isoenzyme activity levels in T1D patients *versus* HC. B – Correlations of total ADA *versus* ADA1 and ADA2 in HC. C – in T1D groups. Data are presented as mean±SEM; **** – p<0.0001 between HC and T1D patient groups.

adolescents compared with children. The comparison of enzyme activity was performed between boys and girls in these groups (Figure 3 B–D). Significant decreases in ADA activity between these T1D age groups were observed only in ADA1, for both girls and boys, with a more pronounced decrease in boys.

Figure 4 shows that no significant difference in isoenzyme activity was observed between groups of disease duration: T1D/NO and T1D/LT. Interestingly, this finding contrasts with T2D, where patients with new-onset diabetes (T2D/NO) typically exhibit the highest ADA2 activity [17, 18].

Determining optimal thresholds for ADA2 isoenzyme activity in T1D patients

To establish optimal threshold values for ADA2 isoenzyme activity, we calculated the Area Under the Curve (AUC) and generated Receiver Operating Characteristic (ROC) curves, given ADA2's prominence in T1D.

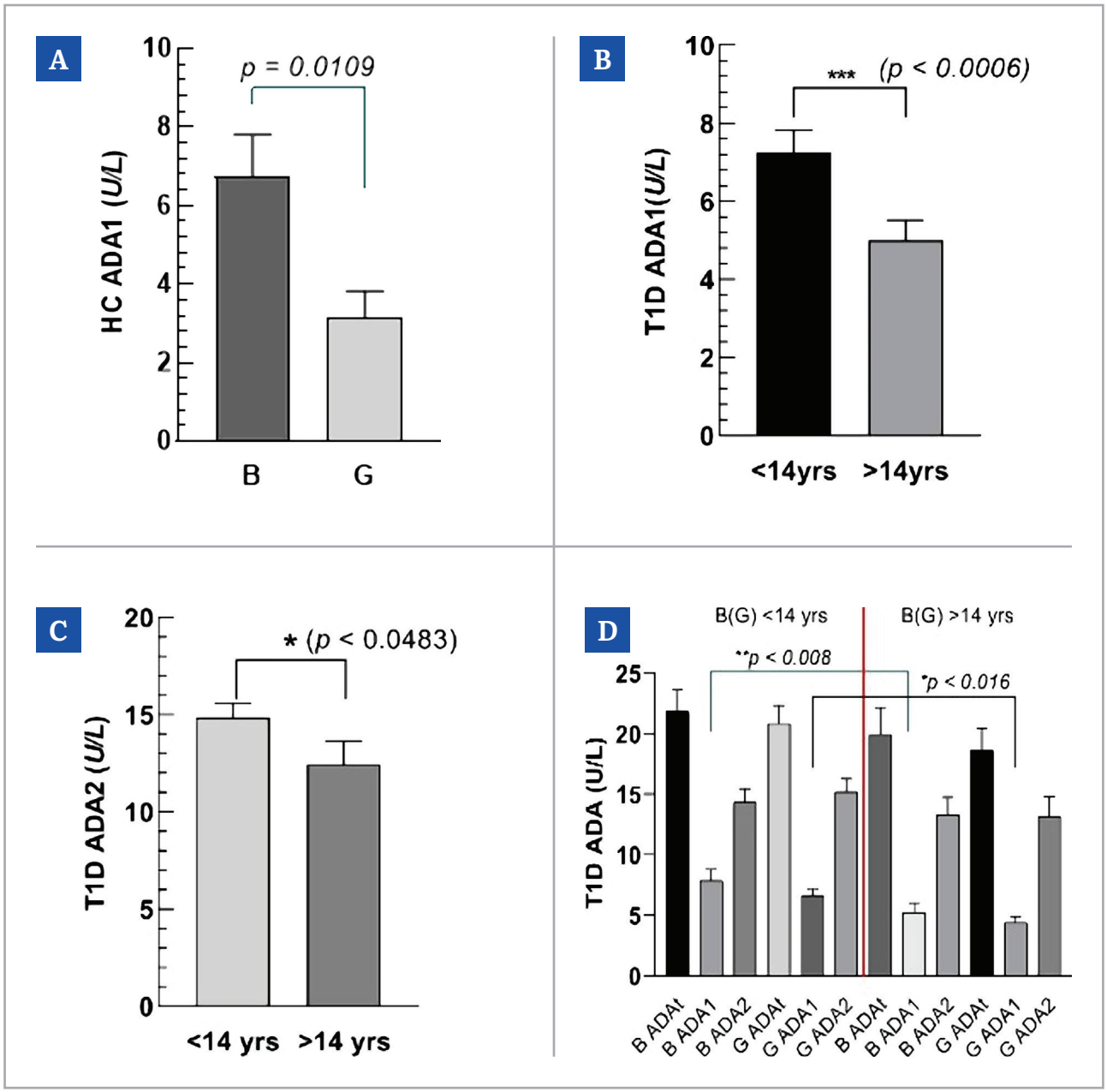

Figure 3: Sex- and age-based differences in ADA activity in HC and T1D patients. A – Comparison of plasma ADA1 activity levels between girls (G) and boys (B) in the HC group (14–19 years). B – Comparison of plasma ADA1 activity levels in T1D age groups (<14 years *vs.* ≥14 years). C – Comparison of plasma ADA2 activity levels in T1D age groups (<14 years *vs.* ≥14 years). D – Comparison of ADAt and isoenzyme activity levels between girls and boys within the T1D cohort, stratified by sex and age.

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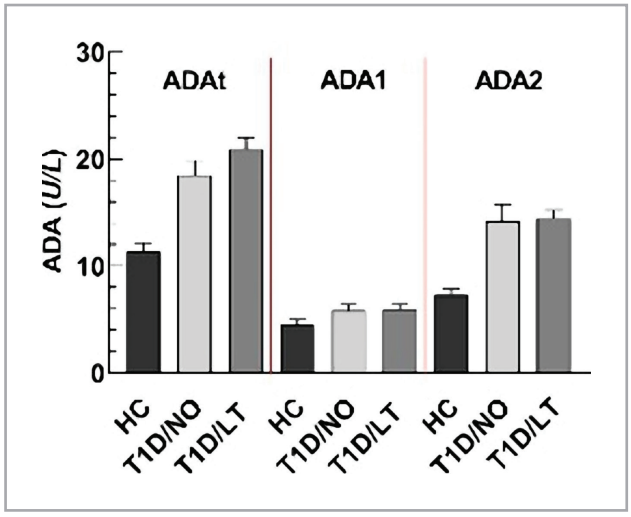

Figure 4: ADA isoenzyme activity in T1D patients: impact of disease duration.

Figure 5 A–C illustrates the ROC curves for plasma ADA2 in patients with T1D/NO, T1D/LT, and the entire T1D patient cohort. The curves plot sensitivity on the Y-axis against 1-specificity on the X-axis. The AUC values were calculated as follows: all T1D patients (n=130): 0.800; T1D/NO (n=45): 0.757; T1D/LT (n=85): 0.822.

Based on these data, an optimal threshold for ADA2 activity in T1D was determined. The optimal results were obtained with an ADA2 level ≥11 U/L, yielding a sensitivity of 67.10%, specificity of 91.04%, positive predictive value (PPV) of 78.57%, and negative predictive value (NPV) of 65.82%.

The relationships between ADA isoenzymes and HbA1c in patients with T1D are illustrated in Figure 6 A–C.

No significant correlations were found between ADA isoenzymes and HbA1c.

Further analysis, which subdivided patients by BMI and by their HbA1c values (below 7% and above 8% as per standard guidelines [25]), showed no additional correlations (data not shown).

Discussion

This study examined ADA levels across various age groups, revealing insights into their distribution and potential variations. We observed an age-related increase in ADA2 activity in the HC, specifically in young adults aged 20 years and older (Figure 1A, Table 1).

This finding, also supported by the correlations between ADA2 activity and age (Figure 1B and C), contrasts with previous data indicating a decrease in ADA2

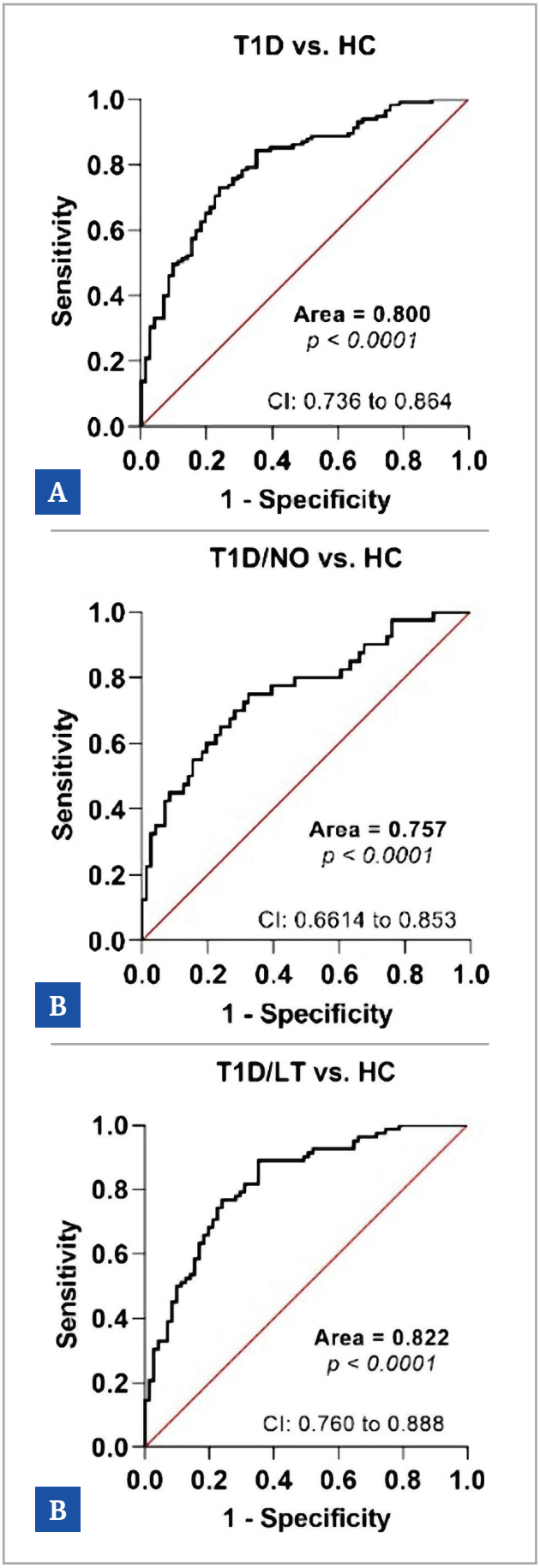

Figure 5: ROC curve analysis of plasma ADA2 in T1D patients.

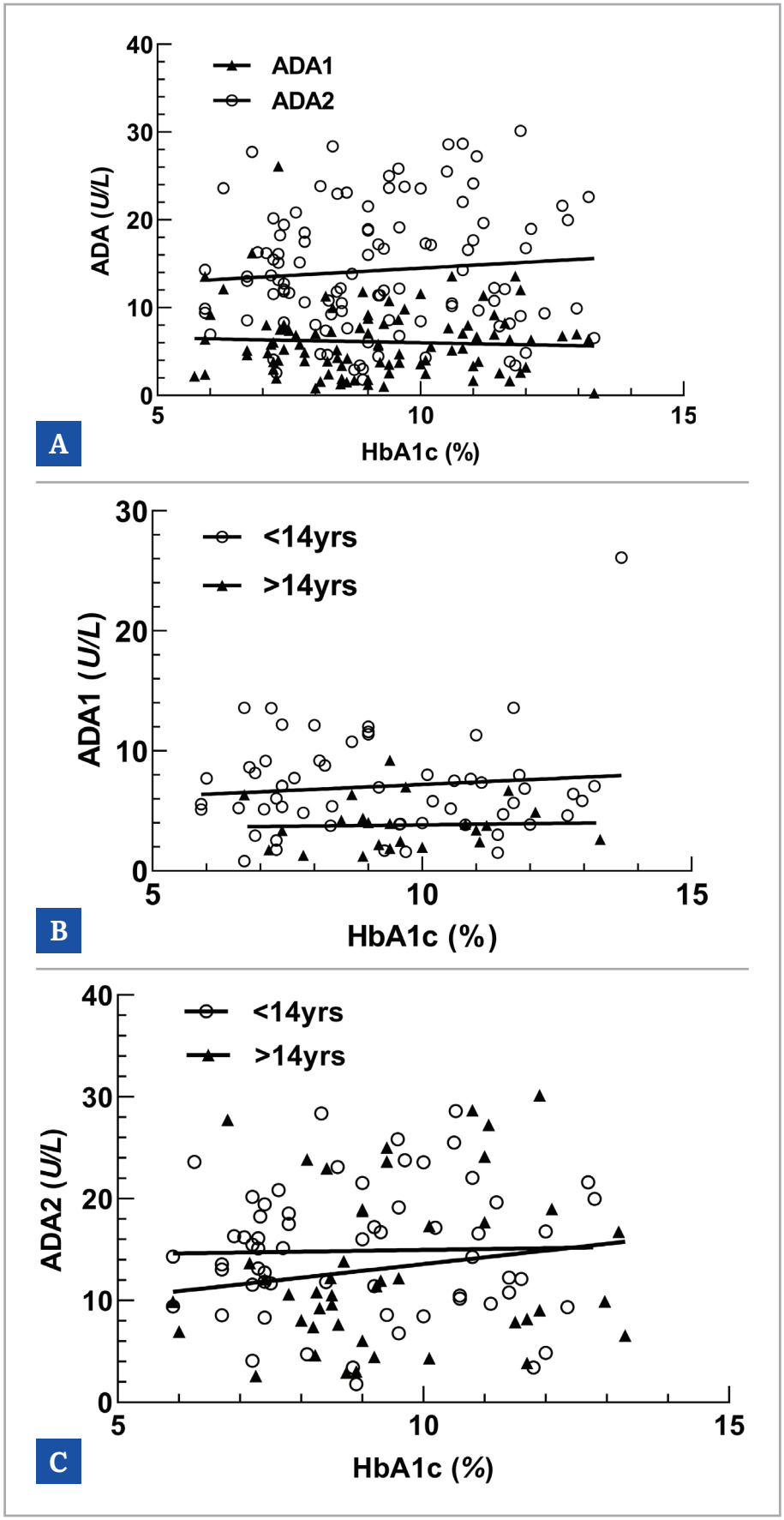

Figure 6: Correlation of ADA isoenzymes with HbA1c in T1D patients. A – Correlation of ADA isoenzymes with HbA1c in the overall T1D patient cohort; B – Correlation of ADA1 and ADA2 activity with HbA1c in T1D patients under 14 years old; C – Correlation of ADA1 and ADA2 with HbA1c in T1D patients older than 14 years. r – Spearman's correlation coefficient.

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Table 1: ADA2 isoenzyme activity in the age groups in T1D.

Age groups, yrs, (N)	ADA2 (U/L)	P-value	95% CI
5–9 (8)	11.07±1.802	0.0066	6.812–15.34
10–13 (23)	10.73±1.098	0.0065	8.45–13.01
14–19 (51)	11.72±1.097	0.0019	9.518–13.93
≥20 (36)	12.37±0.707	-	10.94–13.8

activity with advancing age [26, 27]. In the overall HC group, ADA1 activity showed a weak, non-significant negative correlation with age. Conversely, ADA2 activity demonstrated a moderate, statistically significant positive correlation.

A focused analysis was performed on the HC group aged under 20 years to explore age-related trends during development. In this younger cohort, neither ADA1 nor ADA2 isoenzyme activities showed a statistically significant correlation with age. It is important to note that ADA2, which showed a significant positive correlation in the overall group, had a weak, non-significant positive correlation in the group under 20 years. This result suggests that the significant positive correlation of ADA2 with age is primarily driven by changes occurring in individuals after the age of 20. This implies that while ADA2 levels may fluctuate during early life, a more consistent increase in ADA2 activity in relation to age becomes apparent in adulthood. Further research focusing on specific age intervals within adulthood could help to clarify the precise nature and rate of ADA2 increase with aging. These findings highlight the importance of age as a variable when interpreting ADA2 levels, particularly in adult populations.

ADA levels were significantly elevated in patients with T1D compared to HC, as shown in Figure 2A. Total ADA activity was approximately 76% higher in T1D patients (20.67±0.956 U/L) than in HC (11.71±0.567 U/L). ADA1 levels were about 46% higher in T1D patients (6.055±0.372 U/L) compared to HC (4.14±0.324 U/L). The most pronounced increase was seen in ADA2, which was 81% higher in T1D patients (14.39±0.697 U/L) compared to HC (7.948±0.446 U/L). These differences are statistically highly significant ($p<0.0001$), with no overlap in the 95% confidence intervals between the T1D and HC groups for any of the ADA forms (Figure 2B).

The significant increase in ADA isoenzymes, particularly ADA2, may reflect heightened immune activity and chronic inflammation in T1D. Since ADA2 is primarily secreted by monocytes and macrophages and is linked to inflammation, its elevation could indicate increased monocyte-macrophage activation or a broader dysregulation of the immune system [17]. This suggests that ADA isoenzymes, especially ADA2, could serve as potential biomarkers for assessing the immune and inflammatory status in T1D, warranting further research into their role and utility [28].

As presented in Figure 3, the mean ADA1 level in boys (6.766±1.036 U/L) is notably higher than that observed in girls (3.169±0.653 U/L) in the HC group ($p<0.0109$). The wider range of ADA1 values in boys (14.85) compared to girls (8.387) indicates greater variability. The 95% confidence interval for the mean in boys (4.588 to 8.943) does not overlap with the 95% confidence interval for the mean in girls (1.778 to 4.561), which further reinforces the statistical significance of the sex difference.

Given that ADA1 is involved in purine metabolism and immune system function, its activity is sensitive to physiological changes. The elevated ADA1 levels in healthy adolescent boys (14–19 years old) can be explained by two factors: a surge in testosterone during puberty, which influences cellular and immune metabolism, and high levels of physical activity, which lead to an increase in metabolic processes and cell turnover, stimulating ADA1 activity [29, 30].

There are three main reasons why ADA1 levels may not show sex-based differences in adolescents with T1D, unlike their healthy peers. First, T1D, as an autoimmune disease, causes chronic inflammation and ongoing immune activation. This constant immune response can directly influence ADA1, a key enzyme in immune function, and may mask or counteract the normal ADA1 fluctuations that typically occur during puberty. Second, T1D can cause metabolic disruptions that affect hormonal balance, especially if the disease is poorly controlled. Chronic hyperglycemia can alter how tissues respond to hormones, potentially blunting the pubertal hormonal effects on ADA1 activity. Third, adolescents with T1D often have lower levels of

physical activity due to the need to manage their blood sugar and avoid hypoglycemia. If physical activity is a primary driver of higher ADA1 levels in healthy boys, then the reduced activity in boys with T1D could eliminate this increase, thus removing the sex-based difference seen in healthy adolescents.

The potential role of ADA1 in the pathogenesis of T1D is also supported by the finding that polymorphisms in the ADA1 gene are associated with an increased risk for T1D [31, 32].

There were no statistically significant differences in the mean activity of ADAt, ADA1, or ADA2 between patients with T1D/NO and T1D/LT (Figure 4). This contrasts with T2D, where ADA2 is more prominently expressed in the early stages of the disease [33, 34].

ROC curve analysis consistently demonstrated the high discriminatory capacity of ADA2 isoenzyme activity in distinguishing T1D patients from HC (Figure 5). The AUC values for all three comparisons (T1Dall, T1D/NO, and T1D/LT *vs*. HC) were statistically significant. The ROC curve for T1D/LT patients showed the highest discriminatory power with an AUC of 0.822. This was closely followed by the overall T1D group, which had an AUC of 0.800. Optimal threshold values were obtained with an ADA2 activity greater than 11 U/L for both curves.

The total ADA and isoenzymes did not show a statistically significant correlation with HbA1c for the overall T1D patient cohort: ADAt (r=0.007, p=0.944); ADA1 (r=–0.0004, p=0.997); and ADA2 (r=0.071, p=0.466). These findings, presented in Figure 6A, suggest that the activity of ADA isoenzymes in T1D patients is not systematically related to their long-term glycemic control. Analysis of specific T1D age groups (under 14 and 14 years or older), as shown in Figure 6B and C, reveals that this lack of correlation between ADA isoenzymes and HbA1c persists. This suggests that age does not significantly alter the relationship between ADA activity and long-term glycemic control [35, 36].

Conclusion

This study shows that ADA isoenzyme activity in the young Armenian population has distinct patterns. In healthy individuals, ADA2 activity positively correlates with age, a trend driven by changes in adulthood, while ADA1 levels are significantly higher in boys than in girls. In patients with T1D, total ADA, ADA1, and particularly ADA2 levels are significantly elevated compared to healthy controls, suggesting heightened immune and inflammatory responses. Notably, there were no significant differences in ADA activity between newly diagnosed and long-term T1D patients, and no correlation was found between ADA activity and long-term glycemic control (HbA1c). The statistically significant AUC values across all comparisons underscore ADA2's potential as a valuable diagnostic or monitoring biomarker.

Conflict of interest

The authors declare no conflict of interest.

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