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CHARACTERISTICS OF SOME ENZYMES IN BLOOD PLASMA OF DIABETIC HUMANS

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The enzymes adenosine deaminase (ADA), dipeptidyl peptidase 4 (DPP4) and glutaminase (GL) are involved in the development of both the type 1 (T1DM) and type 2 diabetes mellitus (T2DM). They can be considered as targets in the prevention and/or treatment of these diseases. The autoimmune response of the body is caused by the post-translational protein modifications, one of which is protein citrullination, when arginine residue transforms to citrulline. This work compares the ADA, DPP4, GL enzymes and protein citrullination in blood plasma from T1DM, T2DM patients and relatively healthy individuals. The enzymes were isolated and purified from the blood samples. We found that DPP4 activity was significantly higher in the plasma of patients compared to controls, particularly in T1DM. Currently the medicines based on DPP4 inhibitors are used in the treatment of T2DM. Our results indicate that this treatment strategy can be recommended in the T1DM treatment as well.

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Introduction. Diabetes mellitus (DM) is a heterogeneous group of diseases characterized by high blood glucose level [1]. The disturbance of the functions of islet β-cells and inadequate secretion of glucagon leads to the overproduction of glucose by the liver and its insufficient use by peripheral tissues [2]. For a long time, diabetes was not considered as a disease posing a big problem for world health, but now it ranks fourth or fifth leading causes of death [3]. All forms of diabetes are characterized by chronic hyperglycemia and the development of pathology of retinal microvessels, renal glomeruli and peripheral nerves. Diabetes is one of the main causes of blindness, end-stage mellitus renal disease and various neuropathies [4]. The long-term high glucose level can result in heart diseases, strokes, kidney failure, diabetic retinopathy and reduced blood flow to limbs, leading to blindness, amputation, etc. [5].

Generally, two main forms of DM are known: type 1 and type 2.

Type 1 diabetes (T1DM) is a polygenic disease and risk of its development is associated with more than 50 genes [6]. T1DM accounts for 5 to 10% of all diabetics,

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but there is not any remedy, which can prevent it [7]. T1DM most commonly results from autoimmune-mediated destruction of pancreatic β-cells leading to absolute insulin deficiency. To survive and prevent the development of ketoacidosis, people are forced to take exogenous insulin. T1DM often develops in young people and is accompanied by other autoimmune diseases [8–10].

Type 2 diabetes mellitus (T2DM) is characterized by high blood sugar, insulin resistance, or abnormal insulin secretion [11]. It is a result of resistance of muscle, adipose tissue and liver cells toward insulin, which leads to insufficient utilization of sugar. The pancreas does not produce enough insulin to regulate blood sugar level. Symptoms include increased thirst, frequent urination, and weight loss [12].

The post-translational protein modifications are considered among the main reasons for autoimmunity development. The catalyzed by peptidyl arginine deiminases (PAD) protein citrullination is one of these modifications, when the arginine residues are transformed into citrulline. Increased PAD expression and protein citrullination are involved in various pathologies such as Alzheimer's and Parkinson's diseases, multiple sclerosis, psoriasis, cancer, rheumatoid arthritis, and other [13]. There are cases of co-occurrence in individuals and families of autoimmune diseases, for instance, rheumatoid arthritis (RA) and T1DM [14]. The inhibition of PAD resulted in the retardation of T1DM development in laboratory animals [15]. The development of T1DM upon infection with SARS-CoV-2 was considered as a consequence of PAD expression and increased protein citrullination [16].

The widespread in mammalian tissues multifunctional enzyme adenosine deaminase (ADA, EC: 3.5.4.4) is a key enzyme in the metabolism of purine nucleosides. It catalyzes the deamination of adenosine to inosine, participates in functioning of the immune, nervous and vascular systems [17, 18]. ADA activity increases in biological fluids in various pathologies leading to decrease of the level of its substrate, adenosine. The assessment of the enzyme level is recognized as an ADA-test in the diagnosis of several diseases [19]. The small molecular form of intracellular mammalian ADA (SADA) is a catalytically active monopeptide with a molecular mass (Mm) of 32–42 *kDa*. Its large extracellular form (LADA, Mm ≥ 260 *kDa*) is a non-covalent complex of SADA with dipeptidyl peptidase 4 enzyme (DPP4). The described in our works accumulation of SADA in synovial fluids at RA was a consequence of autoimmune nature of this pathology [20], when SADA citrullination prevented its interaction with DPP4 and transformation into LADA [21, 22]. At T2DM, the observed increase of ADA activity in blood plasma, can lead to changes in immunity and exacerbation of the pathogenesis [23, 24].

Dipeptidyl peptidase 4 (DPP4, EC: 3.4.14.5) is a serine protease that cleaves dipeptides from the N-terminus of polypeptides with proline or alanine in the penultimate position. It is present in mammalian tissues in two forms, localized on cell membranes and circulating [25]. DPP4 is involved in metabolism of peptide hormones, cytokines, and other substrates [26], in activation and proliferation of T cells [27]. In particular, DPP4 inactivates the incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), which promote glucose-dependent insulin secretion by pancreatic β-cells [28]. DPP4 inhibitors prolong the lifetime of these hormones, improve glucose level and the functioning of β-cells [29]. Currently, the Pharmacopoeias in many countries have recognized a number of

DPP4 inhibitors for treatment of T2DM, many others are at the stage of preclinical and clinical studies as potential anti-diabetics [30–32].

γ-Aminobutyric acid (GABA), is the most important inhibitory neurotransmitter of mammalian central nervous system. In diabetes, GABA displays anti-inflammatory, immune-modulatory, trophic and antidiabetic activities stimulating proliferation of pancreatic β-cells, synthesis and release of insulin [33]. Administration of GABA-generating glutamine and ethanolamine-O-sulfate (EOS) to laboratory rats, reduced streptozotocin and alloxan stimulated experimental hyperglycemia [34, 35]. The addition of EOS, GABA and glutamine to pancreatic β-cell culture increased the release of insulin [36]. Glutaminase (Gl, EC: 3.5.1.2, glutamine hydrolase) converts glutamine to glutamate, a precursor of GABA. In mammalians, multiple tissue-specific forms of Gl are presented [37]. There are evidences that Gl is involved in normalization of homeostasis at T2DM [38]. Studies have shown that glutamine synthesis was accelerated in liver of rats with streptozotocin-induced diabetes compared to control animals [39]. In damaged mitochondrial membranes of diabetic rats, the Gl activity was increased by ~2.5 times, suggesting Gl involvement in pathogenesis of diabetes.

The aim of this work was to compare the peculiarities of DPP4, ADA and Gl enzymes activities in the blood plasma from patients diagnosed with T1DM and T2DM and healthy individuals (Control group). The protein citrullination in blood plasma and in the purified from plasma enzymes, was evaluated for all three groups.

Materials and Methods.

Participants. The study involved patients with T1DM (male, $n = 32$; female, $n = 15$), at the age of three months-old to 15 years old. According to the analysis conducted in the Department of Endocrinology of "Muratsan" University Hospital, the absence of macrovascular disease in patients with T1DM was confirmed by the absence of a cardiovascular abnormalities. The absence of microalbuminuria was proved by measurement of urinary albumin/creatinine ratio. The T1DM patients were treated with the fast acting (Humalog), long acting (Glargin), intermediate acting (HumulinN) and regular (HumulinR) human insulin.

The T2DM patients (male, $n = 18$; female, $n = 10$), at the age of ≥ 50 years old were treated with different doses of Metformin and Diabeton. The study involved 5 healthy individuals (male, $n = 3$; female, $n = 2$) as a Control group.

All participants were examined early in the morning, fasted, avoiding caffeinated beverages, cigarettes and strenuous exercise since the previous evening.

Chemicals. L-citrulline, diacetylmonoxime (DAMO), thiosemicarbazide (TSC), substrates of ADA (adenosine), Gl (glutamine), and DPP4 (Gly-Pro-p-nitroanilide-p-toluenesulfonate salt, Gly-Pro-pNA) were purchased from "Sigma Aldrich Ltd" (USA). Other reagents were of the highest purity available.

Equipment. UV-Vis measurements were carried out on the Cary 60 spectrophotometer (USA). The Bio-Rad PowerPac™ Basic equipment was used for PAGE electrophoresis.

Purification of ADA, DPPIV and Gl. The enzymes were purified up to electrophoretic homogenous state using gel-filtration and ion-exchange chromatography procedures, as described earlier [40, 41].

The ADA activity was assayed by the phenol-hypochlorite colorimetric method, evaluating the amount of ammonia, liberated in the catalyzed deamination of adenosine, measuring the absorbance of the assay mixture at 630 *nm* [40]. Gl activity was examined by the same method of evaluation of ammonia liberated in Gl catalyzed glutamine-glutamate conversion. The assay mixture in 0.5 *mL* of 0.08 *M* K-Na phosphate buffer, pH 8.4, contained 2 *mM* glutamine and an aliquot of the sample under study. Ammonium sulphate was used as a standard [40].

DPP4 activity was evaluated measuring the absorbance at 383 *nm* of pNA, liberated from the enzyme substrate Gly-Pro-pNA in the catalyzed enzymatic reaction [41].

Activities of all enzymes were expressed in international units (*U*/*L*, *μmol* of the reaction product per minute) or by the absorbance of the activity assay solution at the corresponding wavelength.

Determination of Citrulline. The presence of citrulline in protein samples was examined using the colorimetric assay based on the specific reaction of DAMO with ureido group under highly acidic conditions according to the method of Boyde, as described earlier [42, 43].

Polyacrylamide Gel Electrophoresis. PAGE in native conditions was performed in Tris-glycine buffer, pH 8.3, according to the method of Davis et al. [44]. The electrophoresis was carried out at 100–120 *V*, 2 *h*, and 25°C. The gels were stained with 0.3% Coomassie Blue G-250 and washed with 7.5% acetic acid.

Gel-filtration Chromatography. The gel-filtration procedures on Sephadex G-200 columns were running with 10 *mM* phosphate buffer, pH 7.4, containing 0.1 *M* KCl at room temperature. Fractions of 2 *mL* were collected and the elution profile was monitored by protein absorption at 280 *nm*. The free volume of the column, V_o, was estimated from the yield of dextran with a molecular mass of 2000 *kDa*. Activities of the studied enzymes were assayed in all fractions.

Statistical Analyses. Statistical analyses were performed using InStat software, version 3 for Windows ("GraphPadSoftware Inc.", CA, USA). The unpaired two-tailed *t*-test with Welch correction was applied. Results were expressed as mean values ± S.E.M.

Results.

Parameters of Blood Plasma. The study used 80 blood plasma samples, of which the Control group included 5 samples, the number of samples from T1DM patients was 47 and from T2DM patients was 28.

Three groups of blood plasma samples were characterized by the average values of glucose level, protein citrullination and the activities of the enzymes under study (Tab. 1). The number of samples, *n*, over which the given parameter is averaged is indicated.

Table 1

Characteristics of the studied blood plasma (mean ± standard error, n – number of samples)

Group	Glucose, *mM*; *n*	Citrulline, *g*/*L*; *n*	ADA, *U*/*L*; *n*	DPP4, *U*/*L*; *n*	GL, *U*/*L*; *n*
Control	5.7 ± 0.1; 5	8.0 ± 3.1; 5	3.4 ± 0.5; 5	48 ± 0.57; 4	2.3 ± 0.1; 4
T1DM	16.4 ± 2.1; 25	10.0 ± 3.8; 10	4.1 ± 0.5; 47	121 ± 8.6; 9	1.9 ± 0.3; 5
T2DM	16.5 ± 1.9; 12	7.5 ± 3.4; 10	3.7 ± 0.7; 28	41 ± 7.6; 10	3.2 ± 0.7; 11

According to the presented data, high glucose level in the T1DM and T2DM groups compared to the control was registered. It is worth to note that there was approximately 3-fold ($p < 0.01$) higher DPP4 activity in T1DM group compared to the other two groups.

Gel Filtration of Blood Plasma on Sephadex G-200$_m$ Containing Column. The blood plasma samples from Control ($n = 5$), T1DM ($n = 21$) and T2DM ($n = 15$) groups were subjected to gel-filtrations on columns filled with Sephadex G-200$_m$. The applied sample volume / column volume ratio usually was approximately 1/100. As is described in the section "Methods", in collected 2 *mL* fractions, the absorbance at 280 *nm* and the activities of the studied enzymes were measured. The obtained data were used for creation the diagrams, which served as the basis for the development of the separation scheme and further purification of the studied enzymes. Fig. 1 shows an example of diagram of gel filtration on Sephadex G-200$_m$ column of the blood plasma sample.

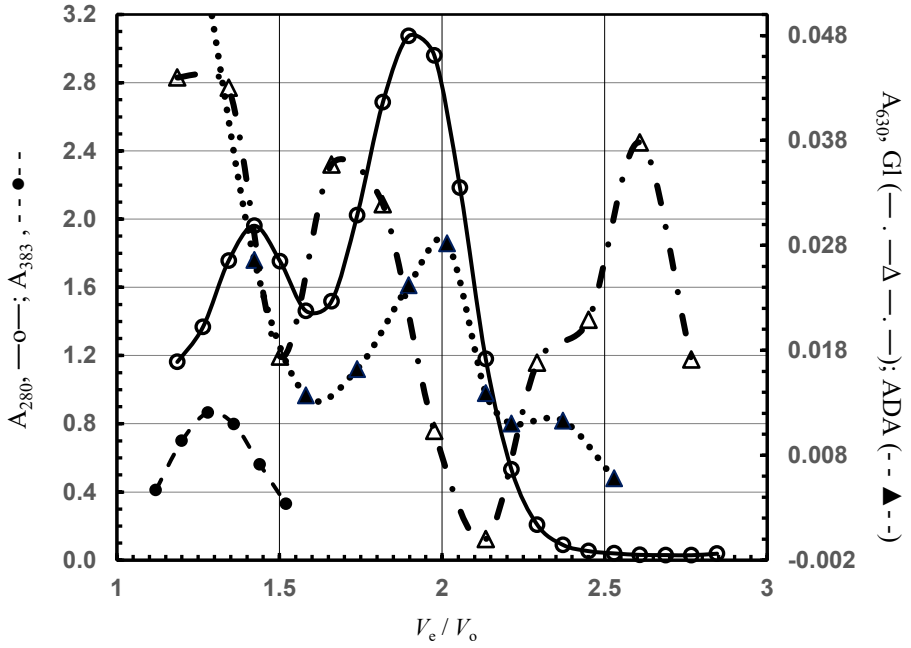

Fig. 1. An example of diagram of blood plasma gel filtration on Sephadex G-200$_m$ column. A_{280} – protein absorbance (o); A_{383} – DPP4 activity (●); A_{630} – Gl (Δ) and ADA (▲) activities.

Purification of Enzymes from Blood Plasma. After described gel filtration on Sephadex G-200$_m$ columns, the fractions of the enzymes of interest were pooled separately for each of the studied groups. The combined fractions were used for purification of the enzymes applying usual gel filtration and ion exchange chromatography procedures. The purified preparations of the enzymes were analyzed by PAGE, as is described in the section "Methods". The results are shown in Fig. 2.

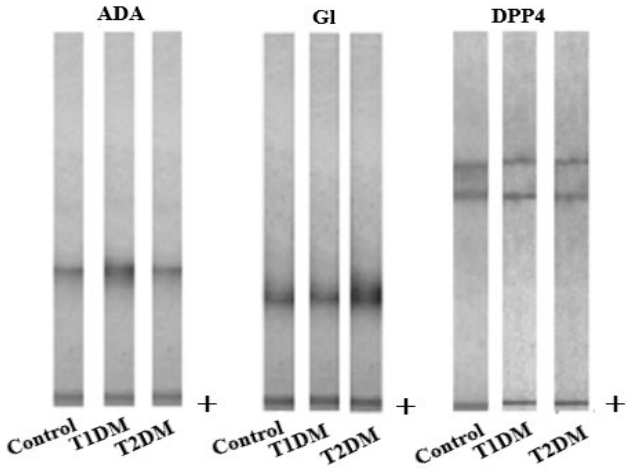

Fig. 2. Electropherograms of ADA, Gl, and DPP4 purified from the blood plasma of Control, T1DM and T2DM groups.

Purification of Dipeptidyl Peptidase 4. To purify the DPP4 enzyme, fractions with the ratio of the yield volume to the free volume of column (V_e/V_o) from 1.1 to 1.3, corresponding to the interval of molecular mass (Mm) between 260 *kDa* and 210 *kDa* were taken. Tab. 2 shows the values of DPP4 activity after gel filtration for T1DM, T2DM and Control groups, expressed as absorbance at 383 *nm* and averaged for the *n* processed samples.

The average DPP4 activity for T1DM in Tab. 2 is by 2.7 times higher than in the Control group ($p < 0.01$) and two times higher than in the T2DM group. These results are in concordance with the 3-fold higher DPP4 activity in the blood plasma of T1DM patients compared to the Control group (Tab. 1).

Table 2

The DPP4 activities in the fractions after gel filtration on G-200m (n is the number of processed blood plasma samples)

Group	*n*	A_{383}
Control	5	0.15 ± 0.03
T1DM	13	0.41 ± 0.04
T2DM	10	0.21 ± 0.02

The gel filtration eluates of the enzyme were collected by three indicated groups and used for purification. The combined DPP4 fractions were subjected to repeated procedures of ion-exchange chromatography on DE-cellulose and gel-filtration chromatography on G-200_{sf} columns. These procedures resulted in the preparation of the enzyme showing two protein bands on the native slab PAGE (Fig. 2). It worth to note that the DPP4 fractions possess ADA activity, because DPP4 usually is presented as ADA–DPP4 complex known also as the large molecular mass ADA (LADA). The appearance of two bands in Fig. 2 electropherograms can be explained by the heterogeneity of the obtained DPP4 sample due to the different steps of saturation with ADA of DPP4 molecules. This is in accordance with the not shown

two DPP4 activity peaks in gel-filtration diagram of purified enzyme, when the high-molecular peak possessed significant ADA activity, but the second one did not.

Tab. 3 shows the specific activities (A_{383}/A_{280}) and the level of citrullination (A_{530}/A_{280}) of DPP4 preparations purified from the high molecular fractions of the blood plasma for three studied groups. According to these data, the specific activities of DPP4 in three groups do not differ significantly contrary to the enzyme activity in the non-purified samples shown in Tabs. 1 and 2.

Table 3

Characteristics of purified DPP4 preparations

Group	A_{383}/A_{280}	A_{530}/A_{280}	A_{530}/A_{383}	A_{630}/A_{280}	A_{630}/A_{383}
Control	0.35 (4.2)	0.13	0.37	0,29	1,1
T1DM	0.25 (0.75)	0.07	0.28	0,1	0.26
T2DM	0.2 (1.7)	0.31	1.55	0,15	0.25

The citrullination per unit of DPP4 activity (A_{530}/A_{383} ratios) shows low value in the preparation from the blood plasma of the T1DM group. The level of citrullination per unit of DPP4 activity in T2DM group is ~ 4–5 times higher than in the enzyme from the Control and T1DM groups.

Tab. 3 shows also the specific ADA activities (A_{630}/A_{280}) in the purified DPP4 preparations. For the preparation from T1DM and T2DM groups these values are lower than for Control group by 3 and 2 times, respectively. This finding is confirmed by ~3.5 times lower ratios of ADA/DPP4 activities (A_{630}/A_{383}) for DM preparations as compared to the Control group. Hence, the saturation of the ADA binding sites on the DPP4 molecule at diabetes is low. Taking in account the significance of ADA-DPP4 interaction for potentiation of T-cells proliferation [45], the hindrance of this interaction can be considered as one of possible mechanisms of immunity diminishing at DM.

Purification of Small Molecular Isform of ADA (SADA). After gel filtration on Sephadex G-200_m column, the SADA fractions (V_e/V_o between 2.1 and 2.4; Mm = 45–30 *kDa*) of blood plasma were combined separately for each group. The collected fractions were used for SADA purification (electropherograms shown in Fig. 2).

Table 4

Characteristics of purified SADA preparations

Group	A_{630}/A_{280}	A_{530}/A_{280}	A_{530}/A_{630}
Control	1.1	0.31	0.3
T1DM	1.03	4.1	3.98
T2DM	0.36	5.7	15.83

Tab. 4 shows the specific activity (A_{630}/A_{280}), the level of protein citrullination (A_{530}/A_{280}) and the citrullination per unit of enzyme activity (A_{530}/A_{630}) for the purified SADA preparations. According to these data, the specific activity of SADA purified from the plasma of patients with T1DM is close to the activity of the preparation of Control group, while the preparation obtained from the blood of T2DM group it is ~3 times less.

Citrullination increases in the range Control < T1DM < T2DM by 13 and 18 times, respectively. Correspondingly, the levels of citrullination per unit of SADA activity in T1DM and T2DM groups are higher than in Control group by 13 and 53 times, respectively (Tab. 4, third column).

Purification of Small Molecular Gl. According to the available scientific publications, the isoform of Gl with the molecular mass less of 30 *kDa*, is poorly studied. After gel filtration of all the blood plasma samples on Sephadex G-200_m column (Fig. 1), the fractions with V_e/V_o from 2.4 to 2.6 (corresponding to Mm = 30–15 *kDa*) were combined separately for three groups. The obtained solutions were subjected to usual gel-filtration and DE-cellulose ion-exchange chromatography procedures, and the low molecular isoform of Gl was purified (electrophoregrams are shown in Fig. 2).

Table 5

Characteristics of preparations of low molecular Gl purified from blood plasma

Group	A_{630}/A_{280}	A_{530}/A_{280}	A_{530}/A_{630}
Control	5.2	2.8	0.54
T1DM	13.2	6.4	0.5
T2DM	23	3.1	0.13

Tab. 5 shows the characteristics of the Gl preparations purified from the blood plasma of the studied groups. The values of specific glutaminase activity (A_{630}/A_{280}), specific protein citrullination (A_{530}/A_{280}), as well as the citrullination per unit of enzyme activity (A_{530}/A_{630}) are demonstrated. According to the presented data, the values of the specific activities of purified Gl increase in the following order: Control < T1DM < T2DM. The level of citrullination is not consistent with this order: Control ≈ T2DM < T1DM. The third column shows that the level of citrullination per unit of Gl activity for the T2DM group is by ≈4 times lower than for the Control and T1DM groups. i.e. T2DM < T1DM ≈ Control.

Discussion. In the "Introduction", we mentioned the involvement of citrullination in development of autoimmune processes and increased expression of PAD and protein citrullination in several pathologies such as: Alzheimer's and Parkinson's diseases, multiple sclerosis, psoriasis, oncology, rheumatoid arthritis and experimental T1DM [13]. However, in the present study, we did not find a significant difference in the degree of protein citrullination in the blood plasma from T1DM and T2DM patients compared to Control (Tab. 1). According to the literature, the autoimmune nature of T1DM in 90% of cases is caused by the presence of autoantibodies to the components of pancreatic β-cells: insulin, glutamic acid decarboxylase, zinc transporter 8 (ZnT8) and secretory protein IA-2 [46], which explains our results. In the pre-symptomatic stage, T1DM is characterized by the presence of two or more autoantibodies toward β-cells. We assume that even if citrullination phenomenon participates in the development of autoimmunity in T1DM, it is expressed less significantly compared to the above-mentioned causes of autoimmunity towards autoantibodies to the components in pancreatic β-cells. Therefore, the citrullination was not detected in our study.

The absence of a significant difference in the levels of ADA activity in the blood plasma of the three studied groups (Tab. 1) is an expected result, since ADA

level can be influenced by many factors of a living organism. In the purified ADA preparations, the ratio of the citrullination degree to the ADA activity is the greatest in the case of T2DM (Tab. 4), but not in the case of T1DM, as we expected. Although, our previous studies demonstrated citrullination of ADA in RA, another autoimmune disease [21].

Despite of detected protein citrullination in the blood plasma (Tab. 1) and in the purified enzyme preparations (Tabs. 3–5), there was no indication of the presence of citrullinated proteins in the native PAGE electropherograms. In contrary the slow mobility of citrullinated ADA from synovial fluids of RA patients was observed in our previous study [47].

However, in T1DM patients we observed a 3-fold increase in DPP4 activity in both, plasma samples and after the first gel filtration on Sephadex G-200$_m$ (Tabs. 1 and 2). Increased activity of DPP4 in T1DM patients, as well as its correlation with the T1DM pathophysiology was mentioned by other researchers [48–50]. It is known that DPP4 inactivates the incretin hormones GLP-1 and GIP. These hormones are secreted in intestine after a meal and promote glucose-dependent insulin secretion by pancreatic β-cells [30–32]. DPP4 is involved in immune cell-mediated modulation of inflammation and β-cells destruction. Therefore, as is mentioned in the Introduction, DPP4 inhibitors prolong lifetime of GLP-1 and GIP hormones, regulate glucose level and the functioning of β-cells by increasing their activity [33]. DPP4 inhibitors reduce insulin dependence, improve β-cells function and attenuate autoimmunity. The review [51] summarizes the data on the role of DPP4 inhibitors in the potential delay of T1DM progression.

However, the medical scientific literature-underlines that the currently applied in T2DM antidiabetic medicines based on DPP4 inhibitors are not extensively used in T1DM.

Based on the obtained in the present work results concerning increased DPP4 activity in plasma of T1DM patients, we can certainly recommend to use the drugs based on DPP4 inhibitors which are used in T2DM, in the treatment of T1DM patients as well.

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The study is approved by the Ethics Committee of the Yerevan State Medical University after Mkhitar Heratsi (IRB Expert Conclusion no. 1-10/2020). The informed consent was obtained from all participants studied (parental consent was obtained for all minors) in accordance with Good Clinical Practice standards and the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (WMA Declaration of Helsinki 2008).

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ՈՐՈՇ ՖԵՐՄԵՆՏՆԵՐԻ ԲՆՈՒԹԱԳՐՈՒՄԸ ՇԱՔԱՐԱՅԻՆ ԴԻԱԲԵՏՈՎ ՀԻՎԱՆԴՆԵՐԻ ԱՐՅԱՆ ՊԼԱԶՄԱՅՈՒՄ

Ադենոզինդեամինազ (ԱԴԱ), դիպեպտիդիլ պեպտիդազ 4 (ԴՊՊ4) և գլուտամինազ ֆերմենտները ներգրավված են 1-ին և 2-րդ տիպի շաքարախտի գործընթացներում: Նշված ֆերմենտները կարող են հանդիսանալ թիրախ պաթոլոգիայի կանխարգելման / բուժման համար: Օրգանիզմի աուտոիմուն պատասխան են առաջացնում սպիտակուցների հետտրանսլիացոն ձևափոխումները, որոնցից է ցիտրուլինացումը, երբ սպիտակուցի արգինինը վերածվում է ցիտրուլինի: Այս աշխատանքում համեմատվել են պայմանականորեն առողջ մարդկանց, 1-ին և 2-րդ տիպի շաքարախտով հիվանդների արյան պլազմայում ԱԴԱ-ի, ԴՊՊ4-ի և գլուտամինազի ակտիվությունները, սպիտակուցի ցիտրուլինացումը: Արյան նմուշներից ֆերմենտները անջատվել և մաքրվել են մինչև էլեկտրաֆորետիկ մաքրության: Գրանցվել է ԴՊՊ4-ի ակտիվության աճ հիվանդների պլազմայում, առավել զգալի 1-ին տիպի շաքարախտի դեպքում: Ստացված արդյունքը թույլ է տալիս առաջարկել 2-րդ տիպի շաքարախտի բուժման համար կիրառվող՝ ԴՊՊ4-ը ընկճող դեղամիջոցները օգտագործել նաև 1-ին տիպի շաքարախտի դեպքում:

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ХАРАКТЕРИСТИКИ НЕКОТОРЫХ ФЕРМЕНТОВ В ПЛАЗМЕ КРОВИ БОЛЬНЫХ ДИАБЕТОМ

Ферменты аденозиндезаминаза (АДА), дипептидилпептидаза 4 (ДПП4) и глутаминаза участвуют в развитии сахарного диабета 1-го и 2-го типа. Эти ферменты можно рассматривать в качестве мишеней для профилактики / лечения патологии. Аутоиммунная реакция организма вызывается посттрансляционной модификацией белков и цитруллинирование белков, при котором аргинин трансформируется в цитруллин, является одной из таких модификаций. В работе сравнены уровни активностей АДА, ДПП4, глутаминазы и белковое цитруллинирование в плазме крови относительно здоровых лиц и больных сахарным диабетом 1-го и 2-го типа. Ферменты из образцов крови очищены до электрофоретической гомогенности. В плазме больных зарегистрировано повышение активности ДПП4, более выраженное при сахарном диабете 1-го типа. Полученные результаты позволяют рекомендовать использование для лечения сахарного диабета 1-го типа ингибирующих ДПП4 лекарственных препаратов, применяемых в лечении сахарного диабета 2-го типа.