REVIVAL OF RADIOIMMUNOASSAY FOR DETERMINATION OF INSULIN AUTOANTIBODIES

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Insulin autoantibodies (IAA) represent the major serological marker of type 1 diabetes mellitus (T1D), the disease resulting from autoimmune damage to β-cells in the pancreatic islets. Testing for IAA is used in early and differential diagnosis of T1D, as well as to perform screening for this disorder. The best foreign diagnostic labs perform IAA tests using different radioimmunoassay (RIA) formats. The RIA performance characteristics, i. e. diagnostic sensitivity (DSe), diagnostic specificity (DSp), and diagnostic accuracy (DA), are on average equal to 44%, 100%, and 81%, respectively. Unfortunately, in Russia RIA has not been used to determine IAA for a long time. All Russian labs use the enzyme-linked immunoassay (ELISA)-based test systems for this purpose. DSe, DSp, and DA of ELISA systems are on average 24%, 87%, and 62%, respectively, i.e. considerably lower compared to RIA systems. Our study aimed to reproduce IAA RIA in the diagnostic lab of the RCCH. The method is based on IAA competitive binding to insulin and ^{125}I-labeled insulin. Serum samples from patients with new onset T1D and patients without diabetes were tested for IAA. DSe, DSp, and DA were 43%, 100%, and 73%, respectively. Thus, performance characteristics of the reproduced IAA RIA are close to those of RIAs used in foreign labs and are significantly superior to the characteristics of ELISA-based tests.

Keywords: insulin autoantibodies, type 1 diabetes mellitus, radioimmunoassay, diagnostic sensitivity, diagnostic specificity, diagnostic accuracy

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Compliance with ethical standards: the study was conducted in accordance with the principles of the Declaration of Helsinki (1964) and further amendments.

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РЕАНИМАЦИЯ РАДИОИММУНОЛОГИЧЕСКОГО МЕТОДА ОПРЕДЕЛЕНИЯ АУТОАНТИТЕЛ К ИНСУЛИНУ

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Аутоантитела к инсулину (insulin autoantibodies, IAA) — один из главных серологических маркеров сахарного диабета 1-го типа (СД1) — заболевания, обусловленного аутоиммунным разрушением β-клеток в островках поджелудочной железы. Тестирование на IAA используют в ранней и дифференциальной диагностике СД1 и при скрининге на это заболевание. Лучшие зарубежные клинико-диагностические лаборатории (КДЛ) тестируют IAA с помощью разных вариантов радиоиммунологического анализа (РИА). Операционные параметры РИА — диагностическая чувствительность (ДЧ), диагностическая специфичность (ДС) и диагностическая точность (ДТ) — в среднем составляют, соответственно, 44%, 100% и 81%. К сожалению, в России РИА уже давно не применяют для определения IAA. Все российские КДЛ с этой целью используют тест-системы, основанные на иммуноферментном анализе (ИФА). У этих тест-систем ДЧ, ДС и ДТ в среднем составляют, соответственно, 24%, 87% и 62%, т. е. существенно ниже, чем у тест-систем РИА. Целью нашей работы было воспроизвести метод РИА IAA в КДЛ РДКБ. Метод основан на конкурентном связывании IAA с инсулином и инсулином, меченным ^{125}I. Тестировали IAA в образцах сывороток пациентов с впервые выявленным СД1 и пациентов без этого заболевания. ДЧ, ДС и ДТ составили, соответственно, 43%, 100% и 73%. Таким образом, операционные параметры воспроизведенного нами метода РИА IAA приближаются к параметрам методов РИА, применяемых в зарубежных КДЛ, и существенно превосходят параметры метода ИФА.

Ключевые слова: аутоантитела к инсулину, сахарный диабет 1-го типа, радиоиммунологический анализ, диагностическая чувствительность, диагностическая специфичность, диагностическая точность

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Соблюдение этических стандартов: исследование проведено в соответствии с принципами Хельсинкской декларации (1964 г.) и ее дальнейшими поправками.

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Type 1 diabetes mellitus (T1D) results from the autoimmune damage to β-cells in the pancreatic islets. Destruction of β-cells leads to insulin deficiency and, consequently, to hyperglycemia and other severe metabolic disorders. All T1D patients need lifelong insulin therapy. T1D affects mostly children and adolescents. There is a hereditary risk of T1D: close relatives of patients have approximately 40 times higher risk of the disease [1].

T1D is characterized by latent preclinical stage (PS), in which the gradual β-cell destruction takes place [2]. PS lasts months to years and ends when the population of β-cells is reduced by 70–80%. At this moment absolute insulin deficiency, hyperglycemia, and its symptoms emerge: the T1D onset occurs and the clinical stage of the disease begins. Approximately 50% of patients develop an acute T1D complication at the onset: diabetic ketoacidosis leading to severe neurocognitive disorders and eventually to death. The delayed insulin prescription is the main cause of ketoacidosis.

The idea that T1D is an autoimmune disease had erased by early 1980s. By that time it had been shown that the majority of T1D patients carry serum autoantibodies (autoAB) binding islet cell structures on the cryostat sections of the pancreas [3]. Such autoAb were named islet cell antibodies (ICA). It was clear that ICA bind to some cytoplasmic antigens of β-cells, the potential autoimmune response targets. The most likely candidate for such antigens seemed to be insulin, the main product of β-cells. This hypothesis was confirmed in 1983 by the group of the US researchers led by Jerry Palmer [4]. Palmer and his colleagues found IAA in patients with the new-onset T1D never treated by insulin, and in some healthy relatives of T1D patients by RIA.

Later, autoABs against other β-cell antigens were discovered, specifically the glutamic acid decarboxylase antibodies (GADA), islet antigen-2 antibodies (IA-2A), and zinc transporter 8 antibodies (ZnT8A) [5]. AutoABs do not play any essential role in destruction of β-cells, but serve its highly specific laboratory markers.

Testing for autoABs is used for:

– early diagnosis of T1D in the PS;

– confirmation of the T1D diagnosis when the clinical picture is confusing;

– differential diagnosis between T1D and other DM types and variants;

– screening for the T1D PS in persons at risk (for example, among the first-degree relatives) and in the population.

The latter task is of special importance for two reasons. First, the detection of the β-cell destruction markers suggests high probability of T1D onset and allows the patients and their parents to get ready. It also allows physicians to timely prescribe insulin therapy and prevent ketoacidosis and its sequelae. Second, screening reveals the patients having indications for drug prevention of T1D involving the use of the drug suppressing the anti-β-cell immune response, for example teplizumab [6]. The screening programs have been conducted for many years in European countries, the USA, Canada, Australia, and Israel [7], and in the end of 2024 such a program was launched in Russia, in the Endocrinology Research Center [8]. The tests for autoABs represent the main screening tool, and the central place is occupied by the test for IAA, since this autoAB emerges as early as in the beginning of the PS and serves as the earliest indicator of the anti-β-cell immune response [9].

Various methods are used for IAA testing in different labs. The most common ones are RIA, LIPS (Luciferase Immunoprecipitation System) assay; electrochemiluminescence (ECL) analysis; ELISA and CLIA (chemiluminescent immunoassay). Performance characteristics of these methods, diagnostic sensitivity (DSe), diagnostic specificity (DSp), and diagnostic accuracy (DA), differ considerably. Comparative assessment of different IAA tests is periodically conducted as part of the international Islet Autoantibody Standardization Program (IASP) [10]. The participating labs receive the sets of sera from patients with new-onset T1D and from healthy blood donors; each lab performs testing of all sera for IAA by its own method. The results of two IASP rounds conducted in 2018 and 2020 are provided in Table 1.

As can be seen, RIA yields the best DSe and DSp, along with the maximum DA; LIPS assay ranks second in DA, ELISA ranks fourth, and CLIA shows no DA (AUC < 0.5). The ELISA and CLIA unsatisfactory characteristics are explained by the fact that in these methods an antigen (insulin) is absorbed on the solid phase (plastic or magnetic particles), which leads to disruption of its conformation and shielding of antigenic determinants.

Unfortunately, absolutely all Russian labs use the commercially available ELISA systems for IAA testing. The operating parameters of those are even worse than that of ELISA systems represented in the IASP. For example, in the widely used Orgentec Anti-Insulin kit (Orgentec Diagnostika GmbH, REF ORG520, Germany) DSe = 4%, DSp = 95.6%, DA = 50%, i.e. its results are of no clinical significance [11]. Recently, the Maglumi IAA CLIA system (Shenzhen New Industries Biomedical Engineering Co., Ltd; China) became available on the Russian market, but the system user manual contains no data on its performance characteristics [12].

Thus, in our country there is a need to develop and introduce reliable, informative test system for IAA determination. In this regard, the Russian Children's Clinical Hospital diagnostic lab attempted to reproduce classical RIA IAA.

METHODS

Study overview

Serum samples from the patients with the maximum and minimum likelihood of being IAA carriers, i.e. patients with

Table 1. Operational parameters of various IAA tests based on the IASP data [7]

Method	DSe, %		DSp, %		AUC		DA, %		N_{CDL}
	Me	IQR	Me	IQR	Me	IQR	Me	IQR	
RIA	44.0	20–56	100.0	99–100	0.811	0.73–0.835	81.1	73–83.5	13
LIPS	46.0	40–51	98.9	97–99	0.804	0.784–0.842	80.4	78.4–84.2	11
ECL	53.0	16–58	97.2	92–99	0.774	0.606–0.824	77.4	60.6–82.4	10
ELISA*	24.0	24–30	87.3	83–90	0.624	0.616–0.629	62.4	61.6–62.9	6
CLIA	11.0	9–14	66.1	56–76	0.254	0.243–0.265	25.4	24.3–26.5	2

Note: AUC — area under receiver operating curve; N_{LAB} — number of participating labs; Me — median; IQR — interquartile range.* — all labs used home-made test systems (commercially available systems were not used).

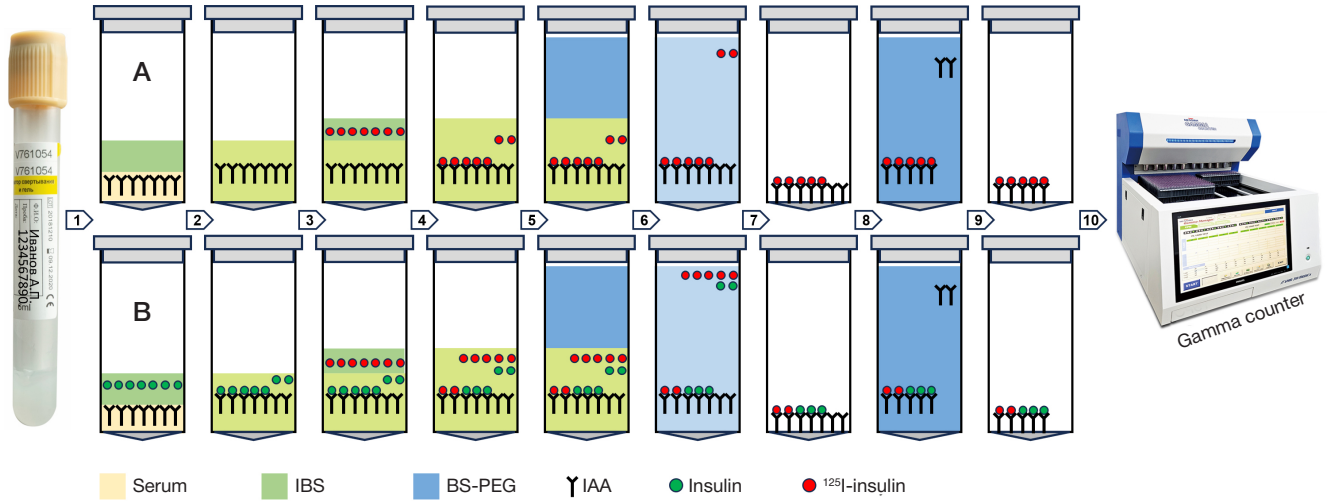

Fig. 1. RIA IAA procedure 1. Serum samples (75 µL) were poured into two series of 1.7 mL Eppendorf conical tubes (Costar 3207, Corning). A total of 75 µL of the 0.23M incubation buffer solution (IBS), pH 7.4 with the following composition were added to each A series tube: NaH_2PO_4 (Sigma-Aldrich, REF S-0751) 0.014M; Na_2HPO_4 (Panreac, REF 141677) 0.067M; NaCl (Sigma-Aldrich, REF S-9625) 0.15M; bovine serum albumin (CDH, REF TC1546) 0.05%; Twin-20 (Panreac, REF 162312) 0.05%. A total of 75 µL of the IBS with the recombinant human insulin (Insulin Reference Standard, Eli Lilly, USA) at a concentration of 9×10^{-3} U/mL were added to each B series tube. **2**. Test tubes of both series were vortexed with a vortex mixer and incubated for 30 min on the на ELMI-ST3 orbital shaker (Elmi, Latvia) with the platform rotation speed 250 rpm at room temperature. IAA bound to insulin during incubation. **3**. A total of 100 µL of IBS with the recombinant human insulin labeled with the ^{125}I (^{125}I-insulin) at a concentration of 7.5×10^{-6} U/mL were added to each tube of both series. Furthermore, 100 µL of IBS with the ^{125}I-insulin were added to each of two tubes to calculate total radioactivity. The ^{125}I-insulin preparation was produced in the Institute of Bioorganic Chemistry by monoiodination of insulin based on tyrosine A14 using chloramine-T as an oxidizing agent, purified by gel filtration of the column with Sephadex G-15. Iodination involved the use of sodium iodide (^{125}I) (ISOTOPE, RF). Finally, we obtained a stabilized ^{125}I-insulin preparation with the following radiochemical charateristics: total activity — 352 kBq, specific activity — 58 TBq/mmol, radiochemical purity — 92%. **4**. All the test tubes were sealed and incubated for 7 days in a refrigerator at +4 °C. During incubation the serum IAA bound to insulin and ^{125}I-insulin, and the equilibrium between IAA binding with the labeled and non-labeled ligands established. **5**. A total of 500 µL of the buffer solution (pH 8.6) containing polyethyleneglycol (BS-PEG) with the following composition added to all tubes, except those for total activity calculation : Tris 0.05M (Sigma-Aldrich REF 7-9 Tris base T13,78); PEG-8000 (Polyethylenglycol 8000 BioChemica AppliChem REF A2204.0500) 14%. BS-PEG was previously cooled to 0 °C. **6**, **7**. The tubes were vortexed with a vortex mixer and centriguged in the Beckman G-2-21 centrifuge at 2000 g for 30 min at +4 °C. The supernatant was removed with an aspirator. As a result, a precipitate was obtained containing the IAA complexes with the labeled and unlabeled insulin, as well as IAA that did not bind to insulin. **8**, **9**. A total of 1000 µL of BS-PEG with the 11% PEG-8000 previously cooled to 0 °C were added to all tubes, except those for TR calculation. The tubes were vortexed with a vortex mixer and centriguged in the Beckman G-2-21 centrifuge at 2000 g for 30 min at +4 °C. The supernatant was removed with an aspirator. As a result, a precipitate was obtained containing the IAA complexes with the labeled and unlabeled insulin. **10**. Radioactivity was measured in all the tubes (including those for total activity calculation) with the Wizard γ-spectrometer (PerkinElmer, USA) at a measuring time of 1 min

new-onset T1D (T1D group) and patients having no such disorder (group C, control), were tested for IAA. The study was conducted in January—February 2024 in the Russian Children's Clinical Hospital and Institute of Bioorganic Chemistry.

Description of patient groups

T1D group (n = 21)
M : F = 8 : 13 (38% : 62%); age 1.1–17.9 years (median age 10.1 years, 95% confidence interval for the median 4.2–12.1 years).

Inclusion criteria: age 0–18 years; diagnosis “type 1 diabetes mellitus, new-onset” (ICD-10 E10.1 or E10.9); T1D duration from the date of the diagnosis to the date of blood sample collection ≤ 3 months; presence of at least two autoAB types out of the following: ICA, GADA, IA-2A, ZnT8A.

Group C (n = 19)
M : F = 12 : 7 (63% : 37%); age 2.5–46.9 years (median age 13.3 years, 95% confidence interval for the median 10.2–16.6 years).

Inclusion criteria for the group: any age, any sex; the patient is generally healthy (ICD-10 Z00) or diagnosed with one of the follwing: type 2 diabetes mellitus (ICD-10 E11), other specified diabetes mellitus forms, including various monogenic DM forms (ICD-10 E13, E13.9), obesity (ICD-10 E66), unspecified DM (ICD-10 E14, E14.9), Cushing syndrome (ICD-10 E24), pituitary-dependent Cushing's disease (ICD-10 E24.0), Turner syndrome (ICD-10 Q96); patient was never diagnosed with T1D; patient never received insulin injections; no GADA, IA-2A, ZnT8A in the patient’s serum.

IAA testing method

Competitive radioimmunoassay (RIA) by J.Palmer, et al. was reproduced [4]. The details of the RIA procedures are provided in Fig. 1.

Calculation of IAA concentration

Stages of calculating the IAA concentration:

– for each serum sample radioactivity (RA), counts per minute (cpm) was registered in the test tube without unlabeled insulin (RAA) and in the tube with unlabeled insulin (RA_B);

– an average total RA (TRA) for two test tubes was calculated. It was equal to 5000 cpm;

– for each serum sample the ^{125}I-insulin binding percent (BP) in the test tube without unlabeled insulin (BP_A) and in the tube with unlabeled insulin (BP_B) was calculated using the formulas: $BP_A = RA_A : TR_A$ and $BP_B = RA_B : TR_A$;

– for each serum sample the difference between the binding percentage values (D, delta) was calculated: $D = BP_A – BP_B$;

– for each serum sample the IAA concentration (C_{IAA}) was calculated:

$$C_{IAA} = (D \times 10{,}000) : 100 \text{ (nU/mL)}.$$

Methods for statistical processing of the results and calculation of the test performance characteristics

To detect outliers in the T1D group and group C, the left-tailed and right-tailed Grubbs’s tests were used, respectively. The method by

Table 2. Results of measuring C_{IAA} in serum samples

T1D group					Group C				
№	Patient			CIAA, nU/mL	№	Patient			CIAA, nU/mL
	Sex	Age	Diagnosis (ICD-10)			Sex	Age	Diagnosis (ICD-10)	
1	m	7.9	n-oT1D (E10.1)	29	22	m	42.0	Healthy (Z00)	6
2	f	14.0	n-oT1D (E10.1)	11	23	m	46.9	MGD MODY2 (E13)	37
3	m	10.1	n-oT1D (E10.1)	102	24	m	40.9	T2D (E11)	15
4	m	4.0	n-oT1D (E10.1)	17	25	m	15.5	T2D (E11)	6
5	f	12.3	n-oT1D (E10.1)	471	26	m	7.6	Healthy (Z00)	24
6	f	3.0	n-oT1D (E10.1)	20	27	f	7.0	Healthy (Z00)	10
7	f	5.2	n-oT1D (E10.1)	24	28	f	10.6	T2D (E11)	172
8	m	13.7	n-oT1D (E10.1)	164	29	f	27.7	UDM (E14)	24
9	f	12.2	n-oT1D (E10.1)	17	30	m	15.4	Healthy (Z00)	29
10	f	4.1	n-oT1D (E10.1)	193	31	f	15.1	T2D (E11. E66)	33
11	m	11.0	n-oT1D (E10.1)	58	32	m	11.8	Healthy (Z00)	12
12	m	13.8	n-oT1D (E10.1)	25	33	m	16.8	UDM (E14)	15
13	m	12.0	n-oT1D (E10.1)	1	34	m	2.5	DMster (E13.9)	17
14	f	11.3	n-oT1D (E10.1)	19	35	f	16.5	T2D (E11. Q96.3)	22
15	f	3.4	n-oT1D (E10.1)	16	36	f	13.3	Obesity(E66)	9
16	f	11.7	n-oT1D (E10.1)	41	37	m	2.8	DMster (E13.9)	20
17	f	8.0	n-oT1D (E10.1)	21	38	m	10.6	DMster (E13.9)	45
18	m	2.6	n-oT1D (E10.1)	256	39	m	8.8	Healthy (Z00)	14
19	f	17.9	n-oT1D (E10.1)	1047	40	f	12.8	T2D (E11. E24.0)	31
20	f	4.2	n-oT1D (E10.1)	83					
21	f	1.1	n-oT1D (E10.1)	73					

Note: № — ordinal number of the serum sample; NOT1D — new-onset type 1 diabetes mellitus; MGD MODY2 — monogenic diabetes mellitus, MODY2 variant (mutation in the hexokinase gene); T2D — type 2 diabetes mellitus; UDM — diabetes mellitus unspecified; DMster — diabetes mellitus caused by taking glucocorticosteroids. The result classified as an outlier is highlighted in *red*

DeLong et al. was used to plot the operating characteristic curve [13], and the T1D prevalence was considered to be 0.123% [14]. DSe, DSp, and DA were calculated based on the AUC. The MedCalc medical statistical software was used for calculations [15].

RESULTS

The C_{IAA} measurement results are provided in Table 2.

One result (of the serum sample No. 28) was classified as an outlier. Thus, statistical analysis included the results of C_{IAA} measurement in 21 serum samples of the T1D group and 18 serum samples of group C. In the T1D group, the C_{IAA} values varied between 1 and 1047 nU/mL, in group C these varied between 6 and 45 nU/mL. When plotting the test operating characteristic curve, the MedCalc software automatically selected the C_{IAA} value exceeding 45 nU/mL as a test positivity criterion (presence of IAA in the serum sample). DSe, DSp, and DA of the test calculated based on the AUC using the above criterion were 42.9%, 100%, and 72.8% with the 95% confidence intervals 21.8–66%, 81.5–100%, and 56.1–85.7%, respectively (Fig. 2).

DISCUSSION

According to IASP data, the median DSe, DSp, and DA of various RIA IAA methods are 44%, 100%, and 81.1 respectively (Table 1). DSe of our method (42.9%) is very close to the median DSe of the IASP RIA, and DSp matches the median IASP DSp, but does not fall into its interquartile range. However, DA of our method (72.8%) turned out to be significantly lower compared to the IASP RIA DA and did not fall into its interquartile range.

We explain discrepancy between the result of our RIA method and the RIA results obtained in other IASP labs (the lower DA of our method) by two factors:

– very small number of individuals in both groups;

– the incubation buffer solution (IBS) used by J. Palmer, et al. [4] contained bovine γ-globulin in a concentration of 0.025% that blocked nonspecific insulin binding with the non-IAA immunoglobulins in the serum samples. There was no such reagent in our IBS.

It should be noted that the performance characteristics of our IAA testing methods turned out to be better than that of the ELISA and CLIA methods represented in IASP, and were significantly superior to performance characteristics of the abovementioned Orgentec Anti-Insulin test system popular in Russian labs.

CONCLUSIONS

Ultimately, we regard our results as successful, since the performance characteristics of our method turned out to be much better than that of the ELISA and CLIA methods. We believe that after appropriate adjustment our RIA IAA test can be used for scientific purposes and in clinical practice. Unfortunately, it is currently impossible to use this method in the diagnostic lab of the Russian Children's Clinical Hospital

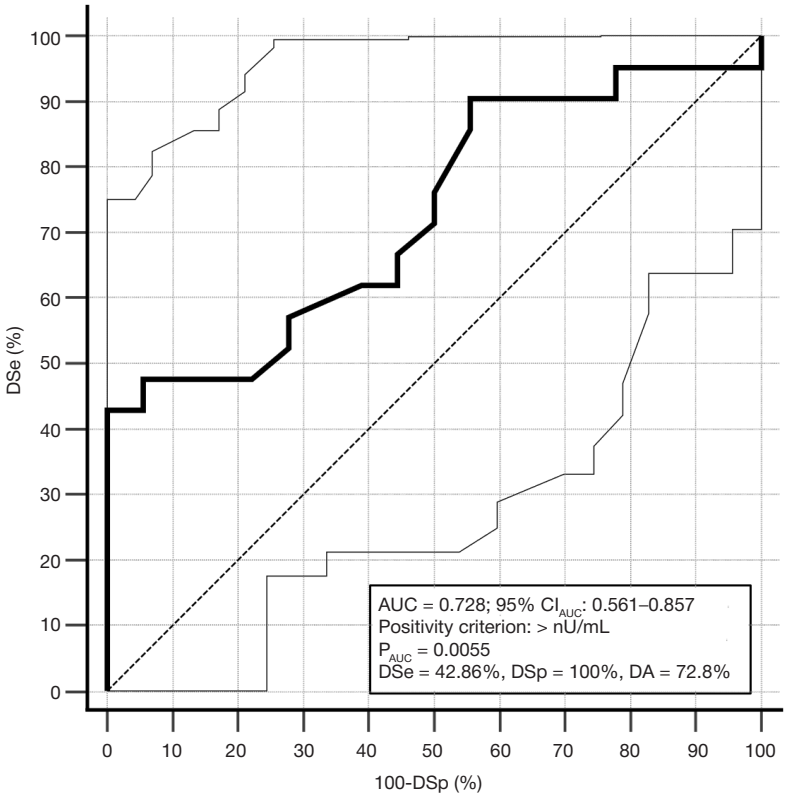

Fig. 2. Receiver Operating Curve of the IAA test. *Dashed curve* — the line bounding the AUC of 0.5. *Solid curve* — the test receiver operating characteristic curve. *Dotted curves* — borders of the 95% confidence interval (95%CI$_{AUC}$) for the operating characteristic curve. P_{AUC} — probability of significance of the null hypothesis about the lack of difference between AUC 0.5 and AUC of the test

due to two factors: lack of the gamma counter; lack of facilities for radionuclide handling licensed by Rospotrebnadzor and Roszdravnadzor. However, we hope that over time we will manage to tune RIA IAA the Russian diabetologic science and practice are in need of in the Russian Children's Clinical Hospital, branch of the Pirogov University.

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