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Evaluation of the Concentration of Bioenzyme Glutamic Acid Decarboxylase in the Sera of Type 1 and Type 2 Diabetic Patients

Conflict of interest: nothing to declare.
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Abstract

Introduction. Currently, great attention is paid to clinical use of biomarkers to diagnose various diseases. Biomarkers are understood to be clinical laboratory tests, whose findings are considered to be characteristic of a particular form of pathology. Their use in the early stages of the disease significantly improves the effectiveness of both diagnosis and treatment. One such biomarker is the test for glutamate dehydrogenase (GDH) activity in blood serum. The interest in its study is determined by the fact that GDH is an enzyme involved in regulating many vital metabolic processes. Therefore, numerous studies are currently being conducted to determine not only levels of the enzyme itself in biological fluids, but also those of its antibodies.
Purpose. To evaluate the prevalence of GAD concentration in patients with type 1 and type 2 diabetes and interpret the results obtained.
Materials and methods. Blood samples were collected from males only, 30 people with T1D diabetes,30 blood samples from people with T2D diabetes, and 24 people without diabetes in Basra Governorate. Serum samples were examined for the presence of GAD by sandwich ELISA.
Results. The results indicated a significant decrease in the concentrations of GAD in the serum of male patients with T1D and T2D diabetes at a rate of (3.41±0.43 ng/ml (mcg/l) and 3.43±0.34 ng/ml (mcg/l)), respectively. In the age groups of T1D diabetes patients, we found a slight variation in the concentrations of GAD for people with the category (≥15) 3.29±0.51 ng/ml (mcg/l) compared to the age group (<15) 3.53±0.73 ng/ml (mcg/l), the age groups of T2D patients (≤45) reached 2.63±0.51 ng/ml (mcg/l), and the second age group (>45) recorded a significant increase the first, which is as the concentrations of GAD reached 4.06±0.41 ng/ml (mcg/l).
Conclusion. The decrease in serum GAD levels observed in patients with diabetes mellitus, reflecting a deficiency of the enzyme required for vital metabolic processes, may affect the production of gamma-aminobutyric acid, which is necessary for maintaining the function of pancreatic beta cells.
Keywords: type 1 and 2 diabetes, GAD, biomarkers, bioenzyme, ELISA

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Возрастные особенности содержания глутаматдекарбоксилазы в сыворотке крови пациентов (мужчин) с сахарным диабетом 1-го и 2-го типа

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Резюме

Введение. В настоящее время большое внимание уделяется использованию в клинической практике биомаркеров различных заболеваний. Под биомаркерами принято понимать клинико-лабораторные тесты, изменение показателей которых оказывается весьма характерным для той или иной формы патологии. Их применение на ранних стадиях заболевания существенно повышает эффективность диагностики и лечения. Одним из биомаркеров является тест определения активности глутаматдегидрогеназы (ГДК) сыворотки крови. Интерес к его исследованию определяется тем, что ГДК является ферментом, регулирующим многие жизненно важные метаболические процессы. Поэтому в настоящее время ведутся многочисленные исследования не только содержания в биологических жидкостях самого фермента, но и антител к нему.
Цель. Провести анализ содержания ГДК в сыворотке крови пациентов с сахарным диабетом 1-го и 2-го типа и интерпретировать полученные результаты.
Материалы и методы. Исследованы образцы крови у лиц мужского пола разного возраста – у 30 пациентов с сахарным диабетом 1-го типа, у 30 пациентов с сахарным диабетом 2-го типа и у 24 лиц, не страдающих диабетом, из провинции Басра. Образцы сыворотки крови были исследованы на наличие ГДК «сэндвич»-методом иммуноферментного анализа (ИФА).
Результаты. Полученные результаты свидетельствуют о достоверном снижении уровня ГДК в сыворотке крови мужчин с СД 1-го и 2-го типа. Содержание ГДК в сыворотке крови 30 пациентов с СД 2-го типа составило 3,43±0,34 нг/мл (мкг/л) при уровне его в контрольной группе (по результатам исследования 14 проб стандартных образцов) 3,9±0,52 нг/мл (мкг/л) ($p \leq 0,05$). У пациентов с СД 1-го типа выявлено незначительное изменение концентрации ГДК в возрастной группе лиц 15 лет и старше: 3,29±0,51 нг/мл (мкг/л). У пациентов с СД 2-го типа возрастной группы 45 лет и менее (≤45 лет) уровень ГДК составил 2,63±0,51 нг/мл (мкг/л). В возрастной группе пациентов старше 45 лет (>45 лет) было констатировано его увеличение по сравнению с таковым в возрастной группе 45 лет и менее: концентрация ГДК в ней достигла значения 4,06±0,41 нг/мл (мкг/л).

Заключение. Отмеченное у пациентов с сахарным диабетом снижение концентрации ГДК в сыворотке крови, отражающее недостаток фермента, требуемого для обеспечения жизненно важных метаболических процессов, может повлиять на выработку гамма-аминомасляной кислоты, необходимой для поддержания функции бета-клеток поджелудочной железы.
Ключевые слова: сахарный диабет 1-го и 2-го типа, глутатиондегидрогеназа (ГДК), биомаркеры, иммуноферментный анализ (ИФА)

■ INTRODUCTION

According to the International Diabetes Federation (IDF), the global report estimates that adults with diabetes are around 537 million. The death rate due to diabetes is 6.7 million, and the cost of care and treatment of the disease is estimated at 966 billion US dollars [1]. It is worth noting that diabetes mellitus (DM) is one of the silent killer diseases worldwide. Abnormally high blood sugar levels characterize this metabolic disorder due to the loss of beta cells in the pancreatic islets. Consequently, it loses its ability to produce and secrete insulin, causing serious dysfunction in the function of target tissues [2–4].

Glutamic acid decarboxylase (GAD) is an important key enzyme that catalyzes the irreversible alpha-decarboxylation of glutamate to produce the neurotransmitter gamma-aminobutyric acid (GABA). This enzymatic reaction is a promising method for the synthesis of GABA. It is a non-protein amino acid that reduces the amount of communication to and from nerves [5]. Many studies and research have proven that systemic treatment with GABA acid prevents or alleviates T1D diabetes by suppressing the autoimmune response and stimulating pancreatic beta cells by increasing insulin secretion. In addition, GABA acid prevents programmed cell death (apoptosis) and stimulates their regeneration. It has an anti-inflammatory effect and suppresses autoimmunity in pancreatic beta cells. However, it is not clear how GABA mediates these effects [6].

Previous clinical trials of interventional therapies for T1D were not able to maintain insulin production in the long term. This led to the belief that combination therapies that control autoimmunity are necessary for effective intervention in T1D are needed [7, 8].

Diabetes mellitus (T1D) leads to serious complications despite intensive treatment. In order for the disease to be more moderate, the remaining beta cell function must be preserved. This prevents complications and increases the patient's survival. It is worth mentioning in the same context that immune interventions have limited effects and may have negative risks. Therefore, one of the promising experiments is injecting the lymph nodes with the GAD enzyme with oral vitamin D [9, 10].

■ PURPOSE OF THE STUDY

To evaluate the prevalence of GAD concentration in patients with type 1 and type 2 diabetes and interpret the results obtained.

■ MATERIALS AND METHODS

Study Design and Setting

The study sample was carefully selected to ensure a diverse representation of the current study community. It is worth noting that ethical insurances were taken according to the contexts followed by the health institution in Basrah Governorate. This was during the period from mid-December 2023 to late May 2024.

Sample Selection

Blood samples were collected from males only, 30 people with T1D diabetes who were less than 30 years old. 30 blood samples were collected from people with T2D diabetes who were more than 30 years old. Also, 24 people without diabetes were collected, 10 of whom were less than 30 years old and 14 of whom were more than 30 years old. The patients attended Al-Shifa Teaching Hospital, the Endocrinology and Diabetes Center at Al-Faihaa Hospital, and the Endocrinology Center at Al-Mawani Hospital in Basra Governorate. Specialist doctors previously diagnosed diabetic patients. As for healthy people, their lack of diabetes was determined through verbal questions directed to them, their parents, or their companions. Regarding the age information of all study samples, it was done through direct oral questioning as before. Thus, the representation of the study samples is balanced to ensure a clear view of the central tendency of these samples.

Blood samples were collected at each collection during the above period. Then, serum was separated from all samples (each 3 ml). Then, serum was isolated in Eppendorf tubes. The samples were tested for the presence of GAD enzyme as a biomarker by Sandwich ELISA from BT LAB, China, according to the instructions of the diagnostic kit manufacturer.

Statistical Analysis

Statistical Package of Social Sciences (SPSS) software was used for statistical analysis. Measured parameter values were given as mean±SE. For group comparisons, Mann – Whitney Test and T-Test were used to analyze the results, When the p-value was less than 0.05, the results were considered statistically significant.

■ RESULTS

Estimation of GAD Enzyme Concentration in T1D Diabetic Patients

The current study showed a significant decrease in GAD enzyme concentrations in the serum of 30 T1D diabetic male patients when compared to standard samples (non-diabetic). The arithmetic mean (SD) and SE for T1D patients were 3.41±0.43 ng/ml, while the concentrations in the serum of the standard sample were the highest, reaching 5.36±1.57 ng/ml. No statistically significant difference was observed in GAD concentration between T1D diabetic patients and the standard sample at $P \leq 0.05$ (Table 1).

We divide the age groups of T1D diabetes patients, the results showed a slight difference in the concentrations of GAD enzyme for people with the age group less than or equal to 15 years (≥15) and their number is 16 patients, which is 3.29±0.51 ng/ml. In comparison with the concentrations of people with this disease in the age group greater than 15 years (<15) and their number is 14 patients, their concentration was 3.53±0.73 ng/ml. Note that the highest age group is 30 years, and the lowest age group is 3 years. The results of the statistical analysis showed that there is no statistically significant difference

Table 1
GAD enzyme concentration in sera of T1D diabetic patients and standard samples

Probability P	CI 95%		Standard sample (10 samples) Mean ± Standard error ng/ml	CI 95%		Pathological sample (30 samples) Arithmetic mean ± standard error ng/ml	T1D patients
	Highest value	Less value		Highest value	Less value		
P≤0.05	18.84	1.81	5.36 ± 1.57	11.79	0	3.41 ±0.43	Enzyme GAD

Table 2
GAD enzyme according to the distribution of T1D patient samples according to age groups

Probability P	95% CI		ELIZA Test Results Mean±SE ng/ml	No. (30)	Age group (years)
	Highest value	Less value			
P≤0.05	6.07	0	3.29±0.512	16	year ≥15
	11.79	0	3.53 ±0.73	14	year <15

in the concentration of GAD between people with T1D diabetes in the two age groups at P≤0.05 (Table 2).

Measuring GAD Enzyme Concentration in T2D Diabetic Patients

The concentration of GAD enzyme was estimated in blood serum samples of 30 T2D diabetic patients (males). A slight variation was observed in their GAD enzyme concentration with its concentration in the standard sample (non-diabetic) of 14 individuals. The arithmetic mean and standard error of GAD enzyme concentrations in the serum of T2D patients was 3.43±0.34 ng/ml. In contrast, its concentration in the standard samples was 3.9±0.52 ng/ml. The results of the statistical analysis showed that there was no statistically significant difference in GAD concentration between individuals with T2D diabetes and the standard sample at a probability level of P≤0.05 (Table 3).

As for the age groups of T2D patients, who numbered 30 patients, they were divided into two age groups. The first age group is less than or equal to 45 years (≤45), and their number is (12 patients). The arithmetic mean and standard error for this group was 2.63±0.517387 ng/ml. In contrast, the second age group recorded a significant increase over the first age group, which includes T2D diabetes patients who are over

Table 3
GAD enzyme concentration in sera of T2D diabetic patients and standard samples

Probability P	95% CI		Standard sample (14 samples) Mean ± Standard error ng/ml	95% CI		Pathological sample (30 samples) Arithmetic mean ± standard error ng/ml	T2D patients
	Highest value	Less value		Highest value	Less value		
P≤0.05	9.57	0.49	3.9±0.52	6.92	0	3.43±0.34	Enzyme GAD

Table 4
Shows the levels of GAD enzyme according to the distribution of T2D patient samples according to age groups

P probability	95% CI		ELIZA Test Results Mean ±Standard Error ng/ml	No. (30)	Age group (years)
	High value	Less value			
P≤0.05	6.69	0	2.63±0.51	12	≤45 year
	6.92	0.91	0.41±4.06	18	>45 year

Table 5
Shows a comparison of the results of GAD enzyme concentration in the serum of T1D and T2D diabetic patients

p	95% confidence limits		Pathological sample (30 samples) Arithmetic mean ± standard error ng/ml	Diabetic patients category
	High value	Less value		
P≤0.05	11.79	0	3.41 ±0.43	T1D
	6.92	0	3.43±0.34	T2D

45 years (>45), and their number is (18 patients). Their arithmetic mean and standard error was 4.06±0.41 ng/ml. The statistical analysis showed in its results that there is a statistically significant difference in the concentration of the GAD enzyme between people with T2D diabetes in the two age groups at a probability level of P≤0.05 (Table 4).

Results of GAD Enzyme Concentration in the Serum of T1D and T2D Diabetic Patients

Suppose the results of GAD enzyme concentration levels in the serum of T1D and T2D diabetic patients are compared. In that case, we notice a slight difference in the arithmetic mean and standard error for patients with the two types of diabetes. The arithmetic mean and standard error for T1D diabetes were 3.41±0.43165 ng/ml, which is the highest concentration. In contrast, the concentration of GAD enzyme in T2D diabetic patients was 3.431±0.348271 ng/ml, which is the lowest. The results of the statistical analysis showed that there was no statistically significant difference in GAD concentration between people with T1D and T2D diabetes at the probability level of P≤0.05 (Table 5).

■ DISCUSSION

The results of the current study showed a significant decrease in GAD enzyme in T1D patients compared to its normal concentrations that we observed in the standard sample group (non-diabetic). The GAD enzyme has been identified as an important autoantigen in the function of pancreatic beta cells. However, it is targeted by autoantibodies that work to weaken the pivotal function of this enzyme and inhibit its activity in insulin secretion. Pancreatic beta cells manufacture this enzyme, which enters into the process of synthesis of the amino acid GABA in beta cells. This acid is later stored in small vesicles in the cytoplasm until it is secreted. It is also secreted by circulating immune cells. It has been mentioned that it often has a suppressive effect on immune cells, preventing them from producing inflammatory cytokines through the GABA-A receptor, which is expressed

in T and B cells and some mononuclear cells [11]. It also has a role in regenerating the islets, especially in cases of diabetes, by maintaining or renewing the mass of beta cells [12, 13]. It has a role in secreting hormones and thus may increase the survival of beta cells. Most importantly, autoantibodies to the GAD enzyme that produces GABA are linked to the development of T1D diabetes. In it, the cell mass decreases or disappears, while in T2D diabetes, the function of beta cells is at risk. All of these events lead to an abnormal increase in blood sugar levels [14,15].

It is clear from the results of the current study that patients have something that contributes to achieving this decrease in the concentration of the GAD enzyme, which is the production of autoantibodies that, in turn, target the GAD enzyme. This is consistent with what was stated by Fahd AL-Mulla, 2023 and a group of researchers in a study conducted at the Dasman Diabetes Institute in Kuwait. The presence of autoantibodies in the peripheral blood and high blood sugar are the main features of type 1 diabetes. However, in contrast, approximately half of new cases of type 1 diabetes in adults are incorrectly diagnosed as type 2 diabetes T2D. This indicates and confirms the importance of testing for autoantibodies to distinguish T1D from other forms of diabetes [16, 17]. One of the most prominent evidence that the immune system contributes to the occurrence and development of the disease is the discovery of autoantibodies directed against pancreatic islets of Langerhans antigens. Specifically, beta cell antigens and one of these autoantibodies is the antibody directed at the enzyme glutamic acid decarboxylase (GAD), known as (anti-GAD IgG). It is found in 50% to 80% of T1D patients [18]. The enzyme GAD catalyzes the synthesis of gamma-aminobutyric acid (GABA), which is an important neurotransmitter in the central nervous system. This enzyme has two forms, GAD65 and GAD67, and they are known to be produced in the brain and pancreas in humans. However, the most prevalent and widespread is GAD65 in pancreatic beta cells [14]. It is worth noting here that antiGAD is likely the first autoantibody to be discovered clinically in the blood [19, 20]. Glutamic acid decarboxylase (GAD) significantly influences glucose metabolism and insulin secretion. It thus contributes to overall metabolic homeostasis. Dysfunction of GAD has been associated with metabolic disorders such as diabetes and obesity. Recent research has explored the complex pathways involved in clinical and laboratory research of GAD, identifying potential therapeutic targets for metabolic diseases. However, challenges and limitations still exist in current research on GAD. Further investigation and ongoing research are warranted [21, 22].

We noticed through the results of the ELISA test for the concentration levels of the GAD enzyme in the serum of T1D diabetic patients according to the ages of these patients for the two age groups less than or equal to 15 years and the second group for patients for ages greater than 15 years. Note that the least that addressed the value of benefiting from the presence of the GAD enzyme naturally in the peripheral blood of the human body as a self-antigen that triggers an autoimmune response of T cells and B cells that produce autoantibodies to this enzyme. Thus, these studies benefited from this sign as a diagnostic method, which is the presence of autoantibodies called GAD autoantibodies. People carrying these antibodies were considered to have type 1 diabetes T1D or latent diabetes mellitus LADA. Among these studies, they indicated the value of predictions of autoantibodies to the GAD enzyme (antiGAD65), which were well validated and suggested as biomarkers and early diagnostic indicators for the stages before the onset of clinical

symptoms of the disease [23, 24]. The results of our study also showed a difference in the concentration of the GAD enzyme in T2D patients with its concentration in the standard sample. Despite that, they suffer from T2D diabetes. Hence, we find it very important to assume that in these patients, the level of GAD is higher than its concentration in the standard sample, which may have led to a clear defect and deficiency in the synthesis of GABA, which is important for the health, reproduction and activity of beta cells, as we mentioned previously. Our hypothesis can be supported theoretically through what was mentioned in some recent studies. GABA is considered an anti-diabetic factor for T2D. It was noted that the low concentration has an anti-diabetic effect through its action on the reproduction of pancreatic beta cells [25]. Another study showed that GABA improves high blood sugar in male mice with fat-induced diabetes by reducing gluconeogenesis. However, this effect was not observed in their offspring [26].

■ CONCLUSION

The current study concluded that there is a relationship between the development of type 1 and type 2 diabetes and GAD enzyme levels. This has an impact in view of many studies in addition to our current study, which confirmed the imbalance in the normal levels required for the vital processes associated with it, especially its entry as an important factor in the formation of gamma-aminobutyric acid to maintain pancreatic beta cells. From this standpoint, it is worth noting the importance of taking it also from the molecular, experimental and therapeutic point of view in an intensive manner.

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