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Original Article / Özgün Araştırma

A Predictive Level of C-peptide for Glutamic Acid Decarboxylase Antibody Positivity in Autoimmune Diabetes

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Abstract

Objective: Diabetes mellitus (DM) is one of the most prevalent chronic diseases and is considered a universal health issue. This study aimed to establish a C-peptide cut-off level to predict glutamic acid decarboxylase antibody 65 (GADA) positivity in autoimmune diabetes.

Methods: Designed as a retrospective methodological study, the study reviewed diabetic patients aged over 16 years who presented to adult internal medicine outpatient clinics between 2008 and 2022. The data were collected retrospectively from the hospital records. Patients were categorized into two groups according to GADA positivity, and their sensitivity and specificity were calculated for fasting C-peptide levels.

Results: GADA positivity was observed in 96 of a total of 343 patients. The group with antibody positivity was younger ($p < .001$), had lower C-peptide levels ($p < .001$) and higher HbA1c levels ($p = .03$). Thyroid antibody positivity was more common in this group ($p = .009$). Sensitivity was 80.2% and specificity was 72.5% for the optimal C-peptide level cut-off point of ≤ 1.35 ng/mL, which predicted GADA positivity.

Conclusion: GADA positivity was highly prevalent at a fasting C-peptide level cut-off point of ≤1.35 ng/mL. Hence, in clinical practice, GADA could be routinely examined in patients with a value below this level for accurate diagnosis and early initiation of treatment in autoimmune diabetes.

Keywords: Glutamic Acid Decarboxylase Antibody 65; C-peptide; Diabetes Mellitus; Autoimmune Diabetes

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Otoimmün Diyabette Glutamik Asit Dekarboksilaz Antikor Pozitifliği İçin Prediktif bir C-peptid Düzeyi

Öz

Amaç: Diabetes mellitus (DM) en yaygın kronik hastalıklardan biridir ve evrensel bir sağlık sorunu olarak kabul edilir. Bu çalışmada otoimmün diyabette glutamik asit dekarboksilaz antikoru 65 (GADA) pozitifliğini öngörmek için bir C-peptid kesim noktasının belirlenmesi amaçlandı.

Yöntemler: Retrospektif metodolojik bir çalışma olarak tasarlanan çalışmada, 2008-2022 yılları arasında erişkin dahiliye polikliniklerine başvuran 16 yaş üstü diyabetli hastalar incelendi. Veriler hastane kayıtlarından retrospektif olarak toplandı. Hastalar GADA pozitifliğine göre iki gruba ayrılarak açlık C-peptid düzeylerine göre duyarlılık ve özgüllükleri hesaplandı.

Bulgular: Toplam 343 hastanın 96'sında GADA pozitifliği gözlendi. Antikor pozitifliği olan grup daha gençti ($p < .001$), daha düşük C-peptit seviyelerine ($p < .001$) ve daha yüksek HbA1c seviyelerine ($p = .03$) sahipti. Bu grupta tiroid antikor pozitifliği daha yaygındı ($p = .009$). GADA pozitifliğini öngören optimum C-peptid düzeyi kesim noktası olan ≤1.35 ng/mL için duyarlılık %80,2, özgüllük ise %72,5 olarak bulundu.

Sonuç: Açlık C-peptid seviyesi ≤1.35 ng/mL kesim noktasında GADA pozitifliği oldukça yaygındı. Bu nedenle klinik pratikte, otoimmün diyabette doğru tanı ve tedaviye erken başlanması için bu düzeyin altındaki hastalarda GADA'nın rutin olarak incelenmesi önerilebilir.

Anahtar kelimeler: Glutamik Asit Dekarboksilaz Antikoru 65; C-peptid; Diabetes Mellitus; Otoimmün Diyabet.

INTRODUCTION

Type 1 diabetes (T1D) and type 2 diabetes (T2D) can present with different clinical manifestations. Both diabetes types and latent autoimmune diabetes in adults (LADA) may occur at any age[1]. Islet cell autoantibodies are very important for predicting T1D[2]. Over 90% of patients with T1D have antibodies against islet cells of the pancreas, one of which is glutamic acid decarboxylase antibody 65 (GADA). GADA positivity may also be observed in LADA[3]. Islet cell autoantibodies are very important for predicting diabetes and consequent requirement for insulin therapy[4].

C-peptide can be quantified and used to evaluate the pancreatic reserve[5]. C-peptide is produced in amounts equimolar to endogenous insulin. C-peptide levels have been shown to be associated with the type of diabetes and duration of disease[6]. Patients with T1D have low levels of C-peptide owing to low endogenous insulin and β-cell function. Patients with T2D have normal to high levels of C-peptide[7]. Guidelines of the American Association of Clinical Endocrinologists and the American College of Endocrinology suggested that examining insulin, C-peptide and autoantibodies in addition to the clinical presentation may help make accurate diagnosis for differentiating between T1D and T2D and initiate appropriate treatment[8].

This study aimed to determine a cut-off point for the C-peptide level that can predict GADA positivity for an accurate classification of diabetes and early initiation of correct treatment in clinical practice.

METHODS

Study design

Patients diagnosed with diabetes mellitus (DM) and >16 years of age who presented to the adult internal medicine outpatient clinics between October 2008 and January 2022 were retrospectively reviewed using the hospital's database. Patients with T1D and T2D whose C-peptide levels were measured at the time of diagnosis were included in the study. Patients

with gestational diabetes and diabetic patients under the age of 16 were excluded. This study was conducted retrospectively, and therefore, informed consent was not obtained from the patients. This study was approved by the Ethics Committee in accordance with the ethical standards set by the principles of the Declaration of Helsinki (date:17 March 2022, no:70/2022). Diabetic patients were classified according to American Diabetes Association (ADA) criterias[1]. Laboratory parameters of the patients, including plasma glucose, fasting C-peptide and HbA1c levels and GADA titters were recorded. Anti-thyroid peroxidase (Anti-TPO) and/or anti-thyroglobulin (Anti-Tg) titres of the patients were recorded. The patients were categorized into two groups according to GADA positivity, and their laboratory parameters were compared.

Quantitative assay of GADA was performed using the enzyme immunoassay method (Medizym GADA, Germany). GADA titre ≥5 IU/mL was considered positive. C-peptide hormone was analysed with the IMMULITE®2000 XPi immunoassay System (Siemens device). HbA1c was measured using automated Agilent 1100 instrument and BioSystems S.A. kits based on the high-performance liquid chromatography method.

Statistical Analysis

Mann–Whitney U test was used to compare the data based on GADA positivity. Chi-squared test was used to compare categorical data. Receiver operating characteristics (ROC) curve was used to determine the sensitivity and specificity of C-peptide in detecting GADA positivity. We considered the optimal cut-off point as the value corresponding to the highest value of the sum of sensitivity and specificity. Area under the curve (AUC) was calculated. The data were exported to the Statistical Package for the Social Sciences (Version 22; IBM Corp., USA) program. Regarding statistical significance, a p level of < .05 at 95% confidence interval was considered statistically significant.

RESULTS

Of a total of 343 patients (40.8% male; 59.2% female), 147 (42.9%) had T1D and 196 (57.1%) had T2D. Demographic characteristics of the diabetic patients are presented in Table I.

Table I: Demographic Characteristics of the Diabetic Patients

	Total n = 343
Sex Male/Female	140/203
Age (years)	34 (16-84)
Glucose (mg/dL)	265 (72-841)
C-peptide (ng/mL)	1.67 (0.01-12.2)
HbA1c (%)	11 (6.5-18.4)

The data were presented as median (min–max). HbA1c: Haemoglobin A1c.

All patients were grouped based on GADA positivity and compared in Table II. The two groups differed in terms of age, C-peptide and HbA1c levels and thyroid antibody positivity (p < .05). The patients in the GADA positivity group were younger, their C-peptide levels were lower and their HbA1c levels were higher; also, thyroid antibody positivity was more prevalent in this group.

Table II: A Comparison of GADA-Positive and GADA-Negative Patients

	GADA Positive n = 96	**GADA Negative n = 247**	**p value**
Sex Men/Women	44/52	96/151	.239
Age (years)	28 (16-76)	37 (16-84)	**< .001***
Glucose (mg/dL)	272 (72-841)	262 (110-612)	.936
C-peptide (ng/mL)	0.74 (0.01-11.82)	2.05 (0.01-12.2)	**< .001***
HbA1c (%)	11.8 (6.5-18.4)	10.8 (6.5-18.2)	**.03***
Anti-TPO (IU/mL) and/or Anti-Tg (IU/mL) Positive/Negative	20/28	19/72	**.009***

*The data were presented in median (min–max). HbA1C: Haemoglobin A1c; GADA: Glutamic acid decarboxylase antibody 65; Anti-TPO: Anti-thyroid Peroxidase; Anti-Tg: Anti-thyroglobulin. *p value: p < .05 was considered statistically significant.*

In this study, lower C-peptide levels were found in patients with GADA positivity. However,

there were a few GADA-positive patients with higher C-peptide levels (Fig. 1).

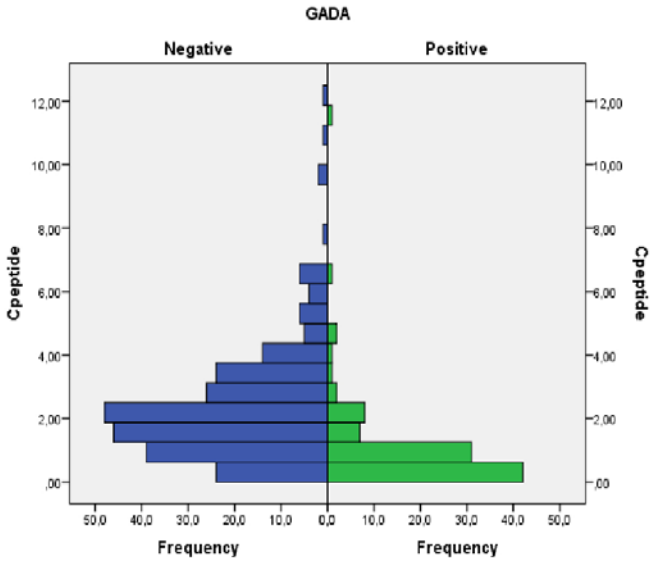
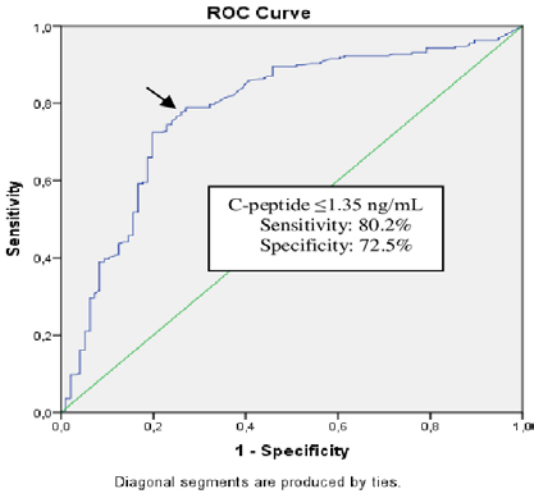


Figure 1: Frequency of C-peptide (ng/mL) levels based on glutamic acid decarboxylase 65 antibody (GADA)

In Figure 2, sensitivity was 80.2% and specificity was 72.5% for the cut-off point of ≤ 1.35 ng/mL for the optimal C-peptide level predicting GADA positivity in the receiver operating characteristic (ROC) curve. AUC (95%) was calculated to be 0.782 (p < .001; 0.726–0.839).



AUC: 0.782 (95% CI) (p < .001; 0.726–0.839)

Figure 2: ROC curve showing the correlation between GADA positivity and C-peptide

Figure 3 shows GADA positivity according to C-peptide cut-off points in diabetic patients. GADA positivity showed a nearly horizontal course above the cut-off point of 1.35 ng/mL for C-peptide.

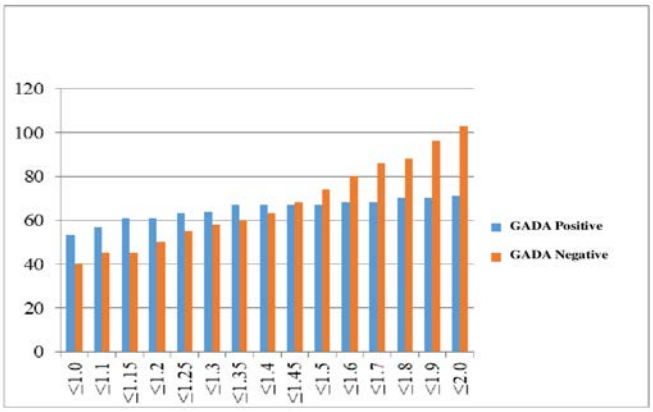


Figure 3: GADA positivity by C-peptide (ng/mL) cut-off points in Diabetic Patients

DISCUSSION

The occurrence of GADA antibodies has been reported to be associated with the development of T1D and LADA[9]. A study has suggested the analysis of C-peptide levels and GADA autoantibodies for the diagnosis of LADA[10]. Previous studies have compared C-peptide levels based on diabetes types. Patients with LADA have been shown to exhibit lower fasting C-peptide levels than those with T2D[11,12]. A Turkish study compared LADA and T2D, and the age of diabetes onset was significantly younger and the body mass index and serum C-peptide levels were lower in patients with GADA positivity[13]. In a prospective cohort of 5.230 Chinese individuals with T2D, 28.6% of patients had low C-peptide level (<200 pmol/L) (<0.60 ng/mL) and 4.9% had GADA positivity[14]. In the present study, the patients with GADA positivity had significantly lower C-peptide levels (Tab. II).

Impaired beta-cell function is a recognized cornerstone of diabetes pathophysiology. Because C-peptide secretion mirrors beta-cell function and helps to classify types of diabetes,

complication risk stratification, and guide treatment decisions, in autoimmune diabetes and especially in adult-onset diabetes[15]. Baseline C-peptide level has been considered to be a good indicator for evaluating β-cell dysfunction in patients with GADA-positive DM. In a study, five hundred and twenty-seven newly diagnosed GADA-positive diabetic patients have been followed to evaluate the natural history of beta-cell function. ROC analysis has showed that fasting C-peptide level of 300 pmol/L (0.90 ng/mL) was optimum in determining beta-cell dysfunction with 90.5% sensitivity and 86.9% specificity[16]. In another study evaluating the prevalence of GADA antibodies and C-peptide levels in T1D, sensitivity has been identified to be 82.4% and specificity 86.3% for low C-peptide secretion. This finding is indicative of a correlation between T1D and GADA/C-peptide. Therefore, it has been considered to be a useful diagnostic tool[5]. In 303 T1D and 841 T2D patients, low C-peptide concentrations have been found to be associated with a high odds ratio for T1D. Fasting C-peptide concentrations of 0.13–0.36 nmol/L (0.39–1.08 ng/mL) have not clearly distinguished between different types of diabetes. This study has suggested that fasting C-peptide levels could help differentiate between T1D and T2D. However, it has been mention a range of C-peptide concentrations that have not provided the distinction[17]. In addition, other studies have also reported lower fasting C-peptide levels in GADA-positive compared with GADA-negative patients[18-20]. GADA/C-peptide has also been suggested to be a good indicator for the diagnosis of autoimmunity in children and young adults[21]. In a study of 859 individuals who had been diagnosed with T1D for at least 3 years by an outpatient clinician, C-peptide levels ≥200 pmol/L (0.6 ng/mL) have been observed in 114 (13.2%) of these patients. 58 individuals have been reclassified (T2D; 44 individuals/monogenic diabetes; 14 individuals)[22]. A rapid decrease in C-peptide levels has been observed in patients with GADA and/or islet cell antibody positivity. These patients do not benefit from oral anti-diabetic agents and require earlier introduction of insulin therapy[23]. In GADA-positive patients, induced low C-peptide levels have been noted in addition to low fasting C-peptide levels[24-26]. The degree of pancreatic β-cell destruction and the rate of decline could be assessed by measurement of C-peptide levels[4].

Measurement of C-peptide levels has found increasingly frequent use in diabetes typing in clinical practice. Not only the presence and levels of autoantibodies but also the plasma levels of C-peptide and insulin are key prognostic indicators for the clinical onset of T1D[27]. A study has reported that T2D could be excluded in case of a C-peptide level of <0.6 ng/mL at the time of diagnosis and that it is not possible to make a T1D diagnosis if the C-peptide level is >3.0 ng/mL[28]. However, in the present study, there was a patient with a C-peptide level of 11.82 ng/mL (Fig. 1). Another study has reported 96% positive predictive value for C-peptide levels of <1.51 ng/mL (0.5 nmol/L) in the diagnosis of T1D in adults and children[7]. In the ADA/European Association for the Study of Diabetes (EASD) consensus report on the management of T1D in adults, it has been recommended that C-peptide evaluation be performed more than 3 years after the diagnosis of diabetes in autoantibody-negative adults on insulin therapy. It has been emphasized that C-peptide levels lower than 0.20 nmol/L (0.6 ng/mL) should suggest a diagnosis of T1D and values higher than 0.60 nmol/L (1.81 ng/mL) should suggest a diagnosis of T2D[29]. The provided research articles highlight the importance of fasting C-peptide levels and GADA positivity in differentiating between types of diabetes and predicting beta-cell dysfuncion. In addition, many studies have mentioned the importance of the presence and

affinity of GADA in the clinical management and classification of diabetes. In the present study, sensitivity was 80.2% and specificity was 72.5% for the optimal C-peptide level cut-off point of ≤1.35 ng/mL, which predicted positive GADA in the ROC curve (Fig. 2). In Figure 3, GADA positivity showed a nearly horizontal course above the cut-off point of 1.35 ng/mL for C-peptide. There was a strong GADA positivity, especially when the C-peptide level was ≤1.35 ng/mL. Consequently, GADA positivity may be detected with a high probability in patients with a C-peptide level of ≤1.35 ng/mL. GADA assay can be performed in patients with a value below this level. However, it should be kept in mind that a small number of patients with very high C-peptide levels may also exhibit GADA positivity. High C-peptide levels and GADA positivity suggested that certain individuals in our adult patient group were diagnosed at a very early stage of the slow-progressing autoimmune diabetes or might have antibody positive diabetes associated with coronavirus disease 2019. It is well-established that viral infections are frequently associated with the pathogenesis of T1D. Several pathogens, including coronavirus, are believed to increase the risk of β-cell autoimmunity in a group of patients[30,31]. SARS-CoV-2 has been considered an inducer of new onset T1D[32].

Thyroid-specific antibody positivity was concluded to be more prevalent in GADA-positive adult patients with T1D than in GADA-negative patients or patients with T2D[33]. Similarly, thyroid-specific antibodies were highly prevalent in those with GADA positivity in the present study.

This study has certain limitations, including its retrospective design. GADA data were collected from patients with low pancreatic reserve with suspected insulin-dependent DM. Therefore, C-peptide levels were lower than expected. In addition, patients with GADA data were included in the younger age group. Prospective random analysis of autoantibodies in patients would help ascertain a more homogeneous distribution. Apart from GADA, other antibodies (insulin autoantibody [IAA], islet cell cytoplasmic autoantibody [ICA], anti-tyrosine phosphatase, zinc transporter-8 antibody [anti-ZnT8]) were not measured. In GADA-negative patients with low C-peptide levels, the diagnosis of autoimmune diabetes may have been missed due to the absence of testing for these antibodies. Additionally, C-peptide levels may be measured lower than expected in diabetic patients due to glucotoxicity effects at high glucose concentrations.

CONCLUSION

Given the higher probability of GADA positivity when fasting C-peptide levels are below the cut-off point of 1.35 ng/mL, it would be a reasonable approach to analyse GADA in patients with a value below this level for determining the type of diabetes and thus deciding the correct treatment.

Ethics Committee Approval: This study was approved by the Ethics Committee in accordance with the ethical standards set by the principles of the Declaration of Helsinki (date:17 March 2022, no:70/2022).

Conflict of Interest: The authors declared no conflicts of interest.

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