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C-peptide Measurement may not be Necessary for Choosing a Treatment Modality in Type 2 Diabetes Mellitus: A Retrospective Analysis

C-peptid Ölçümü Tip 2 Diabetes Mellitusda Tedavi Seçiminde Gerekli Olmayabilir: Retrospektif Bir Analiz

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Abstract

Purpuse: C-peptide (CP), generated during the cleavage of proinsulin to form insulin, serves as a specific marker of insulin-secreting beta cell function. Since CP is utilized to assess the secretion of insulin, it may act as an indicator in the treatment algorithm of diabetes. The present retrospective study aimed to demonstrate whether patients previously diagnosed with type–2 diabetes (T2DM) and on antidiabetic treatment received the recommended CP-guided treatment mentioned in the current guideline.

Material and Method: A total of 179 patients, previously diagnosed with T2DM, were admitted to our outpatient clinic with complete clinical records and simultaneously measured fasting CP, glucose, and hemoglobin A1c (HbA1c) levels. We did not use the CP levels measured during the current course of treatment as a marker to designate or change treatment in the current study. Data were analyzed using the SPSS version 17.0.

Results: The mean CP level for all patients was 2.71 ng/mL. Twelve patients (6.7%) had insufficient reservoir (CP < 0.5 ng/mL), 70 (39.1%) exhibited borderline reservoir (CP: 0.5–2.0 ng/mL), and 97 (54.2%) had sufficient reservoir of beta cells. All three groups were similar regarding age, gender, fasting glucose, and HbA1c. Metformin was more frequent in patients with sufficient reservoir, whereas all patients in the insufficient group were taking insulin.

Conclusion: Although the literature on diabetes provides enough evidence on the use of CP in various indications, such as determining diabetes subtype, predicting treatment response, and residual beta cell reservoir, we conclude that it may have a limited use as factor deciding the choice of treatment in patients with T2DM.

Keywords: C-peptide; insulin; type 2 diabetes mellitus

Özet

Amaç: C-peptid beta hücre fonksiyonunu gösteren özgül bir belirteçtir ve tedavi algoritmasında kullanıma sahip olabilir. Bu retrospektif değerlendirmede, daha önce tanı almış ve tedavi altındaki tip 2 diyabet mellitus (T2DM) hastalarının tedavilerinin güncel kılavuzda yer alan CP güdümlü tedavi önerileri ile uyumunun incelenmesi amaçlandı.

Gereç ve Yöntem: Bu retrospektif çalışmaya kliniğimize başvuran, klinik kayıtları ve eşzamanlı açlık plazma glukozu, c-peptid düzeyi ve HbA1c düzeyi ölçülmüş 179 T2DM hastası alındı. CP düzeyleri tedavi altında ölçüldü ve tedavi değiştirme veya yeni tedavi başlama amacıyla kullanılmadı. Analiz için SPSS 17.0 paket programı kullanıldı.

Bulgular: Ortalama CP düzeyi tüm hastalarda 2.71 ng/mL saptandı. On iki hastada (%6.7) yetersiz rezervuar (CP<0.5 ng/mL), yetmiş hastada (%39.1) sınırda rezervuar (CP: 0.5-2 ng/mL) ve 97 hastada (%54.2) yeterli rezervuar bulunmuştur. Her üç grup da yaş, cinsiyet, açlık kan glukozu ve HbA1c açısından benzerdir. Yeterli rezervuar grubunda metformin kullanımı daha sık iken, yetersiz rezervuar grubundaki tüm hastalar insulin kullanmaktadır.

Tartışma: CP ölçümünün literatürde diyabet tipi belirleme, tedavi yanıtını tahmin etme ve beta hücre rezervuarını gösterme gibi endikasyonları olsa da, bu çalışma sonucunca T2DM hastaları için tedavi seçiminde CP ölçümünün kullanımının kısıtlı olduğunu düşünmekteyiz.

Anahtar kelimeler: C-peptid; insulin; tip 2 diyabetes mellitus

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Introduction

The increasing incidence of diabetes worldwide necessitates the direct measurement of endogenous insulin, which in turn assists in deciding the treatment and clinical management of patients with diabetes. In this regard, c-peptide (CP) serves as a well-documented marker for pancreatic beta cell function, that is, insulin secretion. CP is a 31-amino acid peptide produced during the cleavage of proinsulin to form insulin; the c-peptide test is considered useful in the direct measurement of insulin. It has several advantages over insulin, where the latter may result in false-positive results. Such false-positive results (a) may arise in the patients using subcutaneous insulin, where serum insulin levels are falsely elevated, (b) insulin has a 50% first-pass metabolism in the liver, (c) peripheral clearance of insulin is more variable than CP, and (d) CP is less affected by oral foods (1-4).

CP is used for the assessment and analysis of several clinical indications. For instance, it may help in the differential diagnosis of type-2 diabetes mellitus (T2DM) from type-1 diabetes mellitus (T1DM) along with maturity-onset diabetes of the young (MODY, 5). CP levels may also have a prognostic role in future needs for insulin treatment. Goto et al. (6) demonstrated that CP levels efficiently predicted prognosis in patients with T2DM; however, other clinical aspects, such as lower body mass index, higher fasting glucose, and lower serum and urinary CP levels, were equally predictive. In another study, CP levels corrected by fasting glucose could predict future insulin requirement in Japanese patients (7). In addition, response rates of patients to different antidiabetic medications may be closely associated with remaining beta cell reservoir; therefore, CP may serve as a potential tool for assessing the insulin secretion capability of the residual beta cells. Hermann et al. (8) demonstrated that CP levels acted as a predictor of treatment response in patients on a sulfonylurea as medication; however, pre-treatment glycemia exhibited the same predictive value. Similarly, Iwao et al. (9) demonstrated postprandial CP levels to predict successfully a change from insulin to liraglutide. However, another study with exenatide failed to demonstrate the same result (10).

In "Diabetes Diagnosis and Treatment Guideline 2016," written by Turkish Diabetes Foundation National Diabetes Consensus Group, CP is specified as the most important marker of beta cell function and is presented as an important indicator in the treatment algorithm of diabetes. The guideline categorized the CP levels as sufficient reservoir (CP >2.0 ng/mL), borderline reservoir (CP: 0.5-2.0 ng/mL), and insufficient reservoir (CP <0.5 ng/mL). For patients with sufficient reservoir, the combinations of oral medications were recommended. The patients with borderline reservoirs were recommended a combination of basal insulin and oral drugs, whereas those with insufficient reservoir were suggested metformin with premixed or intensive insulin regimens as the treatment modality (11). However, limited data exist on the use of CP for opting the reliable treatment approach for diabetes in the literature. In the present retrospective study, we assessed whether patients previously diagnosed with T2DM and undergoing antidiabetic treatment were receiving the recommended CP-guided treatment mentioned in the current guideline.

Patients and Methods

The current study was conducted in concordance with the Declaration of Helsinki ethical guidelines. In this retrospective study, we assessed 179 patients with T2DM admitted to our outpatient clinic in 2015, with the complete clinical record and simultaneous fasting CP, plasma glucose, and HbA1c measurements. All patients included in the analysis had a previous diagnosis of T2DM and were on at least one antidiabetic medication. Furthermore, CP levels were measured during the current course of treatment and were not used as a marker to designate or change treatment approach in the current study. Exclusion criteria included patients with missing data, diagnosis of diabetes other than T2DM, end-stage renal disease, and a history of renal transplant.

Age, gender, and treatment modalities (metformin, acarbose, sulfonylureas/glinides, thiazolidinedione, dipeptidyl-peptidase-4 [DPP-4] inhibitors, glucagon-like peptide-1 [GLP-1] analogs, and insulin) were accessed from medical records. Glucose (mg/dL), HbA1c (%), and CP (ng/mL) levels were accessed using the records from biochemistry laboratory. All laboratory measurements were conducted at fasting and under current antidiabetic treatment. Glucose levels were measured by the hexokinase method. We used a turbidimetric inhibition assay (Siemens Dimension Flex, CV: 0.12-0.2%) and a solid phase two-site chemiluminescent immunometric assay (Siemens IMMULITE 2000; reference range: 0.1-20 ng/mL; CV: 0.08 ng/mL) to measure the HbA1c and CP levels, respectively. CP levels were categorized according to "Diabetes Diagnosis and Treatment Guideline 2016" (11).

Data were analyzed using the SPSS version 17.0; continuous variables were presented as a mean and standard deviation and categorical variables as frequency and percentage. Student's *t*-test and Mann-Whitney U test were applied for comparison of groups. Nominal variables were assessed by a chi-square test.

Results

Clinical characteristics and laboratory results of the study population are shown in Table 1. The mean CP level for all patients was 2.71 ng/mL. The choice of treatment modality of patients ranged from the most commonly used to the least used. These included metformin (87.7%), insulin (67%), sulfonylureas/glinides (38%), DPP-4 inhibitors (22.9%), thiazolidinediones (17.9%), acarbose (10.6%), and GLP-1 analogues (2.2%).

Twelve patients out of 179 (6.7%) had insufficient beta cell reservoir (CP < 0.5 ng/mL), 70 (39.1%) had borderline (CP: 0.5-2.0 ng/mL), and 97 (54.2%) exhibited sufficient beta cell reservoir (Table 2). All three groups were similar regarding age, gender, fasting plasma glucose, and HbA1c. Treatment frequencies, with acarbose, sulfonylureas/glinides, DPP-4 inhibitors, and thiazolidinediones, were similar across groups. Patients with sufficient reservoir of beta cells used metformin more frequently, whereas all patients with an insufficient beta cell reservoir commonly used insulin. However, two patients out of 12 patients took sulfonylureas as well.

Discussion

In the current study, we conducted an analysis to check whether patients, previously diagnosed with T2DM and undergoing antidi-

Table 1. The clinical characteristics and laboratory results of patients.

Patient characteristics	
Gender (M/F)	91 male/88 female
Age (years)	53±13 years
Laboratory results	
Glucose (mg/dL)	217±111 mg/dL
HbA1c (%)	9.3±2.2%
C-peptide (ng/mL)	2.71±2.12 ng/mL
Treatments	**n (%)**
Metformin	157 (87.7)
Acarbose	19 (10.6)
Sulfonylurea /Glinides	68 (38)
Glinides	13 (7.3)
Sulfonylurea	55 (30.7)
Thiazolidinedione	32 (17.9)
DPP-4 inhibitors	41 (22.9)
GLP-1 analog	4 (2.2)
Insulin	120 (67)
Basal	29 (16.2)
Premix-2 doses/day	25 (14)
Premix-3 doses/day	10 (5.6)
Premix-Total	35 (19.6)
Basal-bolus/Intensive	56 (31.3)

abetic treatment, received the recommended CP-guided treatment mentioned in the current guideline. Without using CP as a marker to designate treatment or decide the choice of treatment, we demonstrated that the current treatment of patients was compatible with their individual CP levels. Therefore, our data demonstrated that measurement of CP levels might not be necessary, since nearly all patients were receiving treatment consistent with the "Diabetes Diagnosis and Treatment Guideline, 2016.

The guideline recommends CP to be employed as a marker to guide treatment options in type-2 diabetes. During the study, we also noted that hyperglycemic conditions and glucotoxicity might negatively affect CP; however, a higher level of CP even in hyperglycemic conditions was noted to be significant for sufficient beta cell reservoir. In this guideline, authors proposed insulin as the choice of treatment for patients with insufficient beta cell reservoir, regardless of their HbA1c levels. For patients with a diagnosis of the T2DM and HbA1c level of 9% or higher, authors recommended the treatment to be guided by CP levels (11).

The guidelines by the American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), and American College of Endocrinology (ACE) recommend the use of c-peptide in the differential diagnosis of type 1 and T2DM. However, a recent review listed other multiple potential indications for c-peptide measurement. Differential diagnosis of several forms of diabetes, such as maturity-onset diabetes of the young and latent autoimmune diabetes of the adults, may be based on an assessment of c-peptide. In addition, c-peptide levels may serve as a prognostic factor, since its levels are associated with glycemic variability. Several studies also demonstrated patients with lower c-peptide levels to exhibit an inclination toward insulin, whereas those with higher levels displayed a higher response rate to oral antidiabetics. Therefore, c-peptide may act as a crucial player in the designing of future guidelines related to diagnosis and clinical management of diabetes (12).

While planning treatment for patients with T2DM, patient's current glucotoxicity, HbA1c levels, and clinical parameters are important and should be documented. Our data show that CP measurement may not be necessary for selecting the correct treatment approach, since nearly all patients included in the study were receiving CP-guided recommended treatment. However, in our study, two out of 12 patients exhibited insufficient reservoir of beta cells and were administered sulfonylureas/glinides. These drugs act by increasing insulin secretion from beta cells, which, in patients with the insufficient reservoir, have a limited efficacy. Therefore, CP levels may be considered valuable to predict treatment failure in such cases.

The present study suffered from many limitations owing to its ret-

Table 2. Comparison of clinical characteristics and laboratory results of patients with sufficient, borderline, and insufficient reservoir.

	Insufficient reservoir (C-peptide<0.5 ng/mL) (n=12, 6.7%)	**Borderline reservoir (C-peptide 0.5–2 ng/mL) (n=70, 39.1%)**	**Sufficient reservoir (C-peptide>2 ng/mL) (n=97, 54.2%)**	**p**
Gender (M/F)	5/7	38/32	49/48	0.698
Age (years)	53 (32–67)	52 (21–88)	53 (23–84)	0.795
Glucose (mg/dL)	193 (77–563)	178 (71–606)	187 (71–448)	0.923
HbA1c (%)	8.58 (6.3–10.79)	9.22 (5.81–15.34)	9.03 (5.4–15.57)	0.623
Treatments				
Metformin	8 (66.7%)	59 (84.3%)	90 (92.8%)	**0.018**
Acarbose	3 (25%)	7 (10%)	9 (9.3%)	0.243
Sulfonylurea /Glinides (all)	2 (16.7%)	26 (37.1%)	40 (41.2%)	0.25
Thiazolidinedione	2 (16.7%)	16 (22.9%)	14 (14.4%)	0.372
DPP-4 inhibitors	1 (8.3%)	16 (22.9%)	24 (24.7%)	0.447
GLP-1 analog	0 (0%)	0 (0%)	4 (4.1%)	0.177
Insulin (all)	12 (100%)	57 (81.4%)	51 (52.6%)	**0.001**

rospective nature. The study was conducted on a limited number of patients, thereby restricting the outcomes of the study. All patients included in the study were previously diagnosed with T2DM; however, age of T2DM, clinical parameters during diagnosis of T2DM, previous treatment choices, duration of current treatment modality, body mass index, weight gain, and loss and other comorbidities were not well documented for all cases and not evaluated in the present analysis. Another important parameter limiting the study included measurement of CP levels in patients with current treatment modalities, which might have impaired or increased serum CP levels.

In conclusion, our retrospective analysis revealed that routine CP measurement may not serve as a decisive and valuable factor for all patients with regard to choosing treatment modalities in patients with T2DM. To date, no specific retrospective or prospective study exists regarding the use of c-peptide levels in deciding the treatment modality for patients with T2DM. We recommend future prospective studies to focus on the use of CP as a potential marker to guide treatment options in patients with T2DM having a different residual activity of beta cells.

Ethics: The current study was conducted in concordance with the Declaration of Helsinki ethical guidelines.

Author Contributions

Concept: Gokhan Tazegul, Humeyra Bozoglan, Özlem Doğan, Ramazan Sarı, Hasan Ali Altunbaş, Mustafa Kemal Balcı, Design: Gokhan Tazegul, Humeyra Bozoglan, Özlem Doğan, Ramazan Sarı, Hasan Ali Altunbaş, Mustafa Kemal Balcı, Data Collection or Processing: Gokhan Tazegul, Tahir Saygin Ogut, Humeyra Bozoglan, Özlem Doğan, Sebahat Özdem, Analysis or Intrepretation: Gokhan Tazegul, Tahir Saygin Ogut, Humeyra Bozoglan, Özlem Doğan, Sebahat Özdem, Literature Search: Gokhan Tazegul, Humeyra Bozoglan, Özlem Doğan, Ramazan Sarı, Hasan Ali Altunbaş, Mustafa Kemal Balcı, Writing: Gokhan Tazegul, Tahir Saygin Ogut, Humeyra Bozoglan, Özlem Doğan, Sebahat Özdem, Ramazan Sarı, Hasan Ali Altunbaş, Mustafa Kemal Balcı.

Conflict of Interest: The authors declare that they have no conflict of interest

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