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C-peptide concentrations in patients with type 2 diabetes treated with insulin

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ABSTRACT

Aims: To determine beta cell reserves of patients with type 2 diabetes who are treated with insulin by using fasting C-peptide concentrations and to investigate the clinical features related to C-peptide concentrations.
Materials and methods: Patients with type 2 diabetes, who were using insulin as monotherapy or in combination therapy, were divided into three groups; those with an insufficient beta cell reserve (C-peptide: <0.5 ng/mL), borderline reserve (C-peptide: 0.5–2 ng/mL) and sufficient reserve (C-peptide:> 2 ng/mL).
Results: In the 249 patients (mean age, 61.77 ± 9.34 years; 40.6% male), the mean duration of diabetes was 13.9 ± 8.43 years. The mean HbA1c concentrations, fasting glucose and C-peptide concentrations were 8.88 ± 1.87%, 184.29 ± 77.88 mg/dL and 1.95 ± 1.37 ng/mL, respectively. Fifty-seven percent of patients (n = 142) had a borderline beta cell reserve and 37% (n = 92) had high C-peptide concentrations. Only 6% of patients (n = 15) had an insufficient beta cell reserve. C-peptide levels were positively correlated with waist circumference (r: 0.282; p = 0.001), hip circumference (r: 0.251; p = 0.001), body mass index (r: 0.279; p = 0.001), fasting glucose concentrations (r: 0.309; p = 0.001) and triglyceride concentrations (r: 0.358; p = 0.001).
Conclusion: In this study, almost all patients with type 2 diabetes using insulin were found to have sufficient or borderline beta cell reserves and insulin resistance-related parameters were prominent in those with adequate beta cell reserve.
Clinical trials no: NCT04005261

1. Introduction

C-peptide is secreted in equimolar amounts with insulin from pancreatic beta cells and is reported to be a more useful laboratory parameter than insulin in evaluating endogenous insulin reserve [1,2]. C-peptide measurement can be used in the differential diagnosis of type 1 and type 2 diabetes, for the identification of patients with maturity-onset diabetes of the young (MODY) or latent autoimmune diabetes of adults (LADA); for the detection of absolute insulin deficiency; and in planning timely changes of treatment in patients with diabetes using either insulin and other diabetic medications [3]. It has been suggested that C-peptide concentrations correlate with microvascular and macrovascular complications in both type 1 and type 2 diabetes and can be a reliable indicator for predicting future insulin needs [4–6]. In patients with type 2 diabetes, initiation of insulin therapy is indicated in several conditions such as severe insulin resistance, acute metabolic decompensations, surgery, pregnancy, and progression of diabetic complications, and also when glycemic control cannot be achieved with effective lifestyle regulation and non-insulin antidiabetic medications [7,8]. At that point, a low C-peptide level is considered to be a reliable parameter in the decision to start insulin therapy except in extreme hyperglycemic conditions.

In our “National Diabetes Consensus Group Diabetes Diagnosis and Treatment” guideline, it is recommended that glycated hemoglobin (HbA1c), as well as C-peptide concentrations, should be

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considered in the planning of type 2 diabetes treatment [9]. When, in daily practice, C-peptide concentrations are observed to be normal or high in patients with type 2 diabetes who use insulin, it causes confusion about the treatment decision and raises the question as to whether the patients' insulin use is necessary.

The aim of this study was to investigate c-peptide concentrations in patients with type 2 diabetic using insulin as a monotherapy or as part of combination therapy, and to examine the clinical features associated with predetermined C-peptide concentrations.

2. Material and methods

This prospective, observational clinical study was conducted on consecutive patients with type 2 diabetes aged 18 years or older who presented to the Diabetes Outpatient Clinics of Istanbul Medeniyet University Goztepe Training and Research Hospital between November 1st, 2018, and February 1st, 2019. Informed consent was obtained from all subjects included in the study. The trial protocol was approved by the hospital ethics committee (October 24, 2018; 2018/0396) and conducted in accordance with the Declaration of Helsinki.

Sample size: Assuming $\alpha = 0.05$ and 80% power, 249 subjects were included in the study using the simple random sampling method.

Inclusion criteria: Patients with type 2 diabetes who had been treated with insulin as a monotherapy or as a component of combination therapy for at least 3 months.

Exclusion criteria: Diagnosis of other types of diabetes, end-stage renal failure, history of renal transplantation, diabetic acute metabolic decompensation, decompensated heart failure, advanced liver disease, pregnancy, acute or chronic pancreatitis, pancreatic carcinoma, acute infections, use of medications that might affect glucose regulation (e.g. corticosteroids).

Primary endpoint: Determination of C-peptide concentrations in patients with type 2 diabetes using insulin to evaluate pancreatic beta cell reserve and compare clinical characteristics for C-peptide concentrations.

Secondary endpoint: Assessing the correlation between fasting C-peptide concentrations and the clinical features of patients with type 2 diabetes treated with insulin.

2.1. Study design

Duration of diabetes, demographic characteristics, comorbidities, treatment characteristics, and duration of medication use were recorded for participants who met the inclusion criteria. The patients' diabetes type, their medications, the dose of their medications, and the regularity of use was further investigated using the hospital prescription system and the National Medula electronic prescription system (//medeczane.sgk.gov.tr/doktor/login.jsp). Detailed physical examinations were performed. Blood pressure, waist circumference, height, and body weight were measured. Following 12-h fasting glucose, HbA1c, fasting C-peptide, creatinine, alanine aminotransferase (ALT), uric acid, total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol concentrations were measured in the central hospital laboratory from venous blood samples. Urine samples were taken for spot urine protein/creatinine measurements. In this study, fasting C-peptide concentrations of less than 0.5 ng/mL were considered insufficient, between 0.5 and 2 ng/mL as borderline, and more than 2 ng/mL as normal [9]. The groups were compared according to their demographic, comorbidity and treatment characteristics, and to their anthropometric and biochemical data. Correlation analysis was performed to evaluate the relationship between fasting C-peptide and clinical features.

2.2. Anthropometric measurements

Body weight, waist circumference, and height were measured by the same physician using standard measuring instruments. Waist circumference was measured while the patient was standing, at the narrowest part of the waist with a slight expiration on the midpoint between the lowest rib and the iliac crest, as defined by the World Health Organization. Hip circumference was measured at the level of the widest circumference over the greater trochanters. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in square meters). Blood pressure was obtained using an appropriate mercury sphygmomanometer (based on Korotkoff Phase I and Phase V sounds) on both arms with the patient in a comfortable sitting position after at least a 10-min rest. The second measurement was performed on the arm with a higher value. Two measurements were taken at least 3 min apart and averaged to provide the values for systolic and diastolic pressure.

2.3. Analytical measurements

Fasting glucose concentrations were determined using the hexokinase method. Serum creatinine was assayed using the kinetic Jaffe method. For alanine transaminase (ALT) concentrations, an enzymatic (without P-5′-P, NADH) method was used. Fasting plasma total cholesterol, HDL and LDL cholesterol and triglyceride concentrations were determined using enzymatic methods (Abbott Architect c16000 and c8000, Abbott). A Tosoh HLC-723 G8 (Tosoh G8) (Tosoh, Japan) (variant-mode) ion exchange high-performance liquid chromatography (HPLC) system was used for HbA1c measurements. The C-peptide was measured using a chemiluminescence microparticle immunoassay in the Abbott Architect I2000 (Abbott Laboratories, Abbott Park, IL, USA) autoanalyzer.

Glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) formula [10], and the presence of proteinuria was determined using the protein/creatinine ratio in spot urine.

2.4. Statistical methods

Statistical analysis was performed using the Number Cruncher Statistical System NCSS (Number Cruncher Statistical System) NCSS) version 2007 software (Kaysville, Utah, USA). The normal distribution of quantitative data was tested by using the Kolmogorov-Smirnov and Shapiro-Wilk tests and graphical evaluations. For groups with normal distribution, one-way analysis of variance (ANOVA) was used for multiple groups and the Bonferroni test was used to compare two groups of independent samples. For groups with abnormal distribution, the Kruskal Wallis test was used for multiple groups, and the Dunn-Bonferroni test was used to compare two groups. To analyze qualitative data, the Pearson's Chi-square test and the Fisher-Freeman-Halton Exact test were used. A p value of <0.05 was considered statistically significant.

3. Results

A total of 249 patients were recruited for the study. Approximately 60% of the patients were female. The mean age of the patients was 61.8 years. The mean diabetes duration was 13.9 years (Table 1). The mean duration for insulin use and non-insulin antidiabetic medication was 8.1 years and 12.3 years, respectively.

The most common comorbidity was hypertension (74.3%), followed by dyslipidemia (59.8%) and diabetic neuropathy (43.8%).

Table 1
Demographic features of the patients.

Demographic		Beta cell reserves			*p*
		Insufficient (c-peptide<0.5) (n = 15; 6.0%)	Borderline (c-peptide 0.5–2) (n = 142; 57.0%)	Sufficient (c-peptide>2) (n = 92; 37.0%)	
Age (years)	*Mean±SD*	60,9 ± 9,1	62,4 ± 9,7	60,8 ± 8,8	0,381
Gender; *n (%)*	Female	7 (4,7)	76 (51,4)	65 (43,9)	**0,019**
	Male	8 (7,9)	66 (65,3)	27 (26,7)	
Duration of diabetes (year)	*Mean±SD*	14,8 ± 8,2	15,1 ± 9,0	12,1 ± 7,7	**0,023**
Duration of OAD use (year)	*Mean±SD*	11,1 ± 9,3	8,5 ± 7,1	6,9 ± 5,4	0,194
Duration of insulin use (yıl)	*Mean±SD*	12,9 ± 10,4	13,1 ± 9,0	11,1 ± 8,5	0,189
Anthropometric					
SBP (mmHg)	*Mean±SD*	137,6 ± 17,2	149,6 ± 21,9	141,1 ± 20,2	**0,007**
DBP (mmHg)	*Mean±SD*	75,4 ± 10,7	81,3 ± 10,8	80,4 ± 12,0	0,178
Waist circumference (cm)	*Mean±SD*	92,8 ± 12,6	102,3 ± 11,0	106,5 ± 11,8	**0,001**
Hip circumference (cm)	*Mean±SD*	101,8 ± 9,3	108,5 ± 10,5	112,9 ± 11,5	**0,001**
BMI (kg/m^2)	*Mean±SD*	26,3 ± 3,6	30,4 ± 5,2	33,1 ± 5,5	**0,001**
Comorbidities					
Hypertension; *n (%)*		9 (4,9)	100 (54,1)	76 (41,1)	**0,049**
Dyslipidemia; *n (%)*		9 (6,0)	83 (55,7)	57 (38,3)	0,867
Diabetic retinopathy; *n (%)*		7 (8,8)	50 (62,5)	23 (28,8)	0,121
Diabetic neuropathy; *n (%)*		4 (3,7)	67 (61,5)	38 (34,9)	0,262
Coronary artery disease; *n (%)*		5 (5,7)	54 (62,1)	28 (32,2)	0,488
Heart failure; *n (%)*		1 (4,0)	15 (60,0)	9 (36,0)	0,887
Cerebrovascular disease; *n (%)*		0 (0)	7 (87,5)	1 (12,5)	0,252
Peripheric artery disease; *n (%)*		1 (25,0)	3 (75,0)	0 (0)	0,094
Chronic renal failure; *n (%)*		3 (5,2)	28 (48,3)	27 (46,6)	0,224
Liver disease; *n (%)*		1 (11,1)	5 (55,6)	3 (33,3)	0,713
Thyroid disease; *n (%)*		3 (13,6)	13 (59,1)	6 (27,3)	0,229
Habitual					
Smoking; *n (%)*		2 (4,7)	26 (60,5)	15 (34,9)	0,848
Alcohol use; *n (%)*		0 (0)	7 (77,8)	2 (22,2)	0,617

OAD: oral antidiabetic drugs, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index.

Interestingly, significantly more women had diabetic neuropathy than men. Approximately one-third of patients had coronary artery disease (34.9%) (with a male predominance) and diabetic retinopathy with a similar percentage (32.1%). One-quarter of patients had chronic renal failure (stage 1–3) (23.3%), and other comorbidities were seen less frequently, such as heart failure (10%), hypothyroidism (8.8%), chronic liver disease (3.65), cerebrovascular disease (3.2%), and peripheral artery disease (1.6%). The prevalence of smoking and alcohol use was 17.3% and 3.6, respectively.

3.1. Anthropometric and analytic characteristics

The anthropometric and analytic characteristics of the patients are shown in Table 1. The mean BMI was 31.1 ± 5.5 kg/m2 and women had significantly higher BMI values than men ($p = 0.001$; $p < 0.01$). Systolic blood pressure and diastolic blood pressure were 146.0 ± 21.5 mm Hg and 80.6 ± 11.2 mm Hg, respectively, with no sex differences. The mean waist circumference was 103.2 ± 11.8 cm. Hip circumference was significantly greater in women (112.7 ± 12.1) than in men (105.2 ± 7.9) ($p = 0.001$; $p < 0.01$). Mean fasting glucose, HbA1c, and triglyceride concentrations were 184.3 ± 77.9, 8.9% ± 1.9, and 169.6 ± 116.9, respectively. The interesting aspect of these results is their mostly being the diagnostic parameters of metabolic syndrome. LDL cholesterol concentrations were 117.0 ± 37.2 mg/dL slightly higher than what should be expected in a diabetic group, and HDL cholesterol concentrations were 42.0 ± 10.6 mg/dL. As expected women had significantly higher HDL cholesterol concentrations (44.2 ± 10.6 mg/dL) than men (38.8 ± 9.9 mg/dL) ($p = 0.001$; $p < 0.01$).

Non-insulin medications: In our study group, metformin use was 70.7%, followed by dipeptidyl peptidase-4 inhibitor use with 50.6%. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are one of the recently preferred medications for patients with type 2 diabetes, especially if they have cardiovascular disease, because their use decreases insulin dosages and results with less hypoglycemia [7]. Approximately one-sixth of our patients were using SGLT2i. Another recommended non-insulin medication is glucagon-like peptide 1 (GLP-1) analogs, but none of our patients were using them. Alpha-glucosidase inhibitor use was 4.8%. All these medications are preferred in patients with type 2 diabetes because they are weight neutral or help with weight loss. Also, a very critical aspect is their low hypoglycemia risks. Another frequently used antidiabetic medication is thiazolidinedione, namely pioglitazone, which was used in 4.8% of our patients. The non-insulin and insulin medication use distribution is listed in Table 2.

Antihypertensive use was 69.1%, and 41.4% of the patients were taking antihyperlipidemic agents.

3.2. Insulin treatment characteristics

The mean daily insulin use was 43.5 ± 28.9 units. The percentage of patients using only basal insulin was 37.3%. Basal-bolus insulin and basal-plus regimen use were 37.3% and 42.6%, respectively. Different from other regimens, premix insulin use (16.5%) was more predominant in women (20.9%) than in men (9.9%).

3.3. Fasting c-peptide concentrations reflecting beta cell reserves

The mean fasting C-peptide concentrations were 1.9 ± 1.4 (min-max: 0.2–8.2 ng/mL). Women had higher C-peptide concentrations (2.1 ± 1.4 ng/mL) than men (1.7 ± 1.3 ng/mL) ($p = 0.011$) (Table 3). The patients were divided into three groups, those with an insufficient beta cell reserve (C-peptide: <0.5 ng/mL), a borderline reserve (C-peptide: 0.5–2 ng/mL), and a sufficient reserve (C-peptide: > 2 ng/mL). The distribution of patients with insufficient, borderline, and sufficient beta cell reserves was 15 (6%), 142 (57%),

Table 2
Comparison of patients' treatments.

Use of non-insulin medications (total)	Beta cell reserves			*p*
	Insufficient (c-peptide <0.5) (n = 15; 6.0%)	Borderline (c-peptide 0.5–2) (n = 142; 57.0%)	Sufficient (c-peptide >2) (n = 92; 37.0%)	
Metformin; *n (%)*	10 (5,7)	100 (56,8)	66 (37,5)	0,918
Sulfonilurea; *n (%)*	0 (0)	4 (50,0)	4 (50,0)	0,826
Glinids; *n (%)*	0 (0)	1 (25,0)	3 (75,0)	0,461
DPP-4 inhibitors; *n (%)*	5 (4,0)	71 (56,3)	50 (39,7)	0,312
SGLT 2 inhibitors; *n (%)*	2 (5,1)	22 (56,4)	15 (38,5)	0,954
Pioglitazone; *n (%)*	1 (8,3)	5 (41,7)	6 (50,0)	0,389
Alfa glukosidase inhibitors; *n (%)*	0 (0)	8 (66,7)	4 (33,3)	0,892
Anti-hypertensives; *n (%)*	8 (4,7)	92 (53,5)	72 (41,9)	**0,037**
Anti-lipids; *n (%)*	6 (5,8)	53 (51,5)	44 (42,7)	0,279
ASA; *n (%)*	4 (4,3)	58 (62,4)	31 (33,3)	0,368
Insulin applications				
Basal insulin; *n (%)*	6 (6,5)	54 (58,1)	33 (35,5)	0,924
Basal-bolus/Intensive; *n (%)*	7 (6,6)	64 (60,4)	35 (33)	0,539
Basal plus insulin; *n (%)*	0 (0)	3 (33,3)	6 (66,7)	0,239
Premix insulin; *n (%)*	2 (4,9)	21 (51,2)	18 (43,9)	0,595
Total insülin amount *Mean±SD*	40,2 ± 18,8	44,5 ± 30,9	42,5 ± 27,2	0,956

DPP: dipeptidyl peptidase, SGLT: Sodium-glucose cotransporter, ASA: acetylsalicylic acid.

Table 3
Comparison of laboratory parameters of the patients.

Laboratory characteristics		Beta cell reserves			*p*
		Insufficient (c-peptide <0.5) (n = 15; 6.0%)	Borderline (c-peptide 0.5–2) (n = 142; 57.0%)	Sufficient (c-peptide>2) (n = 92; 37.0%)	
Glucose	*Mean±SD*	126,9 ± 61,3	172,9 ± 70,5	211,3 ± 82,2	0,001
HbA1c	*Mean±SD*	8,7 ± 1,8	8,8 ± 1,8	9,0 ± 1,9	0,663
Creatinine	*Mean±SD*	1,0 ± 0,4	0,9 ± 0,3	0,9 ± 0,3	**0,046**
ALT	*Mean±SD*	15,5 ± 4,5	20,7 ± 10,4	24,5 ± 14,0	**0,007**
Uric acid	*Mean±SD*	4,7 ± 1,3	4,8 ± 1,3	5,3 ± 1,6	0,097
GFR	*Mean±SD*	69,6 ± 19,3	78,1 ± 19,0	83,2 ± 18,4	**0,001**
Total cholesterol	*Mean±SD*	186,9 ± 38,2	192,9 ± 45,6	189,8 ± 44,8	0,812
LDL cholesterol	*Mean±SD*	121,4 ± 31,3	121,1 ± 39,1	109,9 ± 34,3	0,080
HDL cholesterol	*Mean±SD*	45,1 ± 12,4	42,4 ± 10,1	40,1 ± 9,8	0,309
Triglyceride	*Mean±SD*	102,8 ± 47,4	154,6 ± 114,4	203,4 ± 119,9	**0,001**
Non-HDL cholesterol	*Mean±SD*	141,9 ± 35,1	150,8 ± 45,5	148,5 ± 46,4	0,754

GFR: glomerular filtration rate.

and 92 (37%), respectively. Age was not correlated with fasting C-peptide concentrations, but there was a statistically significant sex difference between the C-peptide groups ($p = 0.019$; $p < 0.05$). Women were more likely to be in the sufficient beta cell reserve group, and men were mostly in the borderline group.

The mean duration of diabetes was longer in those with a borderline reserve than those with a sufficient reserve ($p < 0.05$). The borderline reserve group also had the most elevated systolic blood pressure ($p < 0.01$). Waist circumference was significantly greater in the sufficient group than in the other two groups ($p < 0.01$), followed by the borderline group. This is a compelling finding because waist circumference is one of the diagnostic parameters of metabolic syndrome, which is insulin resistance related. BMI, another insulin resistance-related parameter, was also significantly higher in the sufficient group than in the others. Also, there were significantly more patients with hypertension in the sufficient and borderline reserve groups than in the insufficient group (Table 1). Fasting glucose concentrations showed the same pattern with having the most significant mean concentrations in the sufficient group, followed by the borderline group and then the insufficient group. In the sufficient reserve group, ALT and triglyceride concentrations were also significantly increased, which are also compatible with metabolic syndrome.

3.4. Correlation analysis

C-peptide concentrations were positively and significantly correlated with waist circumference (r: 0.282; $p = 0.001$), hip circumference (r: 0.251; $p = 0.001$), BMI (r: 0.279; $p = 0.001$), fasting glucose (r: 0.309; $p = 0.001$), and triglyceride concentrations (r: 0.358; $p = 0.001$). The positive correlation of C-peptide concentrations with three parameters of metabolic syndrome is a notable finding, which may further support our hypothesis.

4. Discussion

Our results showed that 94% of patients with type 2 diabetes treated with insulin had borderline or sufficient beta cell reserve as assessed using fasting C-peptide concentrations, and insulin resistance-related parameters were prominent in those with adequate beta cell reserve. These results bring into question the underlying reasons why C-peptide concentrations are largely borderline or sufficient, contrary to expectations, in patients with type 2 diabetes using insulin.

Most of our patients had obesity, especially abdominal obesity, and though they had poor glycemic control, the fact that their beta cell reserve was largely borderline or sufficient might be mainly

related with insulin resistance. When the characteristics of the patients were analyzed, the parameters related to insulin resistance such as waist circumference, hip circumference, BMI, and triglyceride concentrations were found to be higher in patients with sufficient beta cell reserve than in patients who had borderline or insufficient beta cell reserves. The positive correlation found between C-peptide concentrations and these parameters further endorses our belief that insulin resistance, not insulin deficiency, is the primary problem in these patients, and therefore prompts the question as to whether insulin therapy is necessary for these patients.

C-peptide concentrations have been investigated in several studies to assess beta cell insulin reserves in patients with type 2 diabetes. In Deep et al.'s study, patients with type 2 diabetes were categorized as having insufficient (C-peptide <0.5 ng/mL), sufficient (C-peptide: 0.5–3.2 ng/mL), and high (C-peptide: >3.2 ng/mL) insulin reserves, which was found to be 2%, 38%, and 60%, respectively, and they interpreted that high glucose concentrations were a result of insulin resistance rather than insulin insufficiency. They recommended assessing C-peptide concentrations in patients with poor glycemic control to improve treatment choices because C-peptide concentrations reflect endogenous insulin reserves [11].

In a retrospective analysis of 179 patients with type 2 diabetes who were already diagnosed as having diabetes and were under treatment, the mean C-peptide level was found as 2.71 ng/mL, and they stated that 6.7% of patients had insufficient beta cell reserves (C-peptide <0.5 ng/mL), whereas 39.1% had borderline (C-peptide: 0.5–2 ng/mL) and sufficient (C-peptide > 2 ng/mL) beta cell reserves [12].

The possibility that insulin therapy, which is initially started by a physician for any reason, may turn into a permanent treatment in a patient's follow-up could partly explain why patients with adequate or limited beta cells are using insulin.

In current guidelines, it is recommended to initiate insulin therapy in patients with type 2 diabetes with impaired glycemic control, alone or as a component of the combination, especially to reduce glucotoxicity, and then to decide if the treatment should continue by evaluating the glycemic control status and patient characteristics [7,8]. At this point, C-peptide concentrations can be used as a reliable test for treatment decision-making.

There are certain indications, some permanent but others temporary, for the prescription of insulin in patients with type 2 diabetes, such as acute infections, glucotoxicity, hospitalization, inadequate pancreatic beta cell reserves, and end-stage kidney and liver failure. When temporary situations improve, patients should be re-evaluated for their further treatments to prevent clinical inertia.

Exogenous insulin use would prompt excessive hyperinsulinemia, which might be related with poor outcomes because insulin resistance is the predominant feature of type 2 diabetes and patients are hyperinsulinemic for a long time, especially in the early stages of the disease. Disproportional insulin use might cause serious weight gain and possible hypoglycemic episodes, which are important barriers to glycemic control in patients with type 2 diabetes with insulin resistance.

In a study by Ko et al. the authors studied the progression of cardiovascular events and death in patients with type 2 diabetes, which was found to be significantly higher in patients with high C-peptide concentrations and treated with insulin than in the non-insulin user group with high C-peptide concentrations, and the insulin user group with insufficient C-peptide concentrations [13].

In the DIRECT study (Diabetes Remission Clinical Trial) was a primary care-led weight management trial for the remission of type 2 diabetes, which investigated whether the treatment of obesity by lifestyle modifications would lead to diabetes remission in patients with type 2 diabetes. Patients with type 2 diabetes who were not using insulin consumed a very low-calorie replacement diet, and it was observed that 46% of patients achieved diabetes remission at the end of 12 months and glycemic remission continued in more than one-third of the patients in the 24-month follow-up of the same study [14,15].

In another study, Iwao et al. studied 69 patients with type 2 diabetes with sufficient beta reserves who were treated with insulin and evaluated the first-hour C-peptide concentrations to assess beta cell reserves. The patients were switched to liraglutide treatment from insulin instead of insulin, and at the end of the third month, 39 patients reached and maintained the desired glycemic targets without the need for insulin usage [16].

These data support the opinion that in obese and insulin-resistant patients with type 2 diabetes, effective lifestyle modifications and appropriate treatment with antidiabetic agents should allow insulin doses to be reduced or even discontinued while maintaining glycemic control.

4.1. Limitations

One of the potential limitations of our study is the method we used to evaluate beta cell reserves, namely fasting C-peptide concentrations. Though the preferred methods for C-peptide measurement in the evaluation of endogenous insulin reserve are usually glucagon-stimulation C-peptide testing or mixed-meal tolerance test, other tests are available such as random blood C-peptide, fasting blood C-peptide or post-meal urine to C-peptide; creatinine is also indicated [3].

The second possible limitation of our study is the possibility of having patients with different types of diabetes other than type 2 diabetes, like with MODY or LADA. However, during patient selection, we used the patients' verbal confirmation of their diabetes type, their hospital records, and their prescription data history from the National Medula Prescription Inquiry System to at least partially reduce this possibility. The fact that C-peptide concentrations can be suppressed in extreme hyperglycemic conditions should also be taken into consideration when interpreting our results.

Fasting glucose concentrations were significantly higher in patients with borderline and sufficient beta cell reserve when compared with patients with insufficient beta cell reserves. However, most of the patients had borderline or sufficient beta-cell reserve, even though their glycemic control was poor, and C-peptide concentrations would surely become higher after achieving glycemic control.

5. Conclusion

In our study, 94% of patients with type 2 diabetes mellitus who were treated with insulin had either sufficient or borderline beta cell reserves as assessed using fasting C-peptide concentrations.

Intensive lifestyle management and choosing antidiabetic medications that do not cause hypoglycemia and weight gain should be the preferred treatment approach in patients with type 2 diabetes with adequate beta cell reserves.

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