Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.11.712 2020;27(2):648-56

Original Article

Increase in C-peptide levels after resolution of hyperglycemia in patients with type 2 diabetes mellitus: Myths or facts?

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Abstract

Aim: Long term control of glucotoxicity was shown to increase the secretion of insulin and C-peptide (Cp). We aimed to investigate the change in Cp levels after short term glycemic control in patients with uncontrolled type 2 diabetes mellitus (DM).

Material and Methods: Patients with type 2 DM with uncontrolled hyperglycemia were included. Basal fasting Cp levels were measured both at admission (Cp-admission) and after control of hyperglycemia prior to discharge (Cp-discharge). Cp-difference was calculated as (Cp-discharge)-(Cp-admission). The patients were divided as group 1 (positive Cp-difference) and group 2 (negative Cp-difference), and group A (Cp-difference ≥+0.5) and group B (Cp-difference ≤-0.5).

Results: Of the patients (n=123), 61.8% had positive Cp-difference, and mean Cp-differences were 0.16 (±1.59), 0.96 (±1.03), and -1.11 (±1.51) in all patients, group1 and 2; respectively (p=0.001). Mean body weight, creatinine and Cp-discharge were higher in group 1(p=0.045, p=0.013, p=0.001; respectively). Mean age, body mass index(BMI), diabetes duration, hospitalization, proteinuria, fasting and postprandial glucose, glucose-discharge, HbA1c, lipids, TSH, free T4, Cp-admission were similar in group 1 and 2.Cp-difference was correlated positively with Cp-discharge(p=0.001), negatively with Cp-admission (p=0.001). There were no significant differences between subgroups (age, BMI, diabetes duration, use of secretagogue, diabetic ketaoacidosis history, HbA1c (<10 or ≥10%), hyperlipidemia, microvascular complication) regarding to Cp-difference. Positive predictors of positive Cp-difference were cardiovascular disease (p=0.004; Odds Ratio(OR)=3.006) and higher Cp-discharge(p=0.001; OR=6.420);positive predictors of Cp-difference ≥+0.5 were male, lower Cp-admission and higher Cp-discharge.

Conclusion: Our results indicate that short-term glycemic control has little but significant positive effect on basal Cp. Having cardiovascular disease was positive predictor for positive Cp-difference.

Keywords: C-peptide; type 2 diabetes mellitus; glycemic regulation; glucotoxicity

INTRODUCTION

Pancreatic beta cells co-secrete insulin with C-peptide at equimolar concentrations after cleavage of proinsulin. C-peptide has a half-life 3-4 times as that of insulin and was shown to decrease the level of urinary excretion of albumin and improve nerve function in the patients with type 1 diabetes mellitus (DM) (1-4). Based on this knowledge, C-peptide levels may be measured in patients with DM to identify beta cell reserve.

Type 2 DM is a progressive disease characterized by insulin resistance and relative dysfunction of insulin secretion. Increased beta cell function and hyperinsulinemia are observed many years before the diagnosis. Relative dysfunction in insulin secretion is detected earlier stages before diagnosis (5-7). After diagnosis of type 2 DM, endogenous insulin secretion capacity decreases progressively due to both abnormalities in beta cell function and shrinkage of beta cell mass (8-10). Besides endoplasmic reticulum stress and amyloid deposition, glucotoxicity is one of the most important factors contributing to development of beta cell dysfunction (11-19). Hence, as a marker of beta cell function, C-peptide levels increase before diagnosis and then start to decrease

Received: 10.11.2019 **Accepted:** 30.01.2020 **Available online:** 25.02.2020
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in following periods progressively.

Several studies investigated the effect of resolution of glucotoxicity on C-peptide levels in long-term follow-up. However, there are limited reports researching the effect of short-term regulation of hyperglycemia on the level of C-peptide. In our study, we aimed to analyze the change in basal fasting C-peptide levels after short-term control of hyperglycemia in the patients with type 2 DM.

MATERIAL and METHODS

A total of 123 adult patients with type 2 DM who admitted and hospitalized to our clinics with uncontrolled hyperglycemia were included in our study. The study was designed as retrospective cohort. Patients lacking laboratory and clinical data, patients with type 1 DM or LADA (latent autoimmune diabetes of adults), renal failure, history of pancreatitis or pancreas surgery, or liver disease, patients refusing hospitalization or not meeting hospitalization criteria were excluded.

Our study was approved by the Ethics Committee of our university, and we performed our study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was not necessary.

Demographic and clinical data, basic biochemistry and duration of hospitalization were recorded and analyzed. Body weight (kg) and height (m) were measured with patient barefoot and having light clothes. Body mass index (BMI) was calculated as weight/square of height (kg/m2). The diagnosis of type 2 DM was established using "American Diabetes Association 2018 Standards of Diabetes Care" criteria (20). The plasma levels of fasting blood glucose (FBG), transaminases, serum creatinine (SCre), TSH (thyroid stimulating hormone), fT4 (free T4), total cholesterol (Tchol), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG) and were measured after an overnight fasting. Postprandial blood glucose (PPBG) was measured at postprandial 2nd hour. Glucose-discharge was measured as mean blood glucose levels at the day before discharge. FBG, PPBG, SCre, LDL, HDL, TG, Tchol and glucose-discharge were also designated as mg/dL. Measurement of transaminases was designated as IU/L, TSH mIU/L, fT4 ng/dL. Proteinuria was evaluated in untimed urine specimen as urinary albumin to creatinine ratio (mg/g: milligram/gram): ≥30 mg/g was accepted as proteinuria. Screening for diabetic retinopathy was performed by ophthalmologists. Neuropathy was evaluated by screening symptoms and signs of neuropathy in all patients, such as paresthesia or pruritus or burning sensation of hands and foot, palpitation, sweating, orthostatic hypotension, chronic diarrhea or constipation, evaluation of sensation of tactile stimulus and vibration and position by physical examination.

The patients were grouped according to age (<65 or ≥65), BMI (<30 or ≥30 kg/m2), diabetes duration (new onset or known diabetic), presence of cardiovascular disease or microvascular complications (neuropathy, retinopathy or proteinuria), history of diabetic ketoacidosis (DKA), Hemoglobin A1c (HbA1c<10 or ≥10%), ketonuria, hyperlipidemia (LDL<100 or ≥100mg/dL), hypertriglyceridemia (TG<200 or ≥200mg/dL), and cardiovascular drug use or antidiabetic regimen (secretagogue usage positive or negative). Cardiovascular disease was defined as hypertension, coronary artery disease, history of myocardial infarction, coronary artery bypass graft, coronary intervention or cerebrovascular disease. Intensification of therapy was defined as final treatment of the patient at discharge from hospital: basal insulin or intensive insulin regimen. The patient in both regimen groups could take additional oral antidiabetic drug such as metformin or one of DPP-4 (dipeptidyl-peptidase 4) inhibitors but not a secretagouge. Insulin was administered via subcutaneous route. HbA1c was measured with HPLC method (high purification liquid chromatography) as percentage (%).

Basal C-peptide (Cp) levels were measured both at admission to hospital (Cp-admission) and after control of hyperglycemia just prior to discharge (Cp-discharge). Basal Cp levels were measured early in the morning after an overnight fasting with chemiluminescence method by a tool marked Siemens İmmulite 2000(Siemens Medical Solutions Diagnostics 5210 Pacific Concourse Drive, Los Angeles, CA 90045-6900,USA). Intraassay variability of our method was 7.44%. Cp reference range was defined as 0.9-4 ng/mL according to our laboratory analysis. However, we accepted as levels ≥2 ng/mL as sufficient, and <2ng/mL as insufficient basal Cp both for Cp-admission and Cp-discharge, and the patients were further subgrouped according to Cp levels. Cp-difference was calculated as (Cp-discharge)-(Cp-admission). The patients were mainly divided into 2 groups according to Cp-difference: group 1 with positive Cp-difference; group 2 with negative Cp-difference. The patients were also divided into 2 groups according to Cp-difference: group A with Cp-difference ≥+0.5; group B with Cp-difference ≤-0.5.

Cp-discharge and glucose-discharge were measured before discharge and after short-term glycemic control. We defined short-term glycemic control as resolution of hyperglycemia, lack of hypoglycemic episodes and maintenance of normoglycemia depicted as FBG levels of 70-130 mg/dL and PPBG levels of 130-170 mg/dL.

Statistical Analysis

SPSS 22.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of data. We used Shapiro-Wilk test to assess data with normal distribution. Homogeneity of variance was evaluated by Levene test. When comparing independent two groups according to quantitative data, Independent-Samples T test was used. In comparison of categorical variables each other, Pearson Chi-Square test was used. To determine the risk groups for parameters affecting Cp-difference, we used Logistic regression analysis. Odds Ratio (OR) was used

with 95% confidence intervals (CI) to show that risk groups had how higher risk than the other subjects. Pearson correlation(r) analysis was used for correlation among variables. Quantitative variables were defined as mean (X) ±standard deviation (SD) in the tables. Categorical variables were demonstrated as number (n) and percent (%), and p value of <0.05 was accepted as significant.

RESULTS

Mean body weight, creatinine and Cp-discharge were significantly higher in group 1 (p=0.045, p=0.013, p=0.001; respectively). Male/Female ratio was 39/37 in group 1 and 13/34 in group 2; and the percentage of male patients was higher in group 1 (p=0.010). However, mean age, BMI, diabetes duration, hospitalization duration, proteinuria, FBG and PPBG, HbA1c, lipids, TSH, fT4, glucose-discharge and Cp-admission were similar in both groups. Of the patients 61.8% had positive Cp-difference; mean Cp-differences were 0.16(±1.59) ng/mL in all patients (p=0.024). Mean Cp-difference was 0.96(±1.03) in group 1, and -1.11(±1.51) in group 2 (p=0.001) (Table 1).

Baseline characteristics of the patients according to Group A and B were shown in Table 2. Mean Cp-admission was higher in group B; however, mean Cp-discharge was higher in group A (p=0.007, p=0.001; respectively). Mean Cp-difference was +1.41 (±1.07) in group A, -1.69 (±1.68) in group B (p=0.001).

Table 1. Comparison of demographic, clinical and laboratory findings of Groups 1 and 2

	Group 1 (n=76)	Group 2 (n=47)	Total (n=123)	p value
		Mean (±SD)		
Age	57.17 (±12.35)	54.29 (±11.46)	56.07 (±12.05)	0.200
Body weight (kg)	85.69 (±17.89)	79.77 (±14.71)	83.43 (±16.94)	0.045
BMI (kg/m2)	32.12 (±6.66)	30.74 (±6.31)	31.50 (±6.54)	0.338
Diabetes duration (year)	9.32 (±8.17)	7.74 (±6.86)	8.72 (±7.71)	0.441
Hospitalization (day)	8.57 (±5.0)	7.76 (±4.0)	8.26 (±4.64)	0.378
Proteinuria (g/d)	0.64 (±1.46)	0.59 (±1.66)	0.62 (±1.54)	0.406
FBG (mg/dL)	306.68 (±121.94)	310.57 (±110.94)	308.17 (±117.41)	0.638
PPBG (mg/dL)	418.11 (±128.39)	406.34 (±119.62)	413.61 (±124.74)	0.613
HbA1c (%)	10.87 (±1.96)	11.39 (±2.07)	11.07 (±2.01)	0.169
LDL (mg/dL)	121.30 (±43.56)	123.95 (±40.72)	122.31 (±42.35)	0.435
HDL (mg/dL)	41.12 (±8.99)	42.05 (±12.44)	41.47 (±10.41)	0.713
TG (mg/dL)	237.03 (±157.75)	202.08 (±87.57)	223.68 (±135.94)	0.626
Tchol (mg/dL)	212.31 (±62.79)	206.74 (±48.75)	210.18 (±57.68)	0.934
SCre (mg/dL)	1.08 (±0.39)	0.98 (±0.58)	1.04 (±0.47)	0.013
TSH (mIU/L)	1.73 (±3.42)	1.13 (±0.81)	1.50 (±2.74)	0.595
fT4 (ng/dL)	1.17 (±0.26)	1.14 (±0.18)	1.16 (±0.23)	0.711
Cp-admission (ng/mL)	2.11 (±1.37)	2.74 (±2.40)	2.35 (±1.85)	0.244
Cp-discharge (ng/mL)	3.07 (±1.73)	1.62 (±1.22)	2.52 (±1.71)	0.001
Cp-difference (ng/mL)	0.96 (±1.03)	-1.11 (±1.51)	0.16 (±1.59)	0.001
Glucose-discharge	116.75 (±14.59)	115.11 (±14.30)	116.12 (±14.44)	0.542

BMI: body mass index, FBG: fasting blood glucose, PPBG: postprandial blood glucose, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, Tchol: total cholesterol, SCre: serum creatinine, TSH: thyroid stimulating hormone, Cp: C peptide

Table 2. Comparison of demographic, clinical and laboratory findings of Groups A and B

	Cp-difference		p value
	Group A (≥+0.5) (n=47)	Group B (≤-0.5) (n=29)	
Age	56.00 (±12.41)	53.96 (±11.16)	0.239
Body weight	87.19 (±18.66)	81.52 (±12.36)	0.290
BMI	32.48 (±6.30)	31.30 (±5.73)	0.716
Diabetes duration	7.53 (±7.30)	6.65 (±5.86)	0.892
Hospitalization	8.31 (±4.66)	7.86 (±4.11)	0.800
Proteinuria	0.55 (±1.12)	0.47 (±1.14)	0.263
FBG	297.53 (±130.30)	321.24 (±105.02)	0.163
PPBG	422.93 (±141.07)	396.68 (±128.14)	0.418
HbA1c	10.80 (±1.96)	10.98 (±1.75)	0.684
LDL	125.62 (±48.27)	119.46 (±45.90)	0.789
HDL	41.38 (±9.09)	39.81 (±8.83)	0.785
TG	251.02 (±143.64)	217.24 (±87.12)	0.542
Tchol	221.02 (±63.52)	203.03 (±54.66)	0.255
SCre	1.08 (±0.39)	1.04 (±0.71)	0.115
TSH	1.94 (±4.27)	1.15 (±0.87)	0.735
fT4	1.21 (±0.29)	1.15 (±0.182)	0.645
Cp-admission	2.18 (±1.38)	3.51 (±2.68)	0.007
Cp-discharge	3.60 (±1.72)	1.82 (±1.28)	0.001
Cp-difference	1.41 (±1.07)	-1.69 (±1.68)	0.001
Glucose-discharge	113.87 (±12.86)	111.93 (±14.66)	0.463

BMI:body mass index, FBG:fasting blood glucose, PPBG:postprandial blood glucose, LDL:low-density lipoprotein, HDL:high-density lipoprotein, TG:triglyceride, Tchol:total cholesterol, SCre:serum creatinine, TSH:thyroid stimulating hormone, Cp:C peptide

No significant difference was found between group 1 and 2 regarding to distribution of age (<65 or ≥65 year-old) (p=0.102), BMI (<30 or ≥30 kg/m2) (p=0.995), diabetes duration (new onset or known diabetic) (p=0.976), microvascular complications (neuropathy, retinopathy or proteinuria) (p=0.317, p=0.758, p=0.198), history of DKA (p=0.857). Likewise, no significant differences were found between group 1 and group 2 as regards to distribution of HbA1c (<10 or ≥10%) (p=0.224), ketonuria (p=0.309), hyperlipidemia (LDL<100 or ≥100mg/dL) (p=0.910), hypertriglyceridemia (TG<200 or ≥200mg/dL) (p=0.840), antidiabetic regimen (secretagogue positive or negative) (p=0.719), or Cp-admission (p=0.154). The percentage of patients having different final treatment (basal vs intensive) was similar in both groups (p=0.754). 92.1% and 93.6% of the patients in group 1 and group 2 had intensive insulin regimen as final treatment. Thyroid function tests were similar between groups (p=0.546). The ratio of patients

having cardiovascular disease or using cardiovascular drugs was higher in group 1 (p=0.004). The number of patients having adequate levels of Cp-discharge (≥2ng/mL) was higher in group 1 (p=0.001).

The number of patients having cardiovascular disease were significantly higher in group 1 (p=0.004). The ratio of patients with higher Cp-discharge (≥2ng/mL) was higher in group 1 (p=0.001). Positive predictors of having positive Cp-difference were male sex (p=0.011; OR=2.757), history of cardiovascular disease or cardiovascular drug usage (p=0.004; OR=3.006), and higher Cp-discharge (p=0.001; OR=6.420) (Table 3). Positive predictors of having Cp-difference ≥ +0.5 were male sex (p=0.044; OR=2.739), lower Cp-admission (p=0.017; OR=3.25) and higher Cp-discharge (p=0.001; OR=15.18) (Table 4).

Cp-admission was positively correlated with triglyceride, body weight and Cp-discharge (p=0.004, p=0.025, p=0.001; respectively); and negatively correlated with diabetes duration, HbA1c, glucose-discharge and Cp-difference (p=0.009, p=0.043, p=0.020, p=0.001; respectively). Cp-discharge was positively correlated with TG, body weight, Cp-admission and Cp-difference (p=0.001, p=0.001, p=0.001, p=0.001; respectively). Cp-discharge was negatively correlated with glucose-discharge (p=0.031). Cp-difference was positively correlated with Cp-discharge (p=0.001), negatively correlated with Cp-admission (p=0.001) (Table 5).

Table 3. Clinical predictors for positive Cp-difference (Univariate).

Variables	OR (95% CI)	p value
Age	0.458 (0.178-1.182)	0.107
Gender	2.757 (1.262-6.023)	0.011
BMI	1.002 (0.482-2.083)	0.995
Diabetes duration	0.987 (0.405-2.403)	0.976
Cardiovascular disease	3.006 (1.415-6.389)	0.004
Neuropathy	0.68 (0.319-1.450)	0.318
Retinopathy	0.881 (0.394-1.971)	0.758
Proteinuria	0.495 (0.167-1.468)	0.205
Secretagogue	1.155 (0.526-2.539)	0.719
DKA history	1.094 (0.411-2.913)	0.857
Ketonuria	1.555 (0.663-3.649)	0.310
Hyperlipidemia	1.046 (0.480-2.276)	0.910
Hypertriglyceridemia	0.928 (0.448-1.922)	0.840
HbA1c	1.720 (0.714-4.145)	0.227
Cp-admission	0.587 (0.282-1.223)	0.155
Cp-discharge	6.420 (2.850-14.410)	0.001
Final treatment	1.257 (0.299-5.286)	0.755
Glucose-discharge	0.992 (0.967-1.018)	0.539

BMI:body mass index, Cp:C peptide, DKA:diabetic ketoacidosis

Table 4. Clinical predictors for positive Cp-difference ≥+0.5 ng/mL

Variables	OR (95% CI)	p value
Age	0.418 (0.122-1.430)	0.159
Gender	2.739 (1.020-7.400)	0.044
BMI	1.210 (0.470-3.120)	0.690
Diabetes duration	0.900 (0.316-2.560)	0.843
Cardiovascular disease	0.430 (0.169-1.130)	0.086
Neuropathy	0.920 (0.350-2.410)	0.870
Retinopathy	0.680 (0.220-2.050)	0.490
Proteinuria	0.357 (0.091-1.390)	0.127
Secretagogue	0.879 (0.342-2.250)	0.789
DKA history	1.340 (0.330-5.470)	0.670
Ketonuria	1.340 (0.430-4.110)	0.604
Hyperlipidemia	0.600 (0.220-1.580)	0.300
Hypertriglyceridemia	0.860 (0.340-2.180)	0.760
HbA1c	1.460 (0.480-4.410)	0.490
Cp-admission	3.250 (1.190-8.800)	0.017.
Cp-discharge	15.180 (4.740-48.590)	0.001
Final treatment	2.600 (0.270-24.520)	0.387
Glucose-discharge	1.010 (0.970-1.040)	0.541

BMI:body mass index, Cp:C peptide, DKA:diabetic ketoacidosis

Table 5. Correlation of clinical and laboratory parameters in all patients

Variables	Body weight	Diabetes duration	HbA1c	TG	Cp-admission	Cp-discharge	Cp-difference	Glucose-discharge
				r (p)				
Body weight	1 (0.0)							
Diabetes duration	-0.039 (0.670)	1 (0.0)						
HbA1c	-0.035 (0.700)	-0.012 (0.890)	1 (0.0)					
TG	0.150 (0.090)	-0.191 (0.030)	0.026 (0.770)	1 (0.0)				
Cp-admission	0.202 (0.025)	-0.235 (0.009)	-0.182 (0.040)	0.257 (0.004)	1 (0.0)			
Cp-discharge	0.339 (0.001)	-0.153 (0.090)	-0.133 (0.140)	0.304 (0.001)	0.603 (0.001)	1 (0.0)		
Cp-difference	0.129 (0.150)	0.110 (0.220)	0.070 (0.440)	0.027 (0.760)	-0.516 (0.001)	0.371 (0.001)	1 (0.0)	
Glucose-discharge	-0.043 (0.638)	0.103 (0.258)	-0.097 (0.288)	-0.110 (0.228)	-0.209 (0.020)	-0.195 (0.031)	0.034 (0.709)	1 (0.0)

BMI:body mass index, Cp:C peptide, DKA:diabetic ketoacidosis

DISCUSSION

In our study, 61.8% of the patients had positive Cp-difference. Male/female ratio, mean body weight, SCre and Cp-discharge were significantly higher in positive Cp-difference group. Positive predictors of having positive Cp-difference were male sex, positive history of cardiovascular disease or cardiovascular drug usage, and higher Cp-discharge.

Beta cell function decreases in type 2 DM due to progressive loss of beta cell mass. Increased apoptosis impairs the balance and causes decreased number of beta cells (21,22). Histopathological analyses of pancreas from the patients with type 2 DM demonstrated the disruption of structure and decrements of cell numbers (9,23,24). Continuous exposure to hyperglycemia leads to decreased activity of insulin gene transcription activators thereby causing decreased gene expression (25-28). Increased stimulus on endoplasmic reticulum (ER) to synthesize proinsulin causes ER stress and production of unfolded proteins (17,29,30). ER stress may also initiate apoptosis (17). Chronic hyperglycemia also causes oxidative stress (9,25). Metabolic regulation was shown to improve beta cell function (31). Short-term insulin infusion may correct beta cell function and first-phase insulin secretion to some degree in new-onset type 2 DM, and change the course of the disease (32). Insulin was shown to induce differentiation of dedifferentiated beta cells (33).

Nakayama et al investigated the factors contributing to progressive loss of beta cell function in type 2 DM in 382 patients (34). They used glucagon stimulated Cp to measure beta cell function. In minority of the patients, the test was repeated 4-9 years later. They found that diabetes duration, diabetes history in first degree relative, presence of diabetic retinopathy and HbA1c level were negatively associated with Cp increment. In our study, we found that diabetes duration was negatively correlated with Cp-admission but not correlated with Cp-difference. Again, in contrast to their results, we showed that microvascular complications were not associated with Cp-difference. Decreased Cp-admission might already be expected in the patients having longer duration of diabetes due to progressive nature of the disease. Diabetic retinopathy could be detected at the diagnosis of type 2 DM, because pathophysiological changes in type 2 DM have been thought to start years ago. Therefore, development of retinopathy might be expected to be associated with advanced beta cell dysfunction. However, in some rodent studies, the presence of advanced microangiopathy was found also to be associated with islet angiopathy (35). We re-evaluated the patients after short-term glycemic control; however, Nakayama et al. analyzed the patients cross-sectionally (34). In small minority of their patients underwent to a second evaluation, BMI and FBG levels were found to be associated with decrements in stimulated Cp, in a longitudinal manner. Their finding of decreased Cp response longitudinally showed the progressive nature of the disease.

Fujiwara et al. investigated the factors affecting the need of multiple daily insulin injection (MDII) in the patients

with type 2 DM (36). After glycemic control with MDII in 8-9 days, they divided the patients into 3 groups: oral antihyperglycemic agent (OHA), basal insulin plus OHA, MDII. They found that postprandial (2nd hour) Cp and 2nd hour Cp-index were the most reliable factors associated with MDII requirement. Basal Cp after glycemic regulation with MDII was found to decrease comparing to baseline levels in both groups. In our study, 61.8% of the patients had positive Cp-difference; and mean Cp-differences in all patients were 0.16(±1.59) ng/mL. The vast majority (>90%) of our patients had intensive insulin regimen during and after a mean hospitalization duration of 8.26(±4.64) days. As a result, these findings suggested that the change in Cp levels after resolution of glucotoxicity was not a sole factor determining the final treatment protocol. Crisman et al analyzed the change in Cp levels in the intensive care unit settings in 45 patients with type 2 DM (37). They found that insulin administration was independently associated with greater increase in Cp levels comparing to the other patients. We found that Cp-admission was negatively correlated with HbA1c. HbA1c is a dynamic parameter and points to mean blood glucose concentration mostly over last 8-12 weeks (38). Increased HbA1c may be accepted as impaired glycemic regulation, therefore, in states of increased HbA1c and hence glucotoxicity, we expect decreased beta cell function. We re-evaluated Cp after short term glycemic control but not HbA1c. Initial HbA1c was not associated with Cp-difference. In one study, HbA1c was not associated with stimulated Cp increase; however, they evaluated Cp cross-sectionally (34).

In our study, both Cp-admission and Cp-discharge were correlated positively with body weight and triglyceride. Increased triglyceride and body weight may be resulted from insulin resistance. Hence, increased Cp could indicate the patients with higher insulin resistance. Cp-admission was also positively correlated with Cp-discharge, but negatively correlated with Cp-difference. Initial higher Cp might be an indicator of good glycemic regulation, therefore Cp increment could be expected lower. In our study, although there was no significant difference, patients having lower Cp-admission had higher increment in Cp after glycemic regulation. However, higher Cp-discharge was found in positive Cp-difference group. Both Cp-admission and Cp-discharge were negatively correlated with glucose-discharge in our study. This finding indicated that decreased Cp-admission and Cp-discharge would cause increased glucose-discharge even in normoglycemic limits, although we improved hyperglycemia in all patients to a level of glycemic control.

Cardiovascular diseases co-exist frequently with type 2 DM. As a macrovascular complication, co-existence of cardiovascular disease makes us to think that diabetes is advanced and hence beta cell functions might be decreased. Beta cell functions of the patients with advanced diabetes are less likely to increase after glycemic control due to the mechanisms mentioned before. However, we found that the presence of cardiovascular disease was a positive predictor for the patients to have positive Cp-difference. Underlying mechanism of cardiovascular disease to be a predictor for Cp increment could not be explained. We defined cardiovascular disease as a heterogeneous group. The analysis of distinct types of cardiovascular diseases should not be done due to insufficient number of patients for each. When we grouped Cp-difference as in groups A and B, we found that lower Cp-admission and higher Cp-discharge levels were important predictors of having Cp increase ≥ +0.5. Indeed, higher Cp-admission may indicate less worsened beta cell function in hospitalized patients for glycemic regulation. However, a lot of factors may confound the more increase in Cp level according to higher baseline values, because our patients had established beta cell dysfunction irrespective of new or old diabetes. In our study, male sex was found as an important predictor both for positive Cp-difference and for Cp-increase ≥ +0.5.

Impaired renal function is known to decrease the clearance of Cp, however, we found no correlation between Cp and SCre (39). Although SCre levels were significantly higher in positive Cp-difference group, it was not entered to regression model. Cp has also several beneficial effects. In several studies analyzing rats and mice, Cp was found to decrease systemic inflammatory response and thus improve survival (40); however, human studies are limited.

Strengths and Limitations

We evaluated the patients during hospitalization, and measure Cp levels both on admission and just before discharge. Hence, we analyzed the effect of short-term glycemic control on Cp. However, we did not follow-up the patients post-discharge period. To detect the persistence of the changes in Cp levels after short-term glycemic control, further studies analyzing Cp levels during and after hospitalization are necessary. We measured only basal Cp levels after an overnight fasting. Our method was easily accessible, simple and relatively cheap. Different methods have been used to assess beta cell function in clinical investigations. Cp index, postprandial Cp or stimulated Cp after glucagon could also be used. Family history is an important parameter to be evaluated in clinical setting. We did not analyze family history of our patients.

CONCLUSION

Our results showed that short-term glycemic control has little but significant positive effect on basal Cp. Having cardiovascular disease was found as a strong predictor for positive Cp-difference;

however, the mechanism was remained to be explained. Increase in Cp levels after long-term glycemic regulation was shown in so many studies; but we revealed the level of Cp might be elevated even after short-term glycemic control.

Acknowledgements: We are thankful to all authors for contributions in data collection, statistics, article writing and editing. No funding were taken for this study. We declare that no conflict of interest was found for the study.

Competing interests: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports.
Ethical approval: Our study was approved by the Ethics Committee of our university, and we performed our study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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