Original Article

Variables Associated with Persistence of C-Peptide Secretion among Patients with Type 1 Diabetes Mellitus

Ibrahim Abbood Zaboon, Abbas Ali Mansour[1], Nazar S. Haddad[2]

Al-Faiha Specialized Diabetes, Endocrine, and Metabolism Center, Departments of [1]Medicine and [2]Biochemistry, Basrah College of Medicine, Basrah, Iraq

Abstract

Background: C-peptide is a reliable method for estimating the beta-cell residual function. The objective of this study to assess the variables associated with persistence of C-peptide secretion among patients with Type 1 diabetes mellitus (T1DM). **Patients and Methods:** This was a cross-sectional study conducted from October 2015 to September 2016. This study enrolled patients with T1DM with at least 1 year or more duration. Random C-peptide with concomitant plasma glucose at least 144 mg/dl (8 mmol/l) was measured and at this cutoff considered as a stimulated value. Variables that were assessed were age at the time of enrollment, age at the diagnosis of diabetes, gender, family history of diabetes, duration of diabetes, frequency of insulin per day, insulin dose (units/kg/day), type of insulin, devices delivery, body mass index (BMI) at enrollment, blood pressure, glucose (plasma), lipid profile, glycated hemoglobin (HbA1c), thyrotropin (TSH), and antibodies to glutamic acid decarboxylase (GAD65), thyroid peroxidase antibodies (anti-TPO), and tissue transglutaminase antibodies-IgA (anti-TTG-IgA). **Results:** A total 324 patients were included in the study. A higher level of C-peptide has been seen if the disease acquired at the age of 18 years and older with detectable C-peptide observed among 17.7% of those diagnosed at age <18 years versus 31.7% for those aged 18 years or above. The more the duration of diabetes, the more is the loss of C-peptide. On logistic regression analysis, only duration of diabetes <6 years, and insulin dose <1 U/kg/day were statistically significantly associated with the detectable level of C-peptide in this cohort of T1DM. **Conclusion:** Diagnosis of TIDM at a late age, positive family history of diabetes, those requiring <1 U of insulin per kg per day, and higher fasting glucose was associated with higher and more detectable C-peptide. On multivariable analysis, the only duration of diabetes <6 years and insulin dose <1 U of insulin per kg per day remains significantly associated with detectable C-peptide after at least 1 year from the diagnosis of T1DM. The gender, the BMI, blood pressure, the number of insulin injections per day, GAD65, anti-TTG-IgA, anti-TPO antibodies together with random glucose, lipid profile, HbA1c, or TSH levels failed to predict detectable C-peptide at 1 year from the diagnosis of T1DM.

Keywords: *C-peptide, persistence, Type 1 diabetes mellitus*

Introduction

Serum C-peptide levels significantly decreased 5 years after the diagnosis of Type 1 diabetes (T1DM).[1] Residual C-peptide secretion is found in almost one out ofthree individuals three or more years from T1DM diagnosis among cohort in the USA, which is good sign, but indicate that this disease is heterogeneous.[2,3]

The overall frequency of detectable random C-peptide was 29%, decreasing with time from diagnosis regardless of age at diagnosis. The level of C-peptide was higher with diagnosis age >18 years compared with 18 years or less.[3]

The C-peptide level is a surrogate of pancreatic beta-cell mass and insulin secretion and has been, thus, used for diabetes classification.[4] About 93% of individuals have detectable C-peptide 2 years from diagnosis. In 11% of individuals, there was no significant fall from baseline by 2 years .[5]

The objective of this study is to assess the variables associated with persistence of C-peptide secretion among patients with T1DM.

Patients and Methods

Design

This was a cross-sectional study conducted from October 2015 to September 2016. Participants were patients with T1DM.

How to cite this article: Zaboon IA, Mansour AA, Haddad NS. Variables associated with persistence of C-Peptide secretion among patients with Type 1 diabetes mellitus. CHRISMED J Health Res 2017;4:173-9.

Address for correspondence:
Prof. Abbas Ali Mansour, Al-Faiha Specialized Diabetes, Endocrine and Metabolism Center, Department of Medicine, Division of Endocrine and Metabolism, Basrah College of Medicine, P. O. Box: 142, Basrah 61013, Iraq.
E-mail: aambaam@gmail.com

Access this article online

Website: www.cjhr.org

DOI: 10.4103/cjhr.cjhr_2_17

Quick Response Code:

Study procedures

From all, history was taken with clinical examination to assess for the presence of exclusion criteria. Information regarding duration of disease, family history of TIDM, T2DM in the first-degree relatives, insulin frequency per day and type of insulin with device delivery (syringes, pen, human, or analog insulin) was collected.

Anthropometric parameters including weight and height were also measured with bare feet and light clothes using Seca scales, and height measuring equipment and body mass index (BMI) calculated as kg/m^2.

Blood pressure was measured using sphygmomanometer for the right arm in the sitting posture after 5 min rest.

Diabetic foot history was considered positive if the patient currently or in the past has a history of foot ulceration that necessitated local care with or without systemic treatment.[6]

Peripheral neuropathy was diagnosed based on history with objective physical signs.[7]

Inclusion criteria

Patients with T1DM if they agree to participate and has diabetes for at least 1 year or more to avoid partial remission (honeymoon phase).[8]

Eligible patients were clinically classified as having T1DM according to the recommendations of others, but no age excluded if he needs insulin within 1 year of diagnosis.[9-11]

Exclusion criteria

By medical history, physical examination, and routine laboratory test the following were excluded from the study:

- Renal failure (serum creatinine more than 1.4 mg/dl) because C-peptide levels must be interpreted with caution in renal failure (causes the false high level)[12]
- Recent diabetic ketoacidosis within 1 week
- Pregnant women
- Those with random plasma glucose ≤140 mg/dL (They were asked to come next day 2 h after a meal).

Main outcome measure

Study variables associated with detectable levels of C-peptide among patients with TIDM.

Of the 364 patients, 324 were included in the study, all subjects provide verbal informed consent, and the research protocol was approved by the University of Basrah.

Biochemical tests

From each patient, 10 ml of blood was taken during the work time 8:30 am to 2 pm daily. All samples were collected in tubes containing clot activator and ethylenediaminetetraacetic acid (EDTA).

The serum was separated and stored frozen at −20 until analysis, but the plasma test for glucose and whole blood for glycated hemoglobin (HbA1c) was done on the same day of collection.

Grossly hemolytic, lipemic, or icteric samples were excluded from the study.

Fully automated chemiluminescence immunoassay kits, Cobas e411 analyzer series, Roche Diagnostics, Germany, were used for the assay of C-peptide. The performance characteristics of the assay were measuring range 0.01–40 ng/ml (0.003–13.3 nmol/l) with specified intraassay precision 0.5–20 ng/ml, and total variation (sum of intra- and inter-assay variation) was 7%. The normal values kits C-peptide = 0.9–4.3 ng/ml ([0.29–1.43 nmol/L] which mean that 1 ng/mL = 0.333 nmol/L and ng/mL × 331 = C-peptide concentration in pmol/L).

As C-peptide was measured randomly regarding meal consumption at the diagnosis of T1DM, it was considered stimulated.

The preservation of C-peptide, indicating residual beta-cell function, was defined as a stimulated C-peptide level ≥0.6 ng/mL (0.2 nmol/L).[13]

C-peptide and glucose were measured within 7 h of blood sampling to avoid loss of stability.[14] Concomitant serum glucose should be >144 mg/dl (8 mmol/L) because glucose less than that level will suppress insulin and C-peptide) and at this cutoff considered as a stimulated value.[15]

Glucose and lipid profile were measured by clinical chemistry analyzer Bialyzer 300. Lipid estimation was done after at least 8–12 h fast in the morning. Random plasma glucose was measured at the same time of C-peptide, and definition of random was plasma glucose measured at least 2 h from the beginning of the last meal up to <8 h.

Antibodies against the glutamic acid decarboxylase (GAD65) were measured by fully automated chemiluminescent immunoassay MAGLUMI 2000 kit. The measuring range was 1.0–280.0 IU/mL. The cutoff for a positive test is ≥30 IU/mL, and specified the intraassay precision of 12.91 ± 2.75 IU/mL (4.36% CV).

HbA1c was measured by BioRad–D10, high performance liquid chromatography system using blood collected in EDTA tube on the same day of a collected of blood for above biochemical tests.

Thyrotropin (TSH) and thyroid peroxidase antibodies (anti-TPO) were measured in all patients to assess the presence of thyroid autoimmunity using chemiluminescence immunoassay kits Cobas e411 analyzer series (Roche Diagnostics, Germany). Elecsys TSH test is a 3rd generation TSH test. TSH ranged 0.005–100.0 μIU/mL with a reference range of 0.27–4.2 μIU/ml and specified the intraassay precision of 0.1–4 μU/mL (<5% CV). Anti-TPO measuring range 5–600 IU/ml with positive values >34 IU/ml and specified the intraassay precision of >40 IU/ml (<7% CV).

Tissue transglutaminase antibodies-IgA (Anti-TTG-IgA) to screen for associated celiac disease was measured using ELISA (AESKULISA® TTG A). The analytical sensitivity (detection limit) was 1.0 U/Ml. The cutoff value was 15 U/mL for the anti-TTG A. The intraassay precision was 13.8–166.5 U/mL (5.2%–7.0% CV).

Statistical analysis

All data were computed and analyzed using SPSS, (version 23.0, SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as the mean (standard deviation), and categorical variables were summed up as a percentage.

Logistic binary regression was used to see the independent variables significantly associated with detectable C-peptide on univariate analysis.

Statistical significance indicated by a value of $P < 0.05$.

Results

Of the 364 patients, 324 were included in the study and 40 patients were excluded because not completed their investigations.

Table 1 shows baseline characteristics of 324 patients enrolled in this study (180 [55.4%] of them male and 145 [44.6%] female). The age at the diagnosis of T1DM ranges 1–46 year (mean 16.6 ± 8.2 year). Of them, 198 (61.1) patients were below the age of 18 years while 126 (38.9) patients were 18-year-old or more with age at enrollment in the study range from 3 to 50 year. The male constitutes 180 (55.4%) patients, and 145 (44.6%) patients were female. BMI ranges 13.3–38.6 kg/m^2 (mean 23.0 ± 4.6). The family history of diabetes was positive in 105 patients (29.5%) (Whether TIDM of T2DM). The total duration of diabetes was range from 1 to 36 years (mean 7.4 ± 5.9). All patients used insulin therapy with range 2–5 injections per a day (mean 3.5 ± 0.6). Total insulin dose per day ranged 12–160 unit (mean 62.0 ± 22.7). Most of them used human insulin using syringes. The diabetic foot was observed in 18 (5.6) patients, and peripheral neuropathy based on clinical examination was seen in 116 (35.8%) patients.

Table 2 shows baseline biochemical tests. The mean random and fasting serum glucose was 287.8 ± 101.9 mg/dL and 231.5 ± 109.4 mg/dL, respectively, and the mean C-peptide was 0.49 ± 1.03 ng/mL (0.16–0.34 nmol/L). The mean of total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and very LDL-C were 173.9 ± 46.1 mg/dL, 133.9 ± 106.7 mg/dL, 101.7 ± 31.5, 101.7 ± 31.5 mg/dL, and 46.9 ± 13.8 mg/dL, respectively. The mean HbA1c was 10.5% ±2.7%. There were 101 patients (31.2%) GAD65 antibody positive, anti-TPO positive in 58 (17.9%), and 37 patients (11.4%) were positive for anti-TTG-IgA. The mean TSH was 3.7 ± 9.1 μU/mL, and mean C-peptide was 0.49 ± 1.03 ng/mL (0.16–0.34 nmol/L).

Table 1: Baseline characteristics

	Mean±SD or *n* (%)	Range
Age at the diagnosis of diabetes (years)	16.6±8.2	1-46
<18	198 (61.1)	
≥18	126 (38.9)	
Age at enrollment (years)	23.9±9.6	3-50
Gender		
Male	180 (55.4)	
Female	145 (44.6)	
Weight (kg)	58.9±16.3	17-120
Height (cm)	158.5±14.0	98-186
BMI (kg/m^2)	23.0±4.6	13.3-38.6
Family history of diabetes	105 (29.5)	
Duration of diabetes (years)	7.4±5.9	1-36
Insulin injection frequency per day	3.5±0.6	2-5
Total insulin dose/day	62.01±22.71	12-160
Total insulin dose/kg/day	1.06±0.34	0.30-2.50
Type of insulin (human)	322 (99.4)	
Delivery of insulin syringes	322 (99.4)	
Peripheral neuropathy	116 (35.8)	
Diabetic foot history	18 (5.6)	
Systolic blood pressure (mmHg)	118.4±15.5	80-180
Diastolic blood pressure (mmHg)	74.0±10.3	40-120
Total	324 (100)	

BMI: Body mass index, SD: Standard deviation

Table 2: Baseline biochemical tests

	Mean±SD or *n* (%)
Random serum glucose (mg/dL)	287.8±101.9
Fasting serum glucose (mg/dL)	231.5±109.4
Total cholesterol (mg/dL)	173.9±46.1
Triglyceride (mg/dL)	133.9±106.7
LDL-C (mg/dL)	101.7±31.5
HDL-C (mg/dL)	46.9±13.8
VLDL-C (mg/dL)	25.7±20.4
HbA1c (%)	10.5±2.7
GAD65 antibody positive of 285 patients	101 (31.2)*
Anti-TPO positive of 237 patients	58 (17.9)*
TTG antibodies (IgA) (anti-TTG-IgA) positive of 297 patients	37 (11.4)*
TSH (μU/mL)	3.7±9.1
C-peptide (ng/mL)	0.49±1.03 (0.16-0.34 nmol/L)

*Percentage of those underwent testing. LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, VLDL-C: Very low-density lipoprotein cholesterol, HbA1c: Glycated hemoglobin, TPO: Thyroid peroxidase, SD: Standard deviation, TSH: Thyrotropin, TTG: Tissue transglutaminase, GAD: Glutamic acid decarboxylase

Table 3 shows the mean level of C-peptide at the age of disease onset <18 years and those more. A higher level of C-peptide was seen if the disease acquired at age 18 years or more.

Table 4 shows C-peptide levels according to the age ranges (below 18 years and 18 years or more). About 23.1% of the whole cohort has detectable C-peptide. Detectable C-peptide which mean ≥0.6 ng/mL (0.2 nmol/L) was seen in 17.7% of those diagnosed at age <18 years versus 31.7% for those aged 18 years or more that with statistically significant results (P = 0.003). The detectable C-peptide level was more in those with diabetes duration <6 years (33.6.1% vs. 14.9%). This was the strongly significant difference (P < 0.0001). Those with positive family history were more likely to have detectable C-peptide that was statistically significant (P = 0.001). Those with a total daily dose of insulin <1 U/kg/day were more likely to have detectable C-peptide (34.9% vs. 13.5%) with a P < 0.0001. GAD65 antibody positivity dose not associated with the loss of C-peptide. There was no difference in positivity to anti-TTG-IgA in the level of C-peptide. The level of anti-TPO had no effect on the C-peptide level.

Figure 1 shows C-peptide levels according to 6 strata of the duration of diabetes in years. It seems that the more the duration, the more the loss of C-peptide, which was statistically significant (P = 0.002).

Table 5 shows C-peptide levels according to contentious variables.

Only fasting serum glucose and BMI were higher in those with higher C-peptide. None of the other studied variables were statistically significantly associated with higher C-peptide including blood pressure, random glucose, lipid levels, HbA1c, or TSH.

Table 6 shows logistic binary regression for variables significantly associated with detectable C-peptide on univariate analysis. Only duration of diabetes <6 years, and insulin dose <1 U/kg/day were statistically significantly associated with the detectable level of C-peptide in this cohort of T1DM.

Table 3: C-peptide levels- according to the age ranges below 18 years and 18 years or more

	Diagnosed <18 years old	Diagnosed at 18 years and older	Total	*P*
Mean C-peptide levels (ng/mL)	0.3±0.7	0.7±1.2	0.49±1.03	<0.0001
Total, *n* (%)	248 (100)	76 (100)		

Discussion

About 61.1% of patients enrolled in this study had disease onset below the age of 18 years which confirm adolescence prevalence of the disease like that seen by others.[16,17]

Table 4: C-peptide levels- according to multiple variables studied

	C-peptide level ≥0.6 ng/mL (0.2 nmol/L) considered as detectable	C-peptide < level <0.6 ng/mL (0.2 nmol/L) considered as undetectable	*P*
Diagnosed <18 years old, *n* (%)	53 (17.7)	163 (82.3)	0.003
Diagnosed at 18 years and older, *n* (%)	40 (31.7)	86 (68.3)	
Age at enrollment <24 years, *n* (%)	42 (23.5)	137 (76.5)	0.881
Age at enrollment ≥24 years, *n* (%)	33 (22.8)	112 (77.2)	
Duration <6 years, *n* (%)	48 (33.6)	95 (66.4)	<0.0001
Duration ≥6 years, *n* (%)	27 (14.9)	154 (85.1)	
Males, *n* (%)	36 (20.0)	144 (80.0)	0.133
Females, *n* (%)	39 (27.1)	105 (72.9)	
Positive family history, *n* (%)	33 (34.7)	42 (18.3)	0.001
Negative family history, *n* (%)	42 (18.3)	187 (81.7)	
BMI, *n* (%)			
<25	47 (21.2)	175 (78.8)	0.213
≥25	28 (27.5)	74 (72.5)	
2 injections per day, *n* (%)	28 (27.7)	73 (72.3)	0.189
>2 per day, *n* (%)	47 (21.1)	176 (78.9)	
Total insulin per day <1 U/kg/day, *n* (%)	51 (34.9)	95 (65.1)	<0.0001
Total insulin per day ≥1 U/kg/day, *n* (%)	24 (13.5)	154 (86.5)	
GAD65 antibody positive, *n* (%)*	21 (44.1)	45 (43.7)	0.443
GAD65 antibody negative, *n* (%)	81 (79.4)	138 (75.4)	
Anti-TTG-IgA positive, *n* (%)**	8 (21.6)	29 (78.4)	0.925
Anti-TTG-IgA negative, *n* (%)	58 (22.3)	202 (77.7)	
Anti-TPO positive, *n* (%)**	12 (20.7)	46 (79.3)	0.662
Anti-TPO negative, *n* (%)	42 (23.5)	137 (76.5)	

*Only 285 (87.9) patients had GAD65 testing. 35.7% of those tested for GAD were positive, **Only 297 (91.6) patients had anti-TTG-IgA positive testing. 12.4% of those tested for anti-TTG-IgA +ve were positive, ***Only 237 (73.1) patients had anti-TPO testing. 24.4% of those tested for anti-TPO +ve were positive. TPO: Thyroid peroxidase, TTG: Tissue transglutaminase, BMI: Body mass index, GAD: Glutamic acid decarboxylase

Table 5: C-peptide levels- according to continuous variables

	C-peptide level ≥0.6 ng/mL (0.2 nmol/L) considered as detectable[a]	C-peptide < level <0.6 ng/mL (0.2 nmol/L) considered as undetectable[b]	Total	*P*
Systolic blood pressure (mmHg)	120.1±15.2	117.8±15.6	118.4±15.5	0.259
Diastolic blood pressure (mmHg)	73.8±10.3	75.0±10.4	74.0±10.3	0.237
BMI (kg/m^2)	23.9±5.6	22.7±4.3	23.0±4.6	0.009
Random plasma glucose (mg/dL)	289.4±97.3	287.3±103.4	287.8±101.9	0.584
Fasting plasma glucose (mg/dL)	242.8±94.6	227.9±113.8	231.5±109.4	0.024
Total cholesterol (mg/dL)	177.3±52.2	172.7±43.9	173.9±46.1	0.377
Triglyceride (mg/dL)	146.4±152.8	129.4±85.4	133.9±106.7	0.107
LDL-C (mg/dL)	101.0±32.9	102.0±31.2	101.7±31.5	0.908
HDL-C (mg/dL)	45.6±15.2	47.4±13.3	46.9±13.8	0.759
VLDL-C (mg/dL)	28.4±30.6	24.7±15.0	25.7±20.4	0.054
HbA1c (%)	10.6±2.7	10.6±2.7	10.5±2.7	0.729
TSH (μU/mL)	4.3±13.1	3.5±7.6	3.7±9.1	0.095
Total	75 (23.1)	249 (76.9)	324 (100)	

LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, VLDL-C: Very low-density lipoprotein cholesterol, HbA1c: Glycated hemoglobin, TSH: Thyrotropin, BMI: Body mass index

Table 6: Logistic binary regression for variables significantly associated with detectable C-peptide on univariate analysis

	B	SE	*P*	Exp (B)	95% CI for Exp (B)
Age at diagnosis of diabetes (years) <18 years	0.075	0.632	0.906	1.077	0.312-3.721
Duration of diabetes <6 years	1.476	0.453	0.001	4.377	1.801-10.642
Family history of diabetes	0.672	0.449	0.135	1.958	0.812-4.723
Fasting serum glucose	−0.001	0.002	0.573	0.999	0.995-1.003
Insulin dose per/kg/day	1.303	0.450	0.004	3.679	1.523-8.891

CI: Confidence interval, SE: Standard error

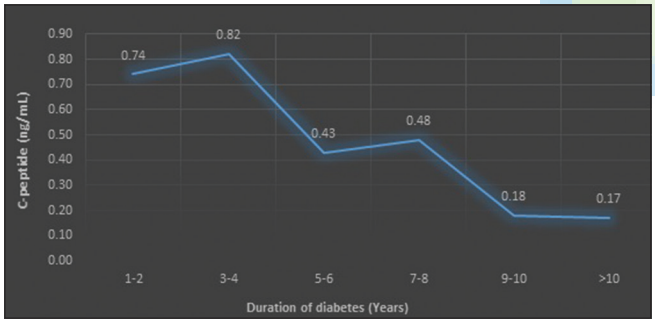

Figure 1: C-peptide levels according to 6 strata of duration of diabetes in years (*P* = 0.002)

Family history of diabetes was positive 29.5% of our patients (both for T1DM or T2DM) while in Hemminki *et al*. study, it was positive in approximately 10% of patients with T1DM.[18]

The total daily insulin dose in the study was 1.06 ± 0.34 with very wide range (0.30–2.5). This is slightly higher than a recommendation, probably because diet education is not integral part of care of diabetes in the third world and the reliance mainly on insulin for glycemic control.[19,20]

Human insulin was the only type of insulin used in most patients in this study. This seems to be a global problem worldwide because of the cost of insulin analogs.[21]

Peripheral neuropathy on clinical criteria was seen in 35.8% and diabetic foot history in 5.6%. Neuropathy was seen in 8.2% among youth with T1DM in the USA cohort.[22,23]

The mean HbA1c in this study was 10.5% ±2.7%. This reflects poor glycemia which was also seen before.[20,24]

About 31.2% of patients in this study were positive for the GAD65 antibody. The prevalence GAD65 antibody was very variable ranges 63%–80%.[25,26] From the same center, of diabetics with age 30 years and more, 26.4% were glutamic acid decarboxylase autoantibodies-positive.[27]

About 17.9% of those tested were anti-TPO positive, which was comparable to other studies, where the prevalence of antithyroid antibodies in children with T1DM at disease onset is about 18%–20%.[25]

About 11.4% of the patients tested for anti-TTG-IgA were positive. The prevalence of anti-TTG-IgA in patients with T1DM is variable. In Egypt, it was seen among 5.4%[28] to 7% in the Czech Republic[26] and reaching to 14.5% in another Iraqi study.[28]

The mean C-peptide was statistically higher among those diagnosed with diabetes at the age of 18 and more. This conclusion was compatible with the newest US study, where diagnosis during adulthood is associated with greater

frequency and higher values of C-peptide.[29] We found that 23.1% of our cohort has detectable C-peptide after at least 1 year after diagnosis of T1DM. However, in US cohort, one out of three has detectable C-peptide.[3]

As regards C-peptide levels, 17.7% of those diagnosed with diabetes before the age of 18 years versus 31.7% of those diagnosed at the age of 18 years or more had detectable C-peptide. This mean diagnosing T1DM at age 18 years or more were associated with more detectable C-peptide and late diagnoses at age 18 years and above associated with less loss of beta cells, which goes with that of study in Belgium and Sweden where younger patients at diagnosis lost more C-peptide after a while.[29,30] Earlier age at diagnosis associated with more loss of a C-peptide level in Spain study.[31] and age at diagnosis is regarded as important cofounder for the persistence of detectable C-peptide.[32] The results of this study were consistent with the USA study diagnosis in adulthood was associated with better and higher C-peptide level.[3]

The more the duration of diabetes, the less the C-peptide level in this study. This relation seems linear over 10 year-period and more.[3] and was similar to other studies.[32]

Duration of diabetes more than 6 years were strongly associated with loss of C-peptide. This was considered as strong predictor of loss beta cells function and subsequent treatment to preserve beta cells and prevention complications in T1DM.[32-34]

As regards the family history of diabetes, detectable C-peptide in this study was more in those with a family history of diabetes. While in Korean study, family history of diabetes was significantly associated with the progressive decline of fasting plasma C-peptide levels, but that was in patients with T2DM.[35]

It seems to be common sense to have more detectable C-peptide in those who need <1 U/kg/day of insulin, and this was the same as we have seen in this study.[13]

None of the autoantibodies screened in our patients predict the persistence of C-peptide after 1 year of T1DM. This was applied for the GAD65 antibody, anti-TTG-IgA, and anti-TPO. The occurrence of autoantibodies did not correlate with C-peptide decline, except possibly for a more rapid loss in insulin autoantibody-positive patients in Sweden study.[30]

The fasting glucose was higher in those with detectable C-peptide may be explained on the basis of mild insulin resistance, but this was not seen before.[33]

Conclusion

Diagnosis of TIDM at a late age, positive family history of diabetes, those requiring <1 U of insulin per kg per day, higher BMI, and higher fasting glucose was associated with higher and more detectable C-peptide. On multivariable analysis, the only duration of diabetes <6 years and insulin dose <1 U of insulin per kg per day remains significantly associated with detectable C-peptide after at least 1 year from the diagnosis of T1DM. The gender, the BMI, blood pressure, the number of insulin injections per day, GAD65, anti-TTG-IgA, anti-TPO antibodies together with random glucose, lipid profile, HbA1c, or TSH levels failed to predict detectable C-peptide at 1 year from the diagnosis of T1DM.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Lee TH, Kwon AR, Kim YJ, Chae HW, Kim HS, Kim DH. The clinical measures associated with C-peptide decline in patients with type 1 diabetes over 15 years. J Korean Med Sci 2013;28:1340-4.
2. Panero F, Novelli G, Zucco C, Fornengo P, Perotto M, Segre O, *et al.* Fasting plasma C-peptide and micro- and macrovascular complications in a large clinic-based cohort of type 1 diabetic patients. Diabetes Care 2009;32:301-5.
3. Davis AK, DuBose SN, Haller MJ, Miller KM, DiMeglio LA, Bethin KE, *et al.* Prevalence of detectable C-Peptide according to age at diagnosis and duration of type 1 diabetes. Diabetes Care 2015;38:476-81.
4. Berger B, Stenström G, Sundkvist G. Random C-peptide in the classification of diabetes. Scand J Clin Lab Invest 2000;60:687-93.
5. Greenbaum CJ, Beam CA, Boulware D, Gitelman SE, Gottlieb PA, Herold KC, *et al.* Fall in C-peptide during first 2 years from diagnosis: Evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. Diabetes 2012;61:2066-73.
6. Frykberg RG, Zgonis T, Armstrong DG, Driver VR, Giurini JM, Kravitz SR, *et al.* Diabetic foot disorders. A clinical practice guideline (2006 revision). J Foot Ankle Surg 2006;45 5 Suppl:S1-66.
7. Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels GJ, Bril V, *et al.* Diabetic polyneuropathies: Update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab Res Rev 2011;27:620-8.
8. ISPAD Clinical Practice Consensus Guidelines Compendium. Phases of Diabetes in Children and Adolescents. [Last accessed on 2015 Apr 25].
9. World Health Organization. Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications. World Health Organization: Diabetes Mellitus: Report of a WHO Study Group. (WHO/NCD/NCS/99.2). Geneva: World Health Organization; 1999.
10. Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, *et al.* Metabolic syndrome in type 1 diabetes: Association with diabetic nephropathy and glycemic control (the FinnDiane study). Diabetes Care 2005;28:2019-24.
11. Lithovius R, Harjutsalo V, Forsblom C, Groop PH; FinnDiane Study Group. Cumulative cost of prescription medication

in outpatients with type 1 diabetes in Finland. Diabetologia 2011;54:496-503.
12. Wahren J, Kallas A, Sima AA. The clinical potential of C-peptide replacement in type 1 diabetes. Diabetes 2012;61:761-72.
13. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med 2013;30:803-17.
14. Jane Ellis M, Livesey JH, Evans MJ. Hormone stability in human whole blood. Clin Biochem 2003;36:109-12.
15. Nosari I, Lepore G, Maglio ML, Cortinovis F, Pagani G. The effect of various blood glucose levels on post-glucagon C-peptide secretion in type 2 (non insulin-dependent) diabetes. J Endocrinol Invest 1992;15:143-6.
16. Skordis N, Efstathiou E, Kyriakides TC, Savvidou A, Savva SC, Phylactou LA, *et al.* Epidemiology of type 1 diabetes mellitus in Cyprus: Rising incidence at the dawn of the 21st century. Hormones (Athens) 2012;11:86-93.
17. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am 2010;39:481-97.
18. Hemminki K, Li X, Sundquist J, Sundquist K. Familial association between type 1 diabetes and other autoimmune and related diseases. Diabetologia 2009;52:1820-8.
19. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, *et al.* Care of children and adolescents with type 1 diabetes: A statement of the American Diabetes Association. Diabetes Care 2005;28:186-212.
20. Mansour AA, Ali Alhamza AH, Almomin AM, Zaboon IA, Al-Ali AJ. Is there is a place for premixed insulin in type 1 diabetes mellitus? Eur J Biomed Pharm Sci 2016;3:89-94.
21. Gill GV, Yudkin JS, Keen H, Beran D. The insulin dilemma in resource-limited countries. A way forward? Diabetologia 2011;54:19-24.
22. Jaiswal M, Lauer A, Martin CL, Bell RA, Divers J, Dabelea D, *et al.* Peripheral neuropathy in adolescents and young adults with type 1 and type 2 diabetes from the SEARCH for diabetes in youth follow-up cohort: A pilot study. Diabetes Care 2013;36:3903-8.
23. Melendez-Ramirez LY, Richards RJ, Cefalu WT. Complications of type 1 diabetes. Endocrinol Metab Clin North Am 2010;39:625-40.
24. Mansour AA, Al-Maliky AA, Kasem B. Determinants of loss of glycemic control in patients with type 1 diabetes mellitus. Prospective cohort study from Iraq. J Diabetes Res Clin Metab 2013;2:1-4.
25. Kawasaki E. Type 1 diabetes and autoimmunity. Clin Pediatr Endocrinol 2014;23:99-105.
26. Prázný M, Skrha J, Límanová Z, Vanícková Z, Hilgertová J, Prázná J, *et al.* Screening for associated autoimmunity in type 1 diabetes mellitus with respect to diabetes control. Physiol Res 2005;54:41-8.
27. Mansour AA, Saead Almomin AM, Ali Alhamza AH. Glutamic acid decarboxylase autoantibodies role in reclassifying diabetes of adulthood in Basrah. Int J Clin Endocrinol Metab 2015;1:13-6.
28. Mansour AA, Najeeb AA. Coeliac disease in Iraqi type 1 diabetic patients. Arab J Gastroenterol 2011;12:103-5.
29. Weets I, Truyen I, Verschraegen I, Van der Auwera B, De Schepper J, Dorchy H, *et al.* Sex- and season-dependent differences in C-peptide levels at diagnosis of immune-mediated type 1 diabetes. Diabetologia 2006;49:1158-62.
30. Ludvigsson J, Carlsson A, Deli A, Forsander G, Ivarsson SA, Kockum I, *et al.* Decline of C-peptide during the first year after diagnosis of type 1 diabetes in children and adolescents. Diabetes Res Clin Pract 2013;100:203-9.
31. Frias MM, Oyakawa YP, Alonso M, Roldan B, Alvarez MA, Barrio A. Residual C-peptide in paediatric patients with type 1 diabetes. ESPE Abstracts 2015;84:3-746. Available from: http://abstracts.eurospe.org/hrp/0084/hrp0084P3-746.htm. [Last cited on 2015 Oct 01].
32. Besser RE, Shields BM, Casas R, Hattersley AT, Ludvigsson J. Lessons from the mixed-meal tolerance test: Use of 90-minute and fasting C-peptide in pediatric diabetes. Diabetes Care 2013;36:195-201.
33. Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, *et al.* C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: Report of an ADA workshop, 21-22 October 2001. Diabetes 2004;53:250-64.
34. Wang L, Lovejoy NF, Faustman DL. Persistence of prolonged C-peptide production in type 1 diabetes as measured with an ultrasensitive C-peptide assay. Diabetes Care 2012;35:465-70.
35. Chung JO, Cho DH, Chung DJ, Chung MY. Plasma C-peptide level is inversely associated with family history of type 2 diabetes in Korean type 2 diabetic patients. Endocr J 2010;57:931-8.