High c-peptide level: marker of mortality in type 2 diabetes mellitus patients

Çiğdem BUDAK ECE[1], Zafer PEKKOLAY*[2], Alpaslan Kemal TUZCU[2]

[1] *Selahattin Eyyubi State Hospital, Clinic of Internal Medicine Diyarbakır/Turkey*

[2] *Dicle University Medical Faculty, Department of Adult Endocrinology, Diyarbakır/Turkey*

Abstract

Objective: We aimed to retrospectively investigate the effect of c-peptide level on mortality in patients with Type 2 Diabetes Mellitus.

Methods: Patients who applied to the Dicle University Medical Faculty in 2012 were screened in the database and included a 1000 DM patient with c-peptide, after 5 years the patients were re-evaluated. The patients were then categorized. The patients were divided into two groups, dead patients and living patients. Two groups of c-peptide levels were compared.

Results: Totally 1000 patients included in the study. 392 (39.2%) of the patients were male and 608 (60.8%) were female, the mean age was 57. Patients were divided into two groups: the patient group who died and the patient group who was living. The number of patients died was 146 (14.6%) and the number of living patients was 844 (75.4%). C-peptide levels were found to be higher in patients who died (3,5 ± 2,7 ng / ml) than those who survived (2,9 ± 1,7 ng / ml) and statistically significant (p<0.05).

Conclusion: The high c-peptide levels in patients with Diabetes Mellitus, it may be an important parameter to predict mortality.

Keywords: Diabetes mellitus, c-peptide, mortality

---

* Corresponding author: Zafer Pekkolay, Assist.Prof. MD , Phone: +90 412 2488001 Internal: 4175, E-mail:drpekkolay@gmail.com

Introduction

Diabetes mellitus is a metabolic disease with insulin deficiency and / or resistance. (1).

The c-peptide was discovered in 1967. The c-peptide is produced by cleavage of the proinsulin from the beta cell. The c-peptide is produced in equal amounts with insulin. Half life is longer than insülin(2). C peptide is biologically active and has been proven by many studies (3,4).

C-peptide exhibit biological activity, induces vascular smooth muscle cells migration and infiltration of inflammatory cells in in vitro studies while promoting atherosclerosis progression in a mouse model (5).

The association between cardiovascular mortality and levels of C-peptide might be explained by the direct role of the C-peptide in promoting atherogenesis. Marx and collaborators showed that C-peptide may facilitate the recruitment of inflammatory cells into early lesions and promote lesion progression by inducing smooth muscle cell proliferation (6,7).

In patients with diabetes mellitus, a positive correlation was found between the level of c-peptide diagnosed and the high-risk disease (8).

Serum C-peptide level in Type 2 DM appears to be significantly associated with atherosclerosis(9).

We aimed to retrospectively investigate the effect of c-peptide level on mortality in patients with Type 2 Diabetes Mellitus.

Materials-methods

Patients who applied to Dicle University Medical Faculty in 2012 were screened from the data base and 1000 DM patient with C-peptide, HbA1c, and glucose levels were included in the study. In March 2017 all patients were screened for mortality. Then the patients were categorized. The two main groups were divided into two groups: those who died and those who were living.

C-peptide level was measured by chemiluminescence method, HbA1c level by HPLC method. Glucose was measured by enzymatic method. Patients had a C-peptide reference range of 1.10-4.40 ng / mL, and a fasting glucose of 70-100 mg / dL.

Data statistical analysis was performed with the SPSS 18.0 program. Categorical and normal distribution was expressed as mean ± standard deviation (SD). The data, which showed no normal

distribution and whose upper and lower limits were wide, were shown as median and (lower limit-upper limit). A binary logistic analysis was performed to compare the group variables with each other. Student's t test was used to compare normal distribution data. Chi square test was used to compare categorical data. Significance was assessed at $p < 0.05$.

An informed written consent was obtained from all participants. The study was approved by the local ethics committee and the reported investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Results

Of the patients included in the study, 392 (39.2%) were male, 608 (60.8%) were female, 146 (14.6%) died, and 844 (75.4%) lived patients.

Table 1: Patients characteristics

	Died patients	**Living patients**	**P value**
C-peptide (ng/ml)	3,5±2,7	2,9±1,7	<0.05
HbA1c (%)	9,4±2,25	%9,1±2,1	0.09
Age(year)	66±11	56±13	<0.01
n(Total: 1000)	146(14.6%)	844(84.4%)	
Female/Male	82/64	526/328	

Mean age in dead patients 66±11 year. Mean age in living patients 56±13 year, C-peptide levels were found to be higher in patients who died (3,5 ± 2,7 ng / ml) than those who survived (2,9 ± 1,7 ng / ml) and statistically significant (p = 0.018) (Table 1).

Discussion

C-peptide level and mortality were found to be higher in patients who died in our study. Cardiovascular diseases were the most common cause of mortality in these patients. This may be related to c-peptide accelerating atherosclerosis.

In the HEAL study, there was a direct correlation between high c-peptide levels and all-cause mortality in breast cancer patients. This relationship was more prominent in patients with type 2 diabetes(10).

Vasic et al. found a positive correlation between insulin resistance and c-peptide levels and high c-peptide levels were observed to accelerate atherosclerosis in animal studies(11).

Rask-Madsen et al. reported that insulin resistance is a marker and risk factor for cardiovascular disease and may be a risk factor for myocardial infarction and stroke(12).

In the mortality studies conducted by Nikolus Marx et al. With 2306 patients, the level of c-peptide was found to be high in patients who died due to all-cause and cardiovascular reasons. Furthermore, patients with high concentrations of c-peptide indicated that endothelial dysfunction, atherosclerosis and coronary lesions were severe(13).

Hirai FE et al. reported that people with high levels of c-peptide and high endogenous insulin had a high risk of all-cause, ischemic heart disease and stroke mortality(14).

Limitations of study: Only patients admitted to our outpatient clinic for one year were included in the study. Data were taken directly from the database. It is also known that the level of C-peptide increases in patients with renal failure. In our study, C-peptide level was not adjusted according to creatinine clearance.

More effective metabolic parameters related to mortality can be obtained from the long-term prospective mortality study in which more patients are received.

In conclusion: The fasting c-peptide level may be used as a new marker of mortality in patients with Type 2 diabetes.

References

1- American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013 Jan;36 Suppl 1:S67-74. doi: 10.2337/dc13-S067.
2- Steiner DF, Cunningham D, Spigelman L, Aten B. Insulin biosynthesis: evidence for a precursor. Science 1967;157:697–700.
3- Wahren J, Ekberg K, Jörnvall H. C-peptide is a bioactive peptide. Diabetologia 2007; 50:503–509.
4- Zhang W, Kamiya H, Ekberg K, Wahren J, Sima AA. C-peptide improves neuropathy in type 1 diabetic BB/Wor-rats. Diabetes Metab Res Rev. 2007 Jan;23(1):63-70.

5- Vasic D, Marx N, Sukhova G, et al. C-peptide promotes lesion development in a mouse model of arteriosclerosis. J Cell Mol Med 2012; 16: 927–935.

6- Marx N, Walcher D, Raichle C, et al. C-peptide colocalizes with macrophages in early arteriosclerotic lesions of diabetic subjects and induces monocyte chemotaxis in vitro. Arterioscler Thromb Vasc Biol 2004; 24: 540–545.

7- Walcher D, Babiak C, Poletek P, et al. C-Peptide induces vascular smooth muscle cell proliferation: involvement of SRC-kinase, phosphatidylinositol 3-kinase, and extracellular signal-regulated kinase 1/2. Circ Res 2006; 99: 1181–1187.

8- Pikkemaat M, Melander O, Mölstad S, Garberg G, Boström KB. C-peptide concentration, mortality and vascular complications in people with Type 2 diabetes. The Skaraborg Diabetes Register. Diabet Med. 2015 Jan;32(1):85-9. doi:10.1111/dme.12608.

9- Nawal C L, Goyal LK, Kumar V, Gautam A, Agrawal A, Mital P. Serum C-peptide level as a predictor of atherosclerosis and cardiovascular disease in type 2 diabetes mellitus. J Mahatma Gandhi Inst Med Sci 2016;21:25-9

10- Irwin ML, Duggan C, Wang CY, et al. Fasting C-peptide levels and death resulting from all causes and breast cancer: the health, eating, activity, and life style study. J Clin Oncol 2011; 29:47 – 53.

11- Vasic D, Marx N, Sukhova G, et al. C-peptide promotes lesion development in a mouse model of arteriosclerosis. J Cell Mol Med 2012; 16: 927–935.

12- Rask-Madsen C and King GL. Vascular complications of diabetes: mechanisms of injury and protective factors. Cell Metab 2013; 17: 20–33.

13- Nikolaus Marx, Guenther Silbernagel, Vincent Brandenburg, et al. Diabetes Care. 2013 Mar; 36(3):708-14

14- Flavio E. Hirai, MPH, Scot E. Moss, MA, Barbara E.K. Klein, Ronald Klein, Diabetes Care. 2008 Mar; 31(3):493-7.