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Internal Medicine

Relation of Fasting C-peptide Level and Occurrence of Hypoglycemia at Insulin Initiation among Patients with Immune Mediated Diseases

Ahmed Ali Abdel-Ati Khedr, [1] MSc, Mohamed Nabil Raafat,[1] MD, Hendawy Abdel-Moety Zedan,[1] MD, Mohamed Abdel Hamid Khedr,[2] MD.

** Corresponding Author:*
Ahmed Ali Abdel-Ati Khedr
aliabdelatikhder@gmail.com

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[1]Internal Medicine Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

[2]Clinical Pathology Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

ABSTRACT

Background: Controlling diabetes is a challenging mission specifically in patients who have an immune-mediated disease. Hypoglycemia is one of the common complications especially during shifting from oral to insulin treatment. So, the Prediction of hypoglycemia may ease diabetes control. C-peptide may have a role in the occurrence of hypoglycemia.
Aim of the study: To assess the relationship between baselines fasting C- peptide (FCP) and hypoglycemia risk at basal insulin initiation in insulin- naïve people with type 2 diabetes.
Patients and Methods: This study was a prospective study conducted on 60 subjects (their age ranging between 40 - 60 years), in which they were divided into 2 groups: Group (A): patients group included 30 patients suffering from type 2 diabetes mellitus with a high level of plasma fasting c-peptide (≥ 2 nmol/L). Group (B): patients group included 30 patients suffering from type 2 diabetes mellitus with a low level of plasma fasting c-peptide (≤ 0.4 nmol/L). Overall Hypoglycemia, nocturnal, and severity of Hypoglycemia were assessed. All patients were selected from the internal medicine department and outpatient clinic (at both Al Hussein and Sayed Jalal University Hospitals).
Results: the comparison between both groups at baseline and after 24 weeks was done regarding Hypoglycemia, overall Hypoglycemia, nocturnal, and severity of Hypoglycemia. Hypoglycemia was statistically significantly found in patients with low plasma fasting C-peptide rather than the patients who had high levels of plasma fasting C-peptide.
Conclusion: Low fasting plasma C-peptide is associated with the risk of hypoglycemia in diabetic patients with the immune-mediated disease who started insulin therapy.

Keywords: *Relation Fasting C-peptide, occurrence hypoglycemia, Insulin Initiation, Immune-Mediated Diseases..*

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by inadequate insulin activity and resistance at first, then progress to a steady reduction in beta cells activity.[1] Because plasma C-peptide is produced in equimolar levels to insulin, it is a straightforward and useful indicator of internal insulin production. C-peptide titer also aids in the process of staging T2DM and prospective clinical care, as well as the classification of diabetic subtypes.[2] In patients with T2DM, the fasting C-peptide (FCP) values > 2nmol/L, suggest insulin resistance activity, correlated with a higher BMI, necessitating higher doses to acquire the targeted HbA1c values.[3] Recent data also support a favorable link between high C-peptide levels and the frequency of cardiovascular disease, as well as an inverse link between diabetic retinopathy progression and high C-peptide levels.[4] Low FCP levels (0.40 nmol/L) in T2DM, on the other hand, suggest advanced insulin deficit and predict a very poor glycemic responsiveness to the secretagogues of insulin, such as glucagon-like peptide-1 (GLP1) receptor stimulators.[5] Contemporary T2DM clinical practices recommendations propose a selected and sequential approach to medicines, with HbA1c readings and the existence of concomitant cardiovascular disease being the most important factors. C peptide is not currently used in clinical practice to identify treatment modalities/strategies or to predict future

hypoglycemia risk.[6] Due to various amounts of the fasting hyperglycemia levels and obesity distribution may promote C- peptide over secretion to varying levels, there is no consensus on what is considered normal and abnormal FCP concentration ranges in T2DM.[7] To investigate if FCP can predict outcomes in persons with T2DM of insulin-naive nature who are taking various oral hypoglycemic medications, including metformin 'MT', sulphonylurea 'SU', thiazolidinediones 'TZD', dipeptidyl peptidase 4 inhibitors 'DPP4', glinides 'GL'; whether alone or combined) after starting basal insulin therapy, we further conducted a post hoc analysis on participant levels from large insulin- naïve cohorts.[7]

In this work we aimed to assess the relationship between baseline fasting C- peptide (FCP) and hypoglycemia risk at basal insulin initiation in insulin- naïve people with type 2 diabetes.

PATIENTS AND METHODS

This study is a prospective study conducted on selected patients from the inward internal medicine department and outpatient internal medicine clinic (at both Al Hussein and Sayed Jalal University Hospitals).

This study included 60 subjects (their age ranging between 40 - 60 years). Subjects are classified into: Group (A): patients group including 30 patients suffering from type 2 diabetes mellitus with a high level of plasma fasting c-peptide ≥ 2 nmol/L. Group (B): patients group including 30 patients suffering from type2 diabetes mellitus with a low level of plasma fasting c-peptide ≤ 0.4 nmol/L.

All participants were subjected to the following workup: Full history and clinical examination, routine chemical analysis (liver function tests and renal function test), routine fasting blood sugar, 2hrs postprandial blood sugar, and HbA1C, plasma fasting C-peptide level, and confirmation of hypoglycemia by measurement plasma glucose level less than 3.9 mmol/L; 70 mg/dL.

The study was performed subjected to Ethical committee regulations of Al Azhar University. Written informed consent from the Patients with an explanation of the procedure's possible hazards & IRB approval was attained.

Statistical Analysis:

The data was initially collected, coded, and eventually entered into the SPSS software v20 package. When the distribution of qualitative data was determined to be parametric, it was provided as a number and a percentage, whereas quantitative data were presented as a mean, standard deviations, and ranges.

The implemented comparison in-between the two included groups with qualitative-type data was conducted through *Chi-square* besides *Fisher exact tests, when appropriate*.

The implemented comparison in-between the two included groups with quantitative-type data and clear parametric distributions was performed through *an Independent t-test.*

The implemented comparison in-between the two included groups with quantitative-type data without clear parametric distributions was attained through the Mann-Whitney test

RESULTS

Table 1: Distribution of the studied cases according to BMI, HbA1c, %, FPG, (mg/dL) and 2-h SMPG overall, (mg/dL) at Baseline.

Baseline	No.= 60 Mean ± SD	Range
BMI	24.01 ± 3.94	16 – 35.1
HbA1c, %	8.81 ± 0.92	7 – 11
FPG, (mg/dL)	195.57 ± 12.15	170 – 220
2-h SMPG overall, (mg/dL)	242.33 ± 15.71	220 – 280

Table 2: Distribution of the studied cases according to BMI, HbA1c, %, FPG, (mg/dL) and 2-h SMPG overall, (mg/dL) After 24 week.

After 24 Week	No.= 60 Mean ± SD	Range
BMI	26.23 ± 3.96	18.3 – 37.1
HbA1c, %	7.28 ± 1.01	6 – 9.9
FPG, (mg/dL)	191.30 ± 12.05	166.6 – 215.6
2-h SMPG overall, (mg/dL)	238.92 ± 15.63	216.5 – 276.7

Table 3: Distribution of the studied cases according to Fasting C-peptide (nmol/L).

Fasting C-peptide (nmol/L)	No.= 60
Group A (≥ 2 nmol/L)	30 (50.0%)
Group B (≤ 0.4 nmol/L)	30 (50.0%)

Baseline		Fasting C-peptide (nmol/L) Group A No.= 30	Group B No.= 30	Test value•	P- value
BMI	Mean ± SD	24.26 ± 2.99	23.77 ± 4.75	0.475	0.637
	Range	20.7 – 35.1	16 – 33.3		
HbA1c, %	Mean ± SD	8.76 ± 0.87	8.86 ± 0.98	-0.429	0.670
	Range	7 – 10	7 – 11		
FPG, (mg/dL)	Mean ± SD	193.00 ± 10.83	198.13 ± 13.01	-1.661	0.102
	Range	170 – 212	180 – 220		
2-h SMPG overall, (mg/dL)	Mean ± SD	242.53 ± 14.38	242.13 ± 17.18	0.098	0.922
	Range	220 – 265	220 – 280		

Table 4: Comparison between Group A (no. = 30) and Group B (no. =30) regarding BMI, HbA1c, %, FPG, (mg/dL) and 2-h SMPG overall, (mg/dL) at Baseline.

After 24 Week		Fasting C-peptide (nmol/L) Group A No.= 30	Group B No.= 30	Test value•	P- value
BMI	Mean ± SD	26.29 ± 3.02	26.17 ± 4.77	0.113	0.910
	Range	22.7 – 37.1	18.3 – 35.6		
HbA1c, %	Mean ± SD	7.19 ± 0.96	7.37 ± 1.07	-0.699	0.488
	Range	6 – 9	6 – 9.9		
FPG, (mg/dL)	Mean ± SD	188.94 ± 10.77	193.65 ± 12.95	-1.534	0.131
	Range	166.6 – 207.9	175.6 – 215.6		
2-h SMPG overall, (mg/dL)	Mean ± SD	239.12 ± 14.36	238.72 ± 17.06	0.097	0.923
	Range	216.5 – 261.5	216.7 – 276.7		

Table 5: Comparison between Group A (no. = 30) and Group B (no. =30) regarding BMI, HbA1c, %, FPG, (mg/dL) and 2-h SMPG overall, (mg/dL) After 24 weeks.

		Fasting C-peptide (nmol/L) Group A No.= 30	Group B No.= 30	Test value•	P- value
Hypoglycemia, overall Incidence	Mean ± SD	44.23 ± 8.63	52.30 ± 7.60	– -3.844	– 0.000
	Range	25 – 59	40 – 75		
Hypoglycemia, nocturnal Incidence	Mean ± SD	16.19 ± 5.14	24.00 ± 6.72	– -5.055	– 0.000
	Range	8 – 35	15 – 40		
Hypoglycemia, severe Incidence	Mean ± SD	1.85 ± 1.19	2.49 ± 1.32	– -1.970	– 0.004
	Range	0 – 3.5	0.5 – 6		
Fasting blood sugar	Mean ± SD	167.03 ± 47.35	175.37 ± 45.86	-0.692	0.491
	Range	110 – 260	86 – 256		

Table 6: Comparison between Group A (no. = 30) and Group B (no. =30) regarding Hypoglycemia, overall, Hypoglycemia, nocturnal, Hypoglycemia, severe and Fasting blood sugar.

There is statistically sig. difference between both groups as regard hypoglycemia. The risk of hypoglycemia increased in patients with low plasma Fasting C-peptide levels.

DISCUSSION

Type 2 diabetes mellitus (T2DM) is a chronic condition associated with insulin insufficiency and insulin resistance at first, followed by a steady reduction in pancreatic beta cells activity.[8] According to the International Diabetes Federation (IDF) figures on worldwide diabetes prevalence, 415 million individuals had diabetes in 2015, with the number expected to rise to 642 million by 2040.[9] Diabetes mellitus comes ninth among the leading causes of death in the world, with one in every eleven adults suffering from the disease, with 90 percent of them suffering from type 2 diabetes (T2DM). T2DM is influenced by lifestyle variables such as age, pregnancy, and obesity, but it also has a substantial genetic component; it refers to those who have insulin resistance and are usually deficient in relative (rather than absolute) insulin. These people do not require insulin medication to survive, at least at first and often throughout their lives.[10] Preproinsulin is generated in the endoplasmic reticulum in response to high blood glucose levels in the -cells of the pancreatic islets of Langerhans, and it is broken by microsomal enzymes to yield proinsulin. Proinsulin

is transported in vesicles from the rough endoplasmic reticulum to the Golgi apparatus in pancreatic -cells, where it is packaged into clathrin-coated secretory granules and processed by a cascade of proconvertases and carboxypeptidases.[11] Plasma C-peptide is typically secreted in an equimolar pattern relative to insulin activity, making it a straightforward indicator for its endogenous production, besides, C-peptide assessment can stage T2DM course and subtypes classifications.[2] Recent data also support a favorable link between elevated plasma C-peptide concentrations and cardiovascular disorder risks, as well as inverse correlations between diabetic retinopathy progression and high C-peptide levels.[4] Low FCP levels (0.40 nmol/L) in T2DM, on the other hand, suggest advanced insulin insufficiency and predict an unpleasant glycemic response after secretagogues of insulin, including the glucagon-like peptide-1 stimulators.[5] Contemporary DM clinical practices recommendations propose a selected and sequential approach to medicines, with HbA1c readings and the existence of concomitant cardiovascular disease being the most important factors. C-peptide is not used in clinical practice to determine treatment modalities/strategies or to forecast the risk of hypoglycemia in the future.[13] Our research found that 60 patients with type 2 diabetes mellitus had a high or low amount of plasma fasting c-peptide. The average age was 54.10 10.90 years. The participants in the study were 33 men and 27 women, with a mean height of 157.32 8.03, a mean weight of 59.25 9.50, a median diabetes duration of 4.0 years, and 27 patients with diabetes in their family. FCP plasma concentrations during insulin commencement can give useful inputs for selecting targeted treatment plans to attain an ideal glycemic goal while avoiding or minimizing the risk of hypoglycemia, according to the current findings. Clinicians will be better able to decide on insulin initiation and titration schemes according to the major defect, whether it is insulin deficit or insulin resistance if FCP levels are known.

The insulin-sensitive person may benefit from a careful and delayed introduction and titration of basal insulin, eventually necessitating prandial supplementation, whereas the insulin-resistant person will benefit from a more aggressive and forced basal insulin titration.

When comparing Hypoglycemia, overall, Hypoglycemia, nocturnal, Hypoglycemia, severe, and Fasting blood sugar levels, there was a highly statistically significant difference between the studied groups for Hypoglycemia, overall, Hypoglycemia, nocturnal, Hypoglycemia, severe, and fasting blood sugar levels. At baseline, there was no statistically significant difference between the study groups in terms of fasting blood sugar, but after 24 weeks, there was a statistically significant negative correlation between fasting C-peptide (nmol/L) and overall hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia.

During 6 months of basal insulin administration, an FCP value over 2nmol/L was correlated to about 10% hypoglycemic risk.[14] Despite an equal reduction in HbA1c in both groups, the lowest FCP group's final basal insulin dose was the lowest, indicating that this group was extremely insulin sensitive and insulin deficient.

In this study, it was discovered that patients with diabetes for an average of 3 to 5 years had a non-statistically significant change between baseline and 24 weeks.

This was in contrast to the findings of Leighton et al.[15] , who found a similar decrease in fasting C-peptide levels with diabetes duration and concluded that the progressive decline in C-peptide levels will contribute to increased blood glucose fluctuations, which in turn will contribute to the development of various vascular complications.[15] They went on to say that, regardless of HbA1c levels, fasting C-peptide estimates can predict the overall fate of diabetic patients in the future.[16] After 24 weeks of follow-up, the relationship between Fasting C-peptide (nmol/L) and overall hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia was shown to be negative. Low C-peptide levels can be considered to be merely a marker of b-cell function, with low levels indicating b-cell failure. Low C-peptide levels are linked to a higher risk of microvascular problems, implying a lack of ability to self-regulate glycaemia, which predisposes to microvascular disease. Patients with greater C-peptide levels, on the other hand, had a slew of risk factors, including hypertension, low HDL cholesterol, hypertriglyceridemia, and obesity, all of which could be linked to insulin resistance and, perhaps, C-peptide resistance. As a result, despite having diabetes for a shorter period, the two C-peptide groups had the same rate of cardiovascular problems.

C-peptide has been shown to have therapeutic effects on arteries by decreasing smooth muscle cell proliferation and migration, as well as anti-inflammatory activities in endothelial cells, in previous studies.[17] C-peptide deposition in diabetic patients' arteriosclerotic lesions, chemotactic action against monocytes and CD4C lymphocytes, and activation of vascular smooth muscle cell proliferation have all been revealed by other kinds of literature.[18]

CONCLUSION

According to our study, there was a negative correlation between fasting c- peptide levels and the occurrence of hypoglycemia in diabetic patients with immune-mediated disease who started insulin therapy. Low fasting plasma C-peptide is associated with an increase in the risk of hypoglycemia, which requires a low initial insulin dose.

Conflict of interest : none

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