American Journal of Medical and Biological Research, 2018, Vol. 6, No. 1, 16-20
Available online at http://pubs.sciepub.com/ajmbr/6/1/4

DOI:10.12691/ajmbr-6-1-4

Importance of Measuring Serum C-peptide in the Biological Care of Hyperglycemia Patients and Diabetics' Patients on Insulin in Côte d'Ivoire

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Abstract Diabetes, the leading cause of high blood glucose, is a pandemic disease with serious complications (paralyzing, deadly) despite the available diabetes treatment. C -Peptide, is generally secreted in amounts equal to insulin in the blood, is a reliable marker of insulin function and production in diabetics patients under insulin therapy. In Côte d'Ivoire, the prevalence of diabetes is 2.3% (2015) and no study has been conducted so far on the C-peptide to evaluate the actual proportion of insulin in high blood glucose. This is a prospective study based on cases-controls conducted on a cohort of 60 patients and 30 controls from the period of November 2015 to February 2016 .The study involved only adult patients' with hyperglycemia blood samples on one hand and those assumed diabetics on insulin therapy. Pregnant women and children were not included. Analysis of C-peptide was performed on the sera from blood samples collected. Using ELISA kit chain PR 4100 by Bio-rad. The results show that the mean value of the C- peptide is normal with no significant difference in patients with hyperglycemia ($P = 0.1343$). However, the difference is significant in diabetics patients on insulin therapy ($p < 0.0001$). In conclusion, the determination of C-peptide level allowed knowing the amount of insulin secreted by the pancreas. It would be better, with the persistence situation of hyperglycemia, to evaluate the concentration level of C-peptide before commencement of any diabetes treatment exogenous insulin in particular.

Keywords: *Côte d'Ivoire, C-peptide, Diabetes, Hyperglycemia, Insulin*

Cite This Article: Lydie Boyvin, Zazou Ange Kevin Zokoré, Aya Jeanne Armande Aké, Yao Nestor N'Guessan, Kipré Laurent Séri, Adou Francis Yapo, and Allico Joseph Djaman, "Importance of Measuring Serum C-peptide in the Biological Care of Hyperglycemia Patients and Diabetics' Patients on Insulin in Côte d'Ivoire." *American Journal of Medical and Biological Research*, vol. 6, no. 1 (2018): 16-20. doi: 10.12691/ajmbr-6-1-4.

1. Introduction

The diabetes pandemic is a major public health problem (400 million worldwide in 2013 [1]. In Africa 20 million people are affected with diabetes and the highest mortality rate 76% of deaths [2]. Côte d'Ivoire belongs to the lower prevalence areas with 2.3% in 2015 [3]. Hyperglycemia occurs when the amount of insulin in the blood is insufficient or ineffective. Glucose cannot enter into the body cells due to lack of insulin, thus leading to its accumulation in the blood, increasing glucose level in the blood [4]. The most common causes of hyperglycemia are diabetes, cardiovascular diseases, renal, hepatic, and endocrine and also risk Factors such as stress, decreased physical activities, unbalanced or poor diet. Insulin plays a major role in blood glucose regulation [5] and maintains the normal levels in the blood constantly (0.75 g / L to 1.10 g / L or 4.13 to 6.05 mmol / L). C-peptide is secreted in equimolar amounts with insulin by cleavage product of proinsulin in the β cells of the islets of Langerhans [6]. Insulin, with a shorter lifespan, is essentially eliminated by the liver, while the C-peptide is decomposed, and eliminated by the kidney and thus less subjected to variations compared to insulin [7].

C-peptide is considered to be a reliable marker of residual insulin function in diabetic patients under insulin therapy [8], it must be evaluated in patients with persistent hyperglycemia. Indeed this hyperglycemia may be due to defective secretion, or inhibition of the activity of insulin or a signaling problem at the receiver target cell [9]. Unfortunately in Côte d'Ivoire, the measurement of C-peptide concentration in blood serum is not performed in people with persistent hyperglycemia. This study is a precept study whose general objective is to ensure improved medical care for people with hyperglycemia or diabetics patients under insulin therapy.

2. Materials and Methods

2.1. Study Setting

This is a prospective study (case/control) conducted from November 2015 to February 2016. It involved blood

samples from patients with hyperglycemia and diabetic patients under insulin treatment followed treated in the diabetology department of the University Hospital Center of Yopougon (Abidjan). Blood Samples from non-diabetic adults with normal blood glucose were used as controls. Pregnant women and children were not included in this study. The assays were performed in the laboratory of the department of Medical Biochemistry and Fundamental at the Pasteur Institute in Côte d'Ivoire.

2.2. Study Type of Participants and Materials Involved

The biological material consisted of fasting venous blood samples, from 30 patients with hyperglycaemia, 30 diabetic patients on insulin and 30 control, in no anticoagulant tubes (dry tubes), and into tubes containing potassium oxalate and sodium fluoride only for the blood glucose measurement. The serum obtained from the dry tubes, centrifuged at 3000 rpm / min for 5 minutes, was aliquot and stored at -20°C until the performance of biochemical analysis. Beside the small equipments and consumables for the determination of various biological parameters, the major technical equipment was made up of components of C-peptide ELISA Kit by Sigma-Aldrich SE 120040-1KT (Lot: CPT 4779), an orbital shaker, a reader microplate ELISA PR 4100 by Bio-rad.

2.3. Determination of C-peptide

Quantitative detection of the C-peptide was carried out by Sandwich ELISA (Enzyme Linked Immuno Sorbent Assay). This is an enzyme immunoassay on solid material, the principle is based on the Ag-Ab reaction, can detect the presence of antibody or antigen in a sample. The absorbance reading was made with an ELISA reader at 450 nm. The color intensity is proportional to the concentration of C-peptide in the sample analyzed.

2.4. Determination of Biochemical Parameters

Moreover, the biochemical parameters like Alpha-Amylase, total cholesterol and its fractions (HDL cholesterol, LDL cholesterol), Creatinine, Glucose, Thyroid Stimulating Hormone (TSH), Transaminases, Triglycerides were measured on automated Cobas C311 and Architect Plus i1000 SR Abbott whose principles are based on the reaction of TRINDER which is an enzymatic and colorimetric method using a chromogene [10]. The intensity of the colors is directly proportional to the concentration.

2.5. Statistical Analysis

Statistical analysis of the results expressed as mean with standard error (mean ± SEM) was carried out using the Graph Pad Prism 5.0 software (Microsoft U.S.A.) using analysis of variance (ANOVA ONE WAY). The differences between means were determined according to the multiple comparison test of Tukey. $P < 0.05$ is considered significant.

3. Results

The mean age of the study population was 55 ± 12.37 years for diabetic patients on insulin; 53 ± 2.86 years for hyperglycemia population, and 53 ± 15.69 years for controls population.

In diabetics patients on insulin, type 2 diabetes was predominant, 93.33% (28/30) against type 1 6.67% (2/30).

The average blood glucose values obtained were significantly higher in diabetics (9.68 ± 0.15 mmol / L) and in hyperglycemic patients (9.46 ± 0.14 mmol /L) than in controls (4.73 ± 0.15mmol / L) with $p < 0.0001$ (Figure 1).

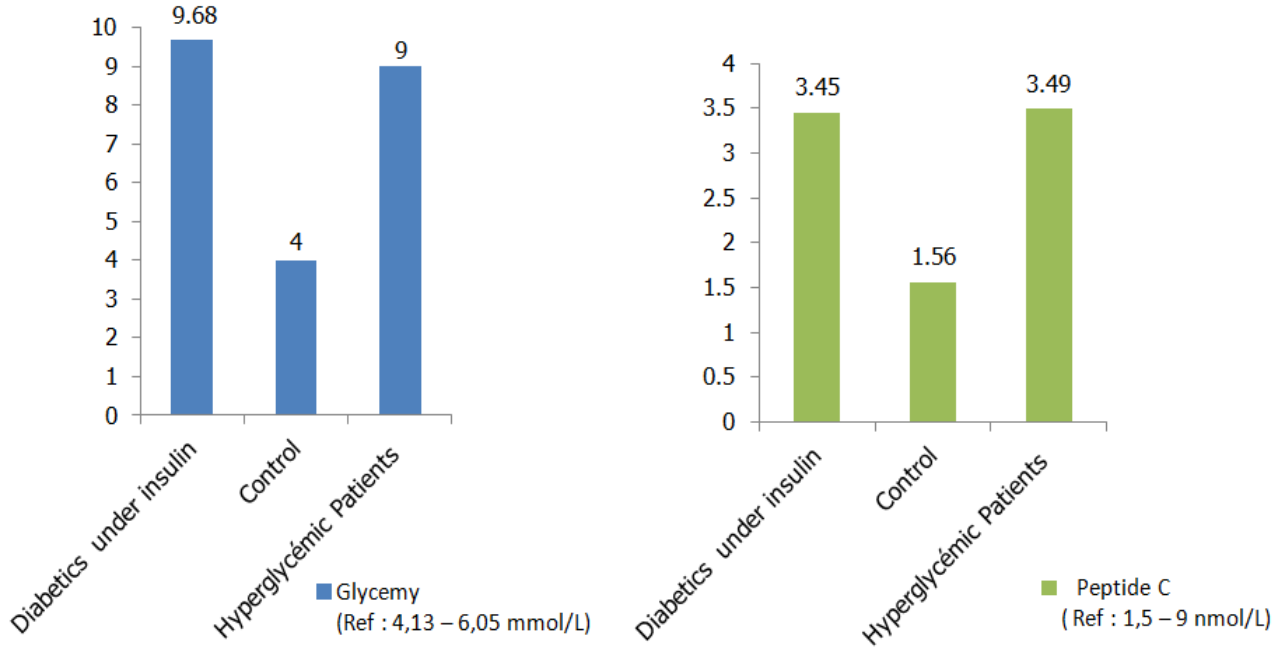

Figure 1. Concentration means value of blood glucose and C Peptide in the study population

As for the average values of C-peptide in hyperglycemic patients (2.49 ± 0.14 nmol / L) and in diabetics on insulin therapy (3.45 ± 0.30 nmol /L), they were in the normal reference range. (Figure 1).

In general, C-peptide concentrations in the study population ranged from 0.75 ± 0.04 to 5.10 ± 0.44 nmol /L.

The average values of C-peptide in clinically confirmed type 1 diabetics (3.87 ± 1.06 nmol / L) and type 2 (3.42 ± 0.32 nmol / L) were normal but higher than in controls population (1.56 ± 0.14 nmol / L) with no significant difference p = 0.196 (Table I).

Forty percent (12/30) of patients have C-peptide mean value below normal (0.75 ± 0.04 nmol / L) against 60% (18/30) of patients who have C-peptide value greater than or equal to normal (5.10 ± 0.44 nmol / L). The difference is significant p < 0.0001 (Table 1).

The biochemical parameters values obtained in patients on insulin therapy indicated that the mean values of total cholesterol (7.35 ± 0.09 mmol / L; 4.48 ± 0.07 mmol / L), triglycerides (2.01 ± 0.09 mmol / L; 0.99 ± 0,05mmol / L), creatinine (345 ± 9.14 mmol / L; 80 ± 0.40 mmol / L), thyroid stimulating hormone (TSH) (6.10 ± 0.72 mIU / L; 1.91 ± 0.24 mIU / L) and alpha-amylase (160 ± 12.35UI / L; 64 ± 6.37UI / L) respectively were significantly higher than the values obtained in controls population p < 0.0001 (Table 2).

Of the 30 hyperglycemia patients, 15 patients received no oral antidiabetic treatment (8.75 ± 0.15 mmol / L) and 15 others on treatment have high blood glucose levels of 10.12 ± 0.24 mmol / L (P = 0.403, not significant). The concentrations of C-peptide were (3.12 ± 0.15 nmol / L) and (1.89 ± 0.13 nmol / L) respectively (P <0.0001, highly significant).

Regardless of patients treatments status either on oral antidiabetes treatments or not the respective average values of biochemical parameters were observed. All belong to the ranges of normal reference values.

Thirteen diabetic patients out of thirty (43.33%) were hypertensive against 17/30 (56.67%) who have normal blood pressure.

Table 1. C-peptide concentrations in diabetic patients on insulin and according to the different types of diabetes highlighted by the physicians

C-peptide Concentration	Diabetics on insulin		Control (n = 30)	P value
	Population (n = 30)	Concentration average value C-peptide Mean ± SD		
< 1.5 nmol/L	n =12	0.75 ± 0.04	1.56 ± 0.14	0. 001*
≥ 1.5 nmol/L	n =18	5.10 ± 0.44		
Concentration average value Peptide C (nmol/L)	**Diabetics Type 1 on insulin (n = 2)** Mean ± SD	**Diabetics Type 2 on insulin (n = 28)** Mean ± SD	**Control (n = 30)**	**P value**
	3.87 ± 1.06	3.42 ± 0.32	1.56 ± 0.14	0.196

Notes: Reference value of C-peptide Concentration**:** 1.5 – 9 nmol/L
* P values < 0.05 significant.

Table 2. Average values of biochemical parameters in diabetic patients on Insulin

Concentration Average value	Control (n = 30) Mean ± SD	Diabetics on insulin (n = 30) Mean ± SD	P value
Total Cholesterol (mmol/L)	4.48 ± 0.07	7.35 ± 0.09	0.0001***
HDL Cholesterol (mmol/L)	1.32 ± 0.09	1.39 ± 0.07	0.612
Triglycerides (mmol/L)	0.99 ± 0.05	2.01 ± 0.09	0.0001 ***
Alpha-amylase (UI/L)	64 ± 6.37	160 ±12.35	0.0001 ***
Creatinine (µmol/L)	80 ± 0.40	345 ± 9.14	0.0001 ***
TSH (mUI/L)	1.91 ± 0.24	6.10 ± 0.72	0.0001 ***
ASAT (UI/L)	18 ± 1.19	49 ± 0.01	0.610
ALAT (UI/L)	16 ± 1.69	18 ± 13.57	0.748

Notes: Reference value of Total Cholesterol Concentration: 2.73 - 6.45 mmol/L
Reference value of HDL Cholesterol Concentration: 1.19- 1.58 mmol/L
Reference value of Triglycerides Concentration : 0.34 - 1.53 mmol/L
Reference value of Alpha-amylase Concentration : < 100 UI/L
Reference value of Creatinine Concentration : 44 - 106 µmol/L
Reference value of Thyreostimulin hormone (TSH) Concentration : 0.35 - 4.94 mUI/L
Reference value of Aspartame aminotransférase (ASAT) Concentration: 7 - 49 UI/L
Reference value of Alanine aminotransférase (ALAT) Concentration : 7 - 46 UI/L.
* P values < 0.05 significant, *** P values < 0.0001 highly significant

4. Discussion

In the study of diabetics on insulin therapy population, the prevalence of type 2 diabetes is in line with the WHO 2015 report which showed that type 2 diabetes accounts for 90% of diabetes cases in the world. The hyperglycemia observed indicating that these patients have an elevated blood glucose levels despite insulin treatment. Patients clinically declared to be type 1 and type 2 diabetics have a normal C-peptide value, which means that they secrete

insulin normally. They do not need exogenous insulin intake. Gaillard's study showed lower secretion of C-peptide than the normal value for the type 1 diabetic and in type 2 diabetic C-peptide secretion equal or above normal value [11]. Therefore type 1 diabetes reported in our study population could be biologically type 2 diabetes.

The average concentration of C-peptide of less than 1.5 nmol / L observed in 12 of 30 patients with diabetes on insulin therapy means that these diabetics patients secrete insulin in a small amount or no secretion of insulin. Therefore they need an exogenous insulin intake to compensate for this deficit. Biologically they belong to Type 1 diabetics.

The average concentration value of C-peptide greater than or equal to 1,5 nmol / L in the other 18 patients out of 30 diabetics on insulin mean that these diabetics patients normally secrete insulin. They have no need for exogenous insulin intake; whereas, they are receiving insulin treatment. They belong biologically to type 2. These results are consistent with the work of Jones and Hattersley who found a C -peptide value of 0.5 nmol / L in type 1 diabetics and 1.5 nmol / L in type 2 diabetics [12].

The biochemical parameters values obtained in or study showed that there are biological risk factors and non-biological (e,g High blood pressure, ...) linked to diabetes. Schnell and Martín-Timón have shown that diseases such as nephropathy, neuropathy, dyslipidemia, hypertension, cardiovascular diseases are linked to diabetes [13,14]. This could explain the persistence of hyperglycemia in diabetic patients on insulin treatment.

In hyperglycemic patients**,** an elevated blood glucose level compared to control population confirms the ir hyperglycaemic status. A Normal C-Peptide level observed in patients indicates that hyperglycemic patients secrete insulin normally. These results are consistent with the work of Grimaldi who showed that insulin is a hormone regulating blood glucose [5]. The study conducted by Akuri has also shown that the C-peptide is a reliable marker of residual insulin function in diabetics on insulin [8]. The lowered average value of C-peptide obtained in patients on oral antidiabetic treatment may be explained due to the fact that the oral antidiabetic treatment reduces insulin resistance and enables its normal secretion by the pancreas [15].

The persistence of hyperglycemia despite oral antidiabetic treatment may be explained by unknown risk factors as demonstrated in Saudi Arabia by Sayed [16]. However, in our study population, the biological risk factors represented by the biochemical parameters in diabetics patients receiving treatment, are known. This could be due to lack of physical exercise, poor or no diet compliance or stress. The work of Umpierrez justify these results by the fact that a diet richer in carbohydrates than usual, decreased physical activity, physical or psychological stress cause hyperglycemia [17].

5. Conclusion

This study clearly shows that some diabetic patients who should not receive insulin are on insulin therapy. It would be better, in view of the persistence of hyperglycemia to measure the concentration of C-peptide before any antidiabetic treatment especially before prescribing exogenous insulin, is good to search for the risk factors through laboratory tests and asking useful questions (balanced diet, physical activity and stress management).

6. Ethical Consideration

The study was conducted in accordance with the Helsinki Declaration 2000 on HIV and AIDS research conducted in poor countries and to the local legislation of the national program on treatment management for People Living with HIV / AIDS (decree No. 411 of December 23, 2001). Informed consent was obtained from patients for the use of their blood for research purpose after completing the standard analyzes prescribed by their doctor.

Acknowledgements

Pr Adrien Lokrou and diabetology department of the University Hospital Center of Yopougon (Abidjan, Côte d'Ivoire).

Pr Dembele and the laboratory of Blood Transfusion Center (Abidjan, Côte d'Ivoire) for ELISA chain.

Pasteur Institut of Côte d'Ivoire for the provision of automatic equipment needed for the study.

Statement of Competing Interests

The authors declare no competing interests.

List of Abbreviations

HIV / AIDS: Human immunodeficiency virus/Acquired immune deficiency syndrome

WHO: World Health Organization

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