The Relation between Serum C-peptide Levels and Diabetic Retinopathy in Type 1 Diabetic Patients in an Egyptian population: An observational retrospective study

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Abstract: Objective: The aim of the study is to confirm the relationship between low serum C-peptide levels and microvascular diabetic complication, especially diabetic retinopathy in Type 1 diabetics in the Egyptian population. **Research Design and Methods**,20 type 1 Egyptian diabetic patients (9 males and 11 females) were selected and included, matching demographic criteria (average age of 18 years, range 14 - 22) and all were diagnosed having diabetes for about 5 years duration (range 4.7 - 6.2). All recruited patients were followed during the 5 years by regular follow-up visits, a visit every 4 months (3 visits per year). Serum C-peptide and Fundus Examination were estimated twice, at year 1 (recruitment period) and at year 5 at the end of the study. **Results**: At the end of our retrospective observational study period (5years) and among the 20 followed patients, 3 patients (15%) - all females - developed moderate NPDR changes, all 3 subjects had very low undetectable serum C-peptide levels (0.01-0.15 ng/ml) (p<0.01)5 patients (25 %) - 2 males and 3 females - developed mild NPDR changes, all 5 subjects had a low serum C-peptide level average 0.2 ng/ml (range 0.15 - 0.3) (p<0.01).No diabetic retinopathy changes could be detected by fundus examination in the remaining 12 patients (60%) at the end of the study period. All 12 subjects had an average serum C-peptide level of 0.4 ng/ml (range 0.2 - 0.7). Average HbA1c level among all patients, was 7.3% (range 6.5- 7.8%). It did not correlate much with the incidence of DR and it was not statistically significant. (p<0.5).**Conclusion**: Diabetic retinopathy is a serious disabling microvascular diabetes complication. Early detection plays a major role for its prevention and prognosis. C-peptide levels could be a valuable diagnostic tool for the prediction of this diabetes complication and deserves more awareness among the healthcare providers for the benefit of our patients.

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Keywords: C-Peptide, Diabetic Retinopathy, Type 1 Diabetes Mellitus in Egypt.

1.Introduction

Diabetes Mellitus

The Global BurdenDiabetes is now considered one of the top non-infectious pandemic diseases. (1) About 382 million diabetics have been diagnosed worldwide with an estimated 46% undiagnosed cases. Furthermore, it is expected to grow, to affect over 592 million people worldwide, (2) making diabetes the 7th leading cause of death (3).(Fig. 1)

This inflation of the disease is seen in both type 1 as much as type 2. (2)

Diabetes prevalence in Egypt

As a global pandemic, affecting mainly low- to middle- income countries, Egypt is highly affected. According to the International Diabetes Federation (IDF), Egypt is ranked as the 9th most affected country in the world, (Fig.2) with more than 7 million diabetic patients reported (2) (~9% of the population)

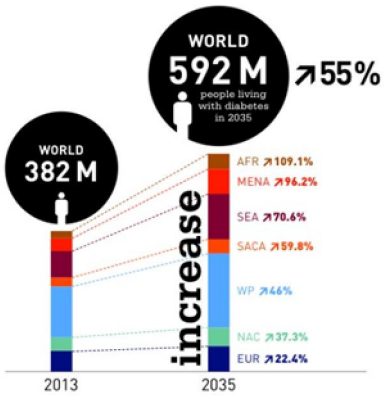


Figure 1: Diabetes Pandemic

Diabetic Retinopathy (DR)

Diabetic Retinopathy is one of the microvascular complications of Diabetes Mellitus. It is the most important cause of visual loss in the world, and is considered the main cause of impaired vision in diabetic patients, affecting ~20%.

According to the World Health Organization (WHO), diabetes is the leading cause of blindness. (3)

Figure 2: Egypt ranking 9th Diabetic Population, 2013

Objective

Chronic hyperglycemia has been linked to the development and progression of diabetes complications. (4) Furthermore, HbA1c was proved to be a sensitive tool that predicts retinopathy in Egyptian diabetic patients. (Fig3) (5).However, HbA1c mirrors Mean Blood Glucose (MBG), but doesn't reflect glycemic variability, a major factor for the development of microvascular complications. (4)

Therefore, in this study, we are aiming to add C-peptide as a predictive marker for the development of diabetes microvascular complications, and to confirm the relationship between low serum C-peptide levels and DR development in T1DM patients.

2. Research Design and Methods

Thirty two type 1 Egyptian diabetic patients were selected from a specialized diabetes clinic located at Cairo, Egypt. 20 of the 32 patients completed the study period. The dropout candidates were mainly excluded due to failure to attend the regular follow up visits and adherence to the therapeutic regimen. All included candidates' parents signed an informed consent. The 20 patients, (11 females and 9 males) were matching demographic criteria; average age of 18 years (ranging from 14 to 22), and all were diagnosed with diabetes for about 5 years duration (ranging from 4.7 to 6.2). (Fig 10,11,12) All recruited patients were followed during the 5 years by regular follow-up visits, a visit every 4 months (~3 visits a year). Every visit included the following; **1-** medical examination. **2-** Growth evaluation, including BMI to age and Height to age, using Egyptian pediatric growth curve charts. **3-** HbA1c was tested using Clover A1c Self device, a fully automated device using 4ul capillary blood

(boronate affinityand spectrophotometry). **4-** Self-monitoring blood glucose results were done by the patients at home in between visits using a self-monitoring accucheck performa blood glucose device. Results were downloaded by the accucheck smart pix program and were further analyzed by a specialized diabetologist. **5-** Insulin Regimen was evaluated and modified to further tailor the treatment for each of the included patient targeting HbA1c <6.5% without hypoglycemic events. (6) **6-** Diabetes and Nutrition Education, and, Behavioral modification, were done, inspired by the English DAFNE (Dose Adjustment For Normal Eating) Program.(7)

Serum C-peptide and fundus examination were estimated at the time of diabetes diagnosis (Table1) (recruitment period) at year 1, and at year 5 (the end of the study).

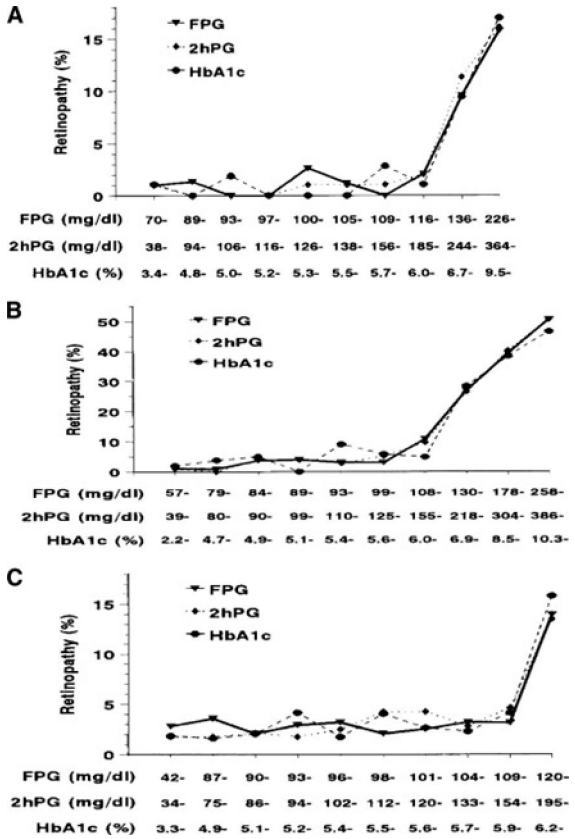


Figure 3: Prevalence of retinopathy by deciles of the distribution of FPG, 2HPG, and A1C in Pima Indians (*A*), Egyptians (*B*), and 40- to 74-year-old participants in NHANES III (*C*)

Serum C-peptide

What is C-peptide?

C-peptide - the Connecting peptide - is a short 31-amino-acid protein that connects insulin's A-chain to its B-chain in the proinsulin molecule (8) (Fig4) It is produced in equal amounts to insulin, therefore can be used to assess endogenous insulin level. This includes patients on insulin replacement therapy. (8)

Why C-peptide

Serum C-peptide was first discovered in 1967. (8) It is produced in equivalent amounts to insulin secretion levels by the pancreas. Furthermore, C-peptide was found to be a superior tool than directly measuring serum insulin, due to its longer half life time (20-30 min versus 3-5 min) and not being influenced by the hepatic first pass metabolism, as the case with insulin., making serum C-peptide 5-10 folds higher than serum insulin, thus, easier and more accurately detectable. (9) Recent discovered assessment methods have made it a less expensive, more reliable and widely available. However, C-peptide should be interpreted with caution in renal impaired patients, to avoid possible false elevation. (8)

How did we measure C-peptide?

We used enzyme-linked immunosorbent assay (ELISA) for a quantitative determination of circulating fasting C-peptide concentrations in human serum to assess body's ability to produce insulin.

Reference range 0.7-1.9 ng/ml.(BIOS Elisa)

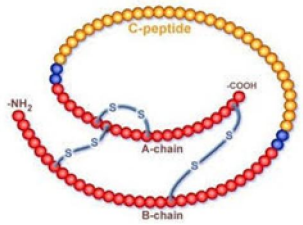


Figure 4: C-peptide Molecule

Fundus Examination

We followed the ADA 2014 recommendations, where eye examination is considered for a child at the start of puberty or after the age of 10 and once a child has had diabetes for 5 years. (7) Follow-up visit were determined by the ophthalmologist in charge.

Table 1: International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity scales (10)

Retinopathy stage	Findings on ophthalmoscopy
No apparent retinopathy	No abnormalities
Minimal NPDR	Microaneurysms only
Mild to moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of the following *More than 20 intraretinal haemorrhages in each of 4 quadrants Definite venous beading in 2+ quadrants *Prominent intraretinal microvascular abnormalities in 1+quadrant AND no signs of proliferative retinopathy
Proliferative DR	One of the following Neovascularisation; Viterous / Preretinal hemorrhage
Macular edema	
Absent	No retinal thickening or hard exudates in posterior pole
Present	Mild – some retinal thickening or hard exudates in posterior pole but distant from the macula
	Moderate – retinal thickening or hard exudates approaching the centre of the macula but not involving the centre
	Severe – retinal thickening or hard exudates involving the centre of the macula

Analysis of variance (ANOVA method) was used for the statistical analysis.

3. Results

At the end of our retrospective observational study period (5 years) and among the 20 followed patients, 3 patients (15%) - all females - developed moderate NPDR changes, all 3 subjects had very low undetectable serum C-peptide levels (0.01-0.15 ng/dl) (p<0.01) 5 patients (25 %) - 2 males and 3 females - developed mild NPDR changes, all 5 subjects had a low serum C-peptide level, average 0.2 ng/ml (range 0.15-0.3). (p<0.01) No DR changes could be detected by fundus examination in the remaining 12 patients (60%) at the end of the study period. All 12 subjects had an average serum C-peptide level of 0.4 ng/ml, (range 0.2 - 0.7).

(Fig5,6,7,8)

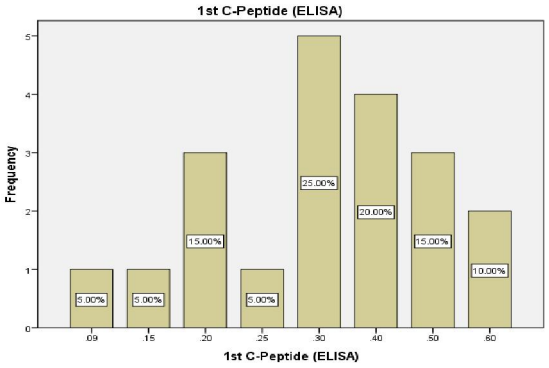


Figure 5

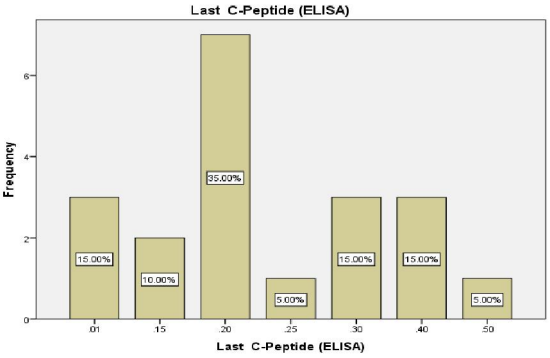


Figure 6

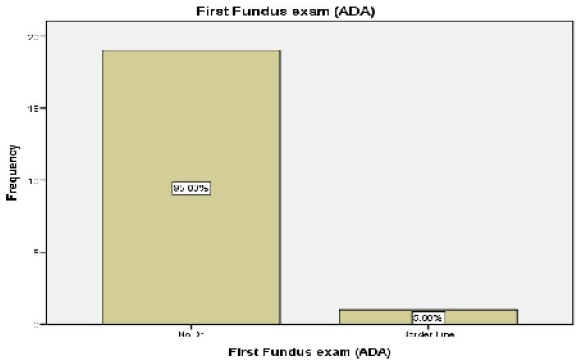


Figure 7

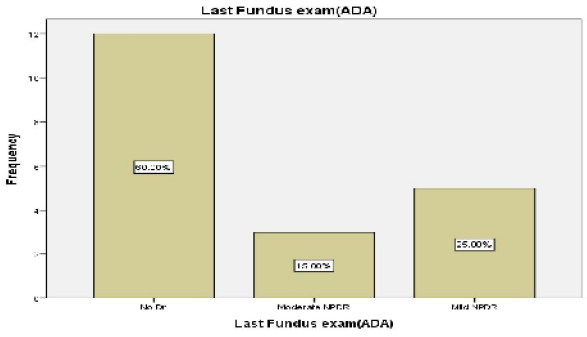
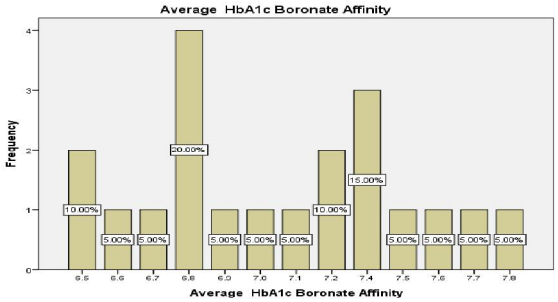


Figure 8

Average HbA1c level among all patients was 7.3% (range 6.5- 7.8%). It did not correlate much with the incidence of DR and it was not statistically significant. (p<0.5)

(Fig9)



Figure(9)

Other variants - age, gender, duration of diabetes - did not show a significant relation to the occurrence of diabetic retinopathy in our study group.

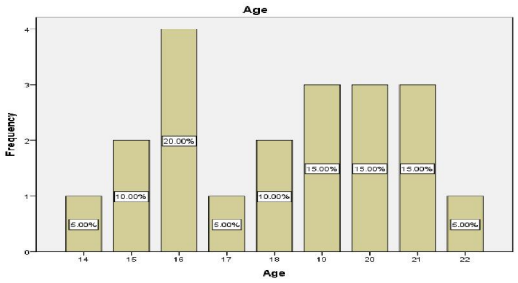
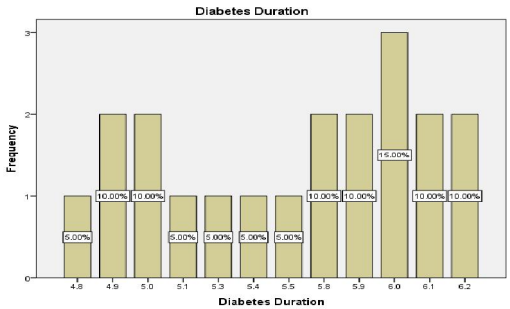
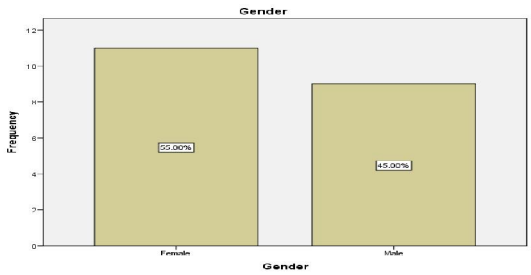


Figure 10: Age group distribution



Figure(11) Diabetes Duration distribution



Figure(12): Gender Distribution

4.Discussion

In our study we found that Diabetic Retinopathy (DR) was more prominent in type 1 diabetic subjects with very low undetectable serum C-peptide levels, which was statistically significant ($p<0.01$).

This correlation occurred even with relatively acceptable HbA1c levels (<7.5%). (11). This finding matches with other previous studies (11) and raises the awareness of the importance of measuring this biomarker in type 1 diabetic patients as an important predictor of Diabetic microvascular complications. It also rings the bell and raises the question: is HbA1c still our only "Gold Standard" for glycemic control. From our point of view it is not. Glycosylated hemoglobin only reflects a glycemic burden rather than the glycemic pattern. This has been raised since the famous Diabetes Control and Complication Trial (DCCT) study back in early 1990s, where HbA1c only explained 11% of the diabetes complication. (12) This fact highlights the value of glycemic variability as a major contributor in the development of diabetic microvascular complications, rather than the mean blood glucose interpreted in HbA1c test. Unfortunately, most diabetologists and internists still mainly rely on glycated hemoglobin as a marker of the glycemic control. This dilemma represents a clinical challenge in our daily practice and causes frustration to the healthcare provider and the patient, especially, when they reach reasonable HbA1c, and yet develop a diabetes complication. Frequent daily self-monitoring blood glucose (SMBG) (4-6 times per day) (7) (14) and Continuous Glucose Monitoring System (CGMS) are extremely valuable diagnostic tools for the diagnosis of glycemic variability, a major factor in the development of microvascular diabetic complications (MVDC) (15). In our study serum C-peptide level is an additional test for the early detection of MVDC as DR in our case, it is relatively stable, easy to measure - unlike HbA1c - with a bearable and comparable cost. Very low levels proved to be a significant biomarker for such a serious and silent complication.

Conclusion

Diabetic retinopathy is a serious disabling microvascular diabetes complication. Early detection plays a major role for its prevention and prognosis. C-peptide levels could be a valuable diagnostic tool for the prediction of this diabetes complication in type 1 Egyptian diabetic patients,and deserves more awareness among the healthcare providers for the benefit of our patients.

Acknowledgments

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