The Effects of GLP-1 Analog Use upon C-peptide levels In Patients with Type 2 Diabetes Mellitus

Elizabeth Hale & Dr. Susan Alexander

College of Nursing, University of Alabama in Huntsville

Introduction

Type 2 Diabetes Mellitus (T2DM) affects growing numbers of patients in the United States.T2DM is characterized initially by an increase in the production of insulin by the pancreas. Over time, as pancreatic beta cells fail to function, levels of circulating insulin are reduced. Alterations in insulin levels can be measured by measuring C-peptide. The purpose of this study is to describe the effects of a class of medications known at GLP-1 analogs on C-peptide levels in patients with T2DM.

Background/Review of Literature

Rates of T2DM in the United States are rising, with an estimated 18.8 million diagnosed with T2DM in 2010 and 7 million undiagnosed patients. In the state of Alabama, Diabetes Mellitus is the 6th leading cause of death. Improving methods of assessing and treating patients with diabetes is an essential component of reducing mortality and expense associated with the disease.

C-peptide is a 31 amino acid residue derived from proinsulin, and was first described in 1967. As insulin is released from pancreatic beta cells, C-peptide is cleaved from insulin; because C-peptide is not extracted from the circulation by the liver as is insulin, it is viewed as a more direct reflection of endogenous insulin secretion.[1] Though initially considered to biologically inert, recent research suggests that alterations in C-peptide levels may play a role in the development of diabetic neuropathy and nephropathy in patients with Type 1 Diabetes Mellitus [T1DM].[1,2] Patients with T1DM who have even minimal sustained secretions of C-peptide have a significant reduction in risk of microvascular complications compared to those patients in which C-peptide secretion is absent.[3,4] This may be due to the proposed anti-inflammatory effects of C-peptide upon the vascular endothelium and vascular smooth muscle cells.[5]

Elevated levels of C-peptide are an indicator of hypersecretion of insulin, caused by the insulin resistance that is characteristic of T2DM. Patients with T2DM who have supranormal C-peptide levels have been associated with the presence of atherosclerotic plaques, possibly because of its role in regulating endothelial cell function and microvascular blood flow.[3,4] Elevated basal C-peptide levels in T2DM patients have been associated with increased carotid intimal medial thickness, and so may be viewed as a surrogate marker for the presence of subclinical atherosclerosis in these patients.[3,6]

A recent development in the field of diabetes care has been the introduction of GLP-1 analogs, a category of drugs that are designed to improve glycemic control while reducing the risk of hypoglycemia in patients with T2DM. In the authors' clinical practice, changes in C-peptide levels have been noted after the addition of GLP-1 analogs to the pharmacologic regimen of patients with T2DM. Though multiple studies on the effects of GLP-1 analogs to weight, glycemic control, and cardiovascular risk in patients with T2DM can be found in the literature, little is known about the effects of the analogs upon discrete clinical markers such as C-peptide and serum creatinine. There is a growing body of evidence that underscores the importance of preserving endogenous insulin secretion[7], which is supported by clinical experiences of the authors.

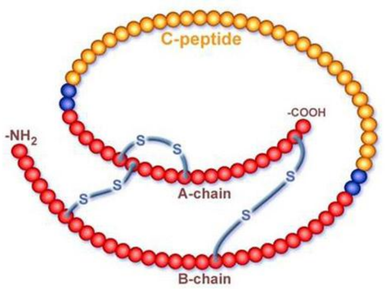

Figure 1. Schematic representation of human proinsulin. C-peptide is in yellow while insullin's A and B chains are in red.
(http://www.cebix.com/index.php/science/c-peptide biology/

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Purpose of the Study

The purpose of the study is to describe the effects of GLP-1 analogs upon the C-peptide levels of patients with T2DM.

Methods

After approval by the Institutional Review Board of the University of Alabama in Huntsville was received, a chart abstraction began. More than 5000 closed charts from a medical practice specializing in endocrinology was conducted.
Inclusion criteria were:

- Age of 19 years or older
- Previous diagnosis of T2DM
- Use of GLP-1 analog therapy (exenatide or liraglutide)
- C-peptide measurement before initiation of GLP-1 analog therapy and minimum of once while using the medication

Sample Characteristics

The sample is composed of 174 patients who met the criteria. The average age of the sample population was 56.1 years. The average number of years since diagnosis of T2DM was 13.07 years.

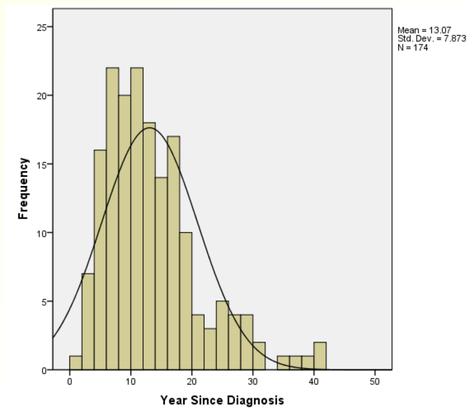

Figure 2. Number of years since diagnosis of T2DM.

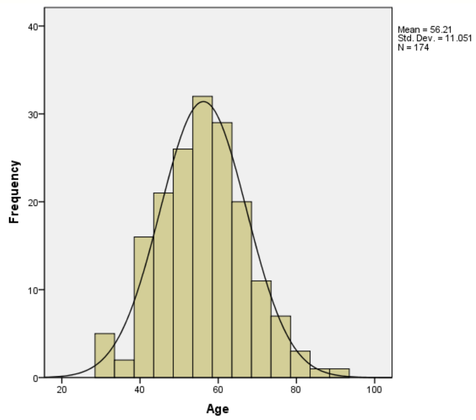

Figure 3. Age of patients in the sample.

Results

Table 1.HBA1c changes derived from sample.

HBA1c changes	Frequency	Total Percent
Over 3% Drop	62	36%
Less than 3% Drop	74	42%
Increased	38	22%
Total	174	100%

Table 2. Patient self-reports of hypoglycemic episodes associated with addition of liraglutide or exenatide to existing medication regimens.

	Frequency	Percent
Yes	**34**	**20%**
No	**139**	**80%**
Total	**174**	**100%**

Table 3. Initial and follow up C-peptide levels for patients grouped by HBA1c changes.

A1CDrop		N	Minimum	Maximum	Mean	Std. Deviation
Over 3% Drop	C-Peptide at baseline	62	0.4	15.6	3.669	2.47417
	C-Peptide at 3 months	28	0.3	9.8	3.296	1.91978
	C-Peptide at 6 months	22	0.6	7.8	3.173	1.82344
	C-Peptide at 9 months	20	0.2	8.8	3.01	2.36151
	C-Peptide at 12 months	33	0.3	7.6	2.491	1.66853
Less than 3% Drop	C-Peptide at baseline	74	0	9	3.128	1.9272
	C-Peptide at 3 months	42	0.4	6.6	2.752	1.75211
	C-Peptide at 6 months	21	0.9	6.2	2.695	1.44308
	C-Peptide at 9 months	14	0.1	7.5	2.207	2.01588
	C-Peptide at 12 months	35	0.7	6.7	2.629	1.56046
Increased	C-Peptide at baseline	38	0.7	8.2	3.388	1.97804
	C-Peptide at 3 months	17	0.6	6.7	3.124	1.44721
	C-Peptide at 6 months	10	0.9	7	3.96	1.67079
	C-Peptide at 9 months	8	0.9	4.5	2.6	1.36382
	C-Peptide at 12 months	19	0.6	10.7	3.037	2.50493

Changes in C-peptide levels after addition of GLP-1 analogs

There were no statistically significant alterations in average C-peptide levels among patients after the addition of GLP-1 analogs, during the 12 month time period. However, it should be noted that in the group of patients with initial C-peptides of 0.9 – 7.1 ng/mL, the maximum initial C-peptide of 15.60 ng/mL (dropped to 10.70 ng/mL after 12 months of therapy, with a reduction in the mean from 3.3779 ng/mL to 2.6655 ng/mL.

Changes in HBA1c after addition of GLP-1 analogs

There were reductions in HBA1c after the addition of GLP-1 analogs, with 62 patients displaying a >/= 3% reduction in HBA1c during the 12 month period. Smaller decreases in HBA1c (0.1-3%) were seen in 63 patients. In the group with initial C-peptide levels >7.1 ng/mL, 7 patients had reductions in HBA1c of 0.1->3%.

Correlation of Serum Creatinine with C-Peptide Levels

Serum creatinine and C-peptide levels prior to initiation of GLP-1 therapy were weakly, related to one another (r = 0.215, p = 0.01). Patients who had low C-peptide levels initially had a mean creatinine of 1.0224 mg/dL (n=67). Patients with normal C-peptide levels initially had a mean creatinine of 1.0139 mg/dL (n=79). After 12 months of GLP-I analog therapy in addition to the existing treatment regimen, there was no statistically significant relationship found between serum creatinine and C-peptide levels. The mean serum creatinine levels in the group with low C-peptide levels after 12 months of therapy was 1.0094 mg/dL (n=53). Mean serum creatinine in the group with normal C-peptide levels after 12 months of therapy was higher at 1.3645 mg/dL (n=31) however this was not statistically significant.

Discussion

Though relationships between C-peptide, HBA1c, and serum creatinine overall lacked statistical significance in this study, the results do seem to suggest that when GLP-1 analogs are added to existing classes of antidiabetic therapy (biguanides, thiazolidinediones, insulin, and sulfonylureas) there is the potential for reductions in both C-peptide and HBA1c levels. There was also a lack of correlation between serum creatinine and C-peptide levels, both initially and after 12 months of GLP-1 analog addition. However, the sample consisted of 174 patients with an average age of 56.1 years andwho had been diagnosed with T2DM for more than 13 years. The mean initial serum creatinine of this sample population was within normal range, regardless of C-peptide levels, which may be atypical when considering the natural progression of T2DM. The incidence of self-reported hypoglycemia was 20% in the sample population, which is higher than the 11-12% reported in other studies.

Conclusions and Future Research

This study reports real-world effects of GLP-1 analog use in patients with T2DM upon clinical markers linked to microvascular and macrovascular complications. Outcomes and effectiveness research involving larger groups of patients for more sustained time periods would be beneficial in determining the significance of GLP-1 analog use upon clinical markers of complications in this patients affected by T2DM. In addition, research upon the identification and description of the the receptor for proinsulin C-peptide, including the possible differences in receptor sites and action for patients with both T1DM and T2DM, is also warranted.

Acknowledgements

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