# THERAPEUTICAL OPTIONS FOR OPTIMIZING THE GLYCEMIC PROFILE IN A PATIENT WITH TYPE 2 DIABETES MELLITUS - CASE REPORT

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**Abstract**

*Incretin-based therapies address some of the mechanisms of T2DM by improving β-cell function, inhibiting glucagon secretion, stimulating insulin secretion, reducing appetite and promoting weight loss. We present the case of a patient with type 2 diabetes mellitus who was admitted in the Diabetes, Nutrition and Metabolic Diseases Clinic for high blood glucose values and polyuria. Because the patient had high glycemic values during self-monitoring of blood glucose (SMBG) and also symptoms of hypoglycemia, we decided to evaluate the glycemic variability using the recordings of the continuous glucose monitoring system (CGMS). The CGMS indicated that the patient had episodes of hypoglycemia and also high glucose values. The treatment was changed and the therapy with exenatide was initiated together with reinforcement of lifestyle optimization. The CGMS and SMBG three months after the treatment change indicated the improvement of glycemic control, weight reduction and cardiovascular risk reduction. The GLP-1 receptor agonists are a very good therapeutical option in subjects with T2DM where the HbA1c value is not very high, the duration of T2DM is small, weight loss is a very important issue and there is a high risk of hypoglycemia.*

***keywords**:* GLP-1 receptor agonist, continuous glucose monitoring system, self monitoring blood glucose, Hypoglycemia

## Introduction

The pathophysiology of type 2 diabetes mellitus (T2DM) includes three mechanisms: insulin deficiency due to insufficient pancreatic insulin production, excessive hepatic glucose release and insulinresistance in peripheral tissues and liver [1]. The defects of the α-cells that produce excess glucagon and the continuously decline of the β-cells are responsible for deterioration of glycemic control and increased cardiovascular risk. Incretin-based therapies address some of the mechanisms of T2DM by improving β-cell function, inhibiting glucagon secretion, stimulating insulin secretion, reducing appetite and promoting weight loss [1]. Therefore, glucagon-like peptide-1 receptor agonist (exenatide) treatment is a good option for some patients when weight loss and low hypoglycemic risk are important targets.

## Case report

It is the case of a 51 years old engineer that exemplifies the benefits of exenatide treatment and we would like to present it. He was admitted in the Diabetes, Nutrition and Metabolic Diseases Clinic for high blood glucose values and polyuria.

From the clinical examination we noticed that the patient was diagnosed with type 2 diabetes mellitus four years ago. He had stage 2 arterial hypertension for five years and now the blood pressure was controlled with 5mg Perindoprilum and 1,5mg Indapamidum. The patient also had NYHA stage II chronic cardiac failure and mixed dyslipidaemia for which he was receiving 20mg Simvastatin. It was also noticed that he did not obey the meal timetable and the recommendations for lifestyle optimization.

At the physical examination, we noticed that the blood pressure was 125/70mmHg and the heart rate was 76 bpm. From the blood tests, we noticed a total cholesterol value of 256mg/dl, HDL-cholesterol=42mg/dl, LDL-cholesterol=100mg/dl, triglycerides=158mg/dl. The liver enzymes, blood creatinine and urea were in normal range and the abdominal ultrasonography indicated the presence of liver steatosis.

Combining the clinical and paraclinical data, the following diagnose was established: Type 2 Diabetes Mellitus. Moderate Mixed Dyslipidaemia. Class II Obesity. Abdominal Obesity. Stage 2 Arterial Hypertension with high cardiovascular risk. NYHA Stage II Chronic Cardiac Failure. Liver steatosis.

## The dynamic of antidiabetic treatment

The history of antidiabetic treatment told us that the patient initially received Metformin. The dose was increased up to 2g a day (the maximum tolerated dose). In 2009, Glimepirid up to 6mg/day was added. The dose was reduced to 4mg when the patient changed his job and the new one implied irregular meals.

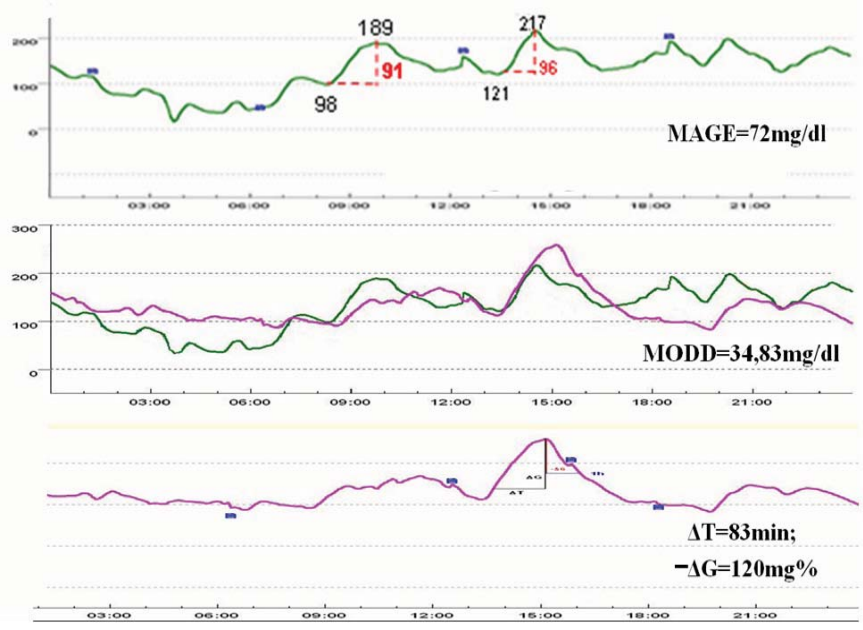


**Figure 1.** The charts of the initial recordings and the determination of the main indices.

The patient performed a self-monitoring of blood glucose (SMBG) and the preprandial blood glucose levels were between 100mg/dl and 140mg/dl, while the postprandial glycemic values were between 180mg/dl and 220mg/dl. The HbA1c value was 7,7% and the fasting insulin level was 7,8 µUI/ml. Therefore we could calculate the HOMA-B index and its value was 54%.

Due to the fact that the patient described symptoms suggestive for hypoglycemia but low blood glucose levels could not be observed during the SMBG, we decided to evaluate the glycemic variability using the recordings of the continuous glucose monitoring system (CGMS).

The charts obtained by the CGMS during the initial follow-up are displayed in Figure 1. Low and also high glycemic values can be observed in the charts.

Because of the high glycemic values and recognized hypoglycemia, treatment had to be revised. The possible treatment options and the impediments in applying them are exemplified in Table 1.

**Table 1. The possible treatment options and their impediments.**

| Options | Impediments |
|---|---|
| SU – Increase the dose | Hypoglycemia (irregular meals time table)<br>Weight gain |
| Pioglitazone | Edema, CCF, Weight gain |
| Insulin | Hypoglycemia (irregular meals time table)<br>Weight gain |
| GLP-1 receptor agonists | Subcutaneous injection (the patient accepts this way) |
| Acarbose | The therapy was initiated but the patient had gastro-intestinal disorders because he did not obey the initial dosage |
| Glinids | Risk of hypoglycemia. No effect on lipid profile. |
| Sitagliptin | Low effect on weight loss. |

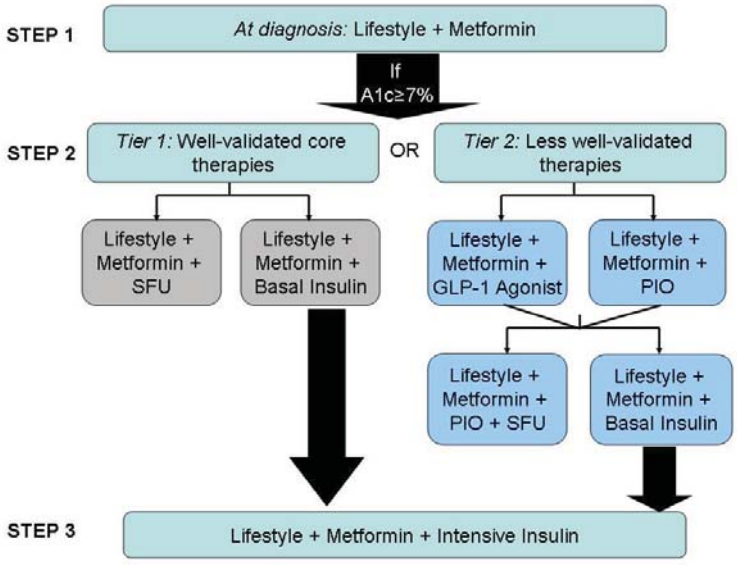


**Figure 2.** ADA/EASD Consensus 2008

In deciding the best treatment option, the HbA1c value of 7.7% and the guidelines were taken into consideration. The ADA/EASD Consensus from 2008 [2] is indicated in Figure 2 and the AACE/ACE Diabetes Algorithm for Glycemic Control [3] is indicated in Figure 3.

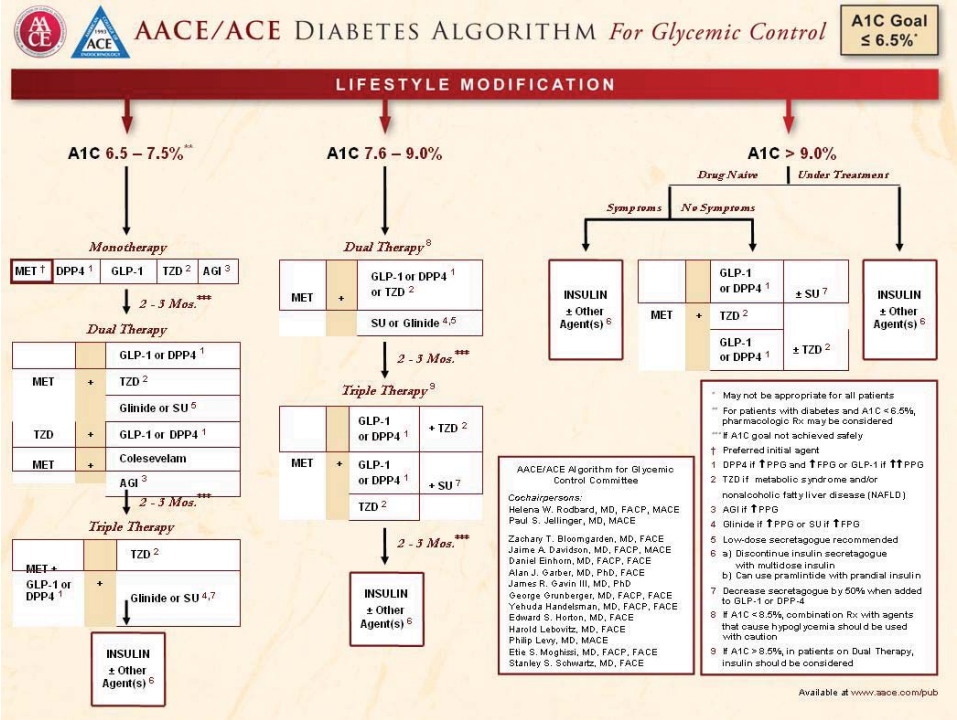


**Figure 3.** AACE/ACE Diabetes Algorithm for Glycemic Control

It was decided that the patient should continue the treatment with Metformin in the same dose, Glimepiride 3mg/day and 5 μg Exenatide subcutaneous twice daily was initiated. In the same time, we reinforced the lifestyle interventions, explaining to the patient the benefits of a healthy program. He was also told that exenatide is to be injected twice daily, almost 60 minutes before meals. After 1 month, the dose was increased to 10 μg Exenatide twice daily.

### Evolution

Three months after exenatide-based therapy initiation, the patient was reevaluated completely. The main clinical and paraclinical parameters before and after the change of the treatment are indicated in table 2.

**Table 2. The clinical and paraclinical parameters before and after Exenatide-based therapy initiation.**

| PARAMETER | BEFORE EXENATIDE | 3 MONTHS AFTER EXENATIDE |
|---|---|---|
| Weight (kg) | 104 | 94.5 |
| BMI (kg/m$^2$) | 32.1 | 29.3 |
| Waist circumference | 104 | 99 |
| HbA1c (μUI/ml) | 7.7 | 6.4 |
| Insulinemia | 7.8 | 8.6 |
| HOMA-B | 54 | 96.7 |
| Preprandial glucose | 100-140 | 70-100 |

| PARAMETER | BEFORE EXENATIDE | 3 MONTHS AFTER EXENATIDE |
|---|---|---|
| Postprandial glucose | 180-220 | 100-138 |
| Total Cholesterol | 256 | 167 |
| Triglycerides | 158 | 143 |
| HDL-cholesterol | 42 | 47 |
| LDL-cholesterol | 182 | 111 |

Besides good glycemic values observed during SMBG, the CGMS was used again in order to evaluate the glycemic variability. The charts are indicated in Figure 4.

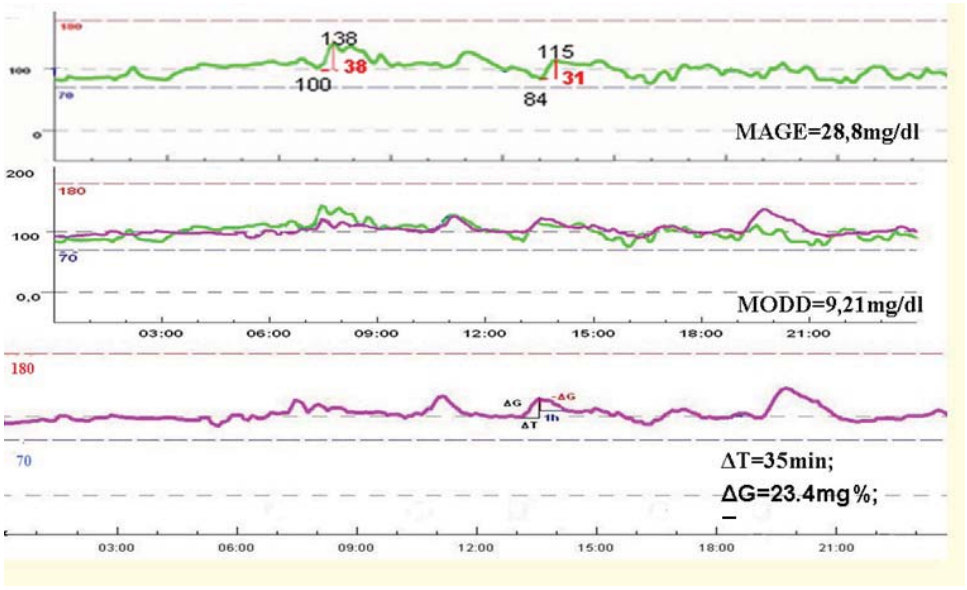


**Figure 4.** The assessment of CGMS charts 3 months after Exenatide-based therapy initiation.

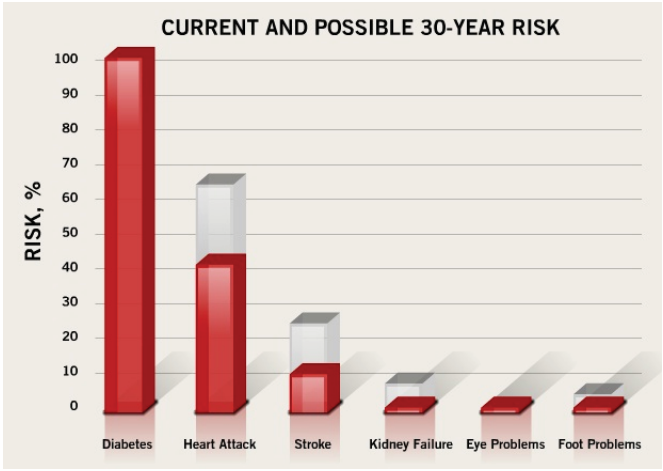


**Figure 5.** The evaluation of 30-year risk before (white color) and after the exenatide treatment initiation (red color).

The evaluation of glycemic variability indicates that after exenatide therapy initiation, the decrease of the amplitude of postprandial glycemic excursions (low ΔG) and also the reduction of the amplitude of the daily glycemic excursions (low MAGE), the reproductivity of the glycemic profile from one day to another (low MODD) and the absence of hypoglycemia. Moreover, the improvement of the glycemic profile is regarded also in the lowered HbA1c and the increase of HOMA-B index.

The reduction of body mass index and waist circumference and the good the glycemic profile lead to improvement of cardiovascular risk assessed using the Archimedes model (available at https://www.diabetesarchive.net/phd/profile/start.jsp) (Figure 5).

**Discussions**

This CGMS automatically records the glucose value in the subcutaneous tissue every five minutes for up to 72 hours. Besides determining 288 glucose values per day, this system can automatically create charts regarding the glucose variability and it allows the healthcare providers to evaluate the glycemic profile and to adjust the treatment. Modern devices, Real Time CGMS (RT-CGMS), can display the glucose value and this can help both the healthcare provider team and also the patient in adjusting the treatment.

With the help of CGMS, specific variability indices can be calculated. The main indices are MAGE, MODD and MIME. MAGE – Mean Amplitude Glycemic Excursion – remains the most comprehensive index for evaluating the intraday glycemic variability [4]. It can be calculated by measuring the arithmetic mean of the differences between consecutive peaks and nadirs if these differences are greater than one standard deviation (SD) of the mean glucose value. The main advantages of this index are: it is not dependent on the mean glucose value and it is designed to include major glucose swings and exclude minor ones [4].

The only index for estimating interday glycemic variability is the mean of daily differences (MODD) [5]. It is calculated as the mean of the absolute differences between glucose values at the same time on two consecutive days [4]. MIME (Mean Indices of Meal Excursions) assesses the glycemic excursions in connection with food ingestion.

Exenatide was originally isolated from the venom of the Gila lizard (Amylin Pharmaceuticals, San Diego, CA, USA). The peptide from the lizard had similarities with GLP-1, but it had greater affinity with the receptor and was resistant to DPP-4. Exenatide is produced synthetically and it has a short half-life of about 4 hours [6].

From the time of its apparition many trials emerged comparing the usefulness of exenatide with other therapies (oral medication and/or insulin therapy) [6]. For example, Kendall *et al.* recruited 733 people with type 2 diabetes whose control was inadequate (HbA1c level 7.5–11%) on dual therapy with metformin and a sulfonylurea [7]. Their average age was 55 years (range 22–77), and mean BMI was around 34 kg/m$^2$. Most of them were Caucasian, with about 11% being black people and 16% Hispanic. Mean duration of diabetes was about 9 years. There were three arms: placebo controls, exenatide 5 μg b.i.d. (twice a day) and exenatide 10 μg b.i.d. (after 4 weeks on 5 μg). The results of this study indicate that in those whose glycemic control was inadequate on dual therapy, the addition of exenatide reduced the value of HbA1c by about 1% [7]. Moreover, the changes in HbA1c at 30 weeks were greater in those whose baseline level was higher.

In another study, Zinman *et al.* recruited 233 patients whose control was inadequate on a glitazone with or without metformin (about 80% of them were on metformin). Their mean age was 56 (range 21–75) years, and their

mean BMI was 34 kg/m$^2$ [8]. This study confirmed the reduction of HbA1c by about 1% [8].

In these two studies, there was only one case of severe hypoglycemia [7] and all the studies have indicated that exenatide treatment is associated with weight reduction [7,8]. Although nausea seems to be an important symptom causing subjects to stop exenatide, it was mild or moderate in most of the cases and it is not the only cause of weight loss [6]. The patient we discussed about presented weight loss but without nausea determining him to be more adherent to the treatment.

## Conclusions

The GLP-1 receptor agonists are mentioned in ADA/EASD Consensus at Step 2, Tier 2 (less well-validated strategies) but they are, as our case and several other studies indicated, a very good therapeutical option in subjects with T2DM when the HbA1c value is not very high (<9%), the duration of T2DM is small, weight loss is a very important issue and there is a high risk of hypoglycemia.

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