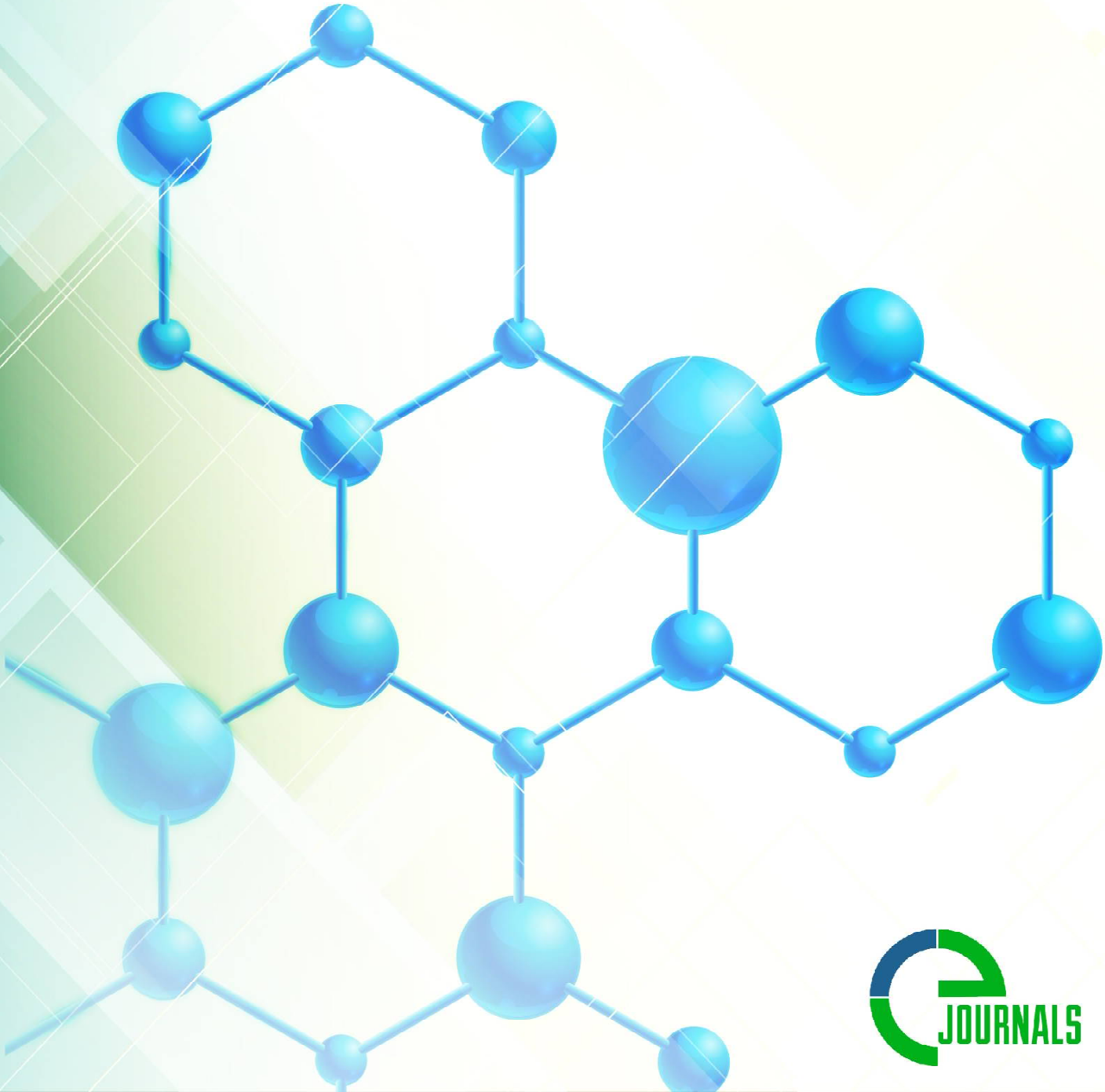
EUROPEAN JOURNAL OF

MOLECULAR MEDICINE



JOURNALS

European Journal of Molecular medicine

Volume 1, No.4, September 2021

Internet address: ttp://ejournals.id/index.php/EJMM/issue/archive
E-mail: info@ejournals.id
Published by ejournals PVT LTD
DOI prefix: 10.52325
Issued Bimonthly
Potsdamer Straße 170, 10784 Berlin, Germany

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INTENSIVE HYPOGLYCEMIC THERAPY AS A TRIGGER FOR ELECTRICAL MYOCARDIAL INSTABILITY

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Abstract. In this article, we have highlighted our own results on the use of basal insulin Degludec in combination with other antihyperglycemic drugs in patients with type 2 diabetes using long-term ECG monitoring and FreeStyle Libre glycemia. In our patient, with a favorable glycated hemoglobin level, according to the CGM, frequent episodes of hypoglycemia were observed, which were associated with paroxysms of atrial fibrillation. This situation testified in favor of resolving the issue of revising the therapy. Thus, we have replaced the basal insulin Glargin with the newer generation insulin Degludek, which has a more pronounced effect on glycemic variability, therefore, its effect is more predictable. Currently, there is convincing evidence of the effect of hypoglycemia on the development of electrical instability of the myocardium with the occurrence of fatal arrhythmias. The use of systems for synchronous long-term monitoring of glycemia and heart rate will allow more accurate recording of episodes of hypoglycemia and correction of insulin therapy, thereby reducing the risk of arrhythmias.

Key words: hypoglycemic therapy, diabetes mellitus, glycated hemoglobin, atrial fibrillation.

Diabetes mellitus is one of the most powerful risk factors for cardiovascular diseases (CVD). In 50% of patients with type 1 diabetes mellitus (T1DM) and in 80% of people with type 2 diabetes mellitus, early disability and premature death due to cardiovascular complications are recorded. Despite the achievements of medical science in early diagnosis and treatment of patients with diabetes, there are many problems that need to be addressed to improve the prognosis and quality of life in patients with diabetes and concomitant CVD.

It should be noted that insulin therapy remains the most effective treatment option for T2DM and the only pathogenetically substantiated and vital treatment for T1DM [1].

However, hypoglycemia and weight gain are the most significant adverse effects of insulin therapy, and the complexity of the regimen used and the need for constant adjustment of lifestyle to treatment are the main limitations of insulin therapy [2].

The studies ACCORD, ADVANCE, VADT showed the danger of hypoglycemia against the background of intensified insulin therapy in patients with T2DM with concomitant cardiovascular diseases [3].

In the 1990s, based on the analysis of cases of sudden death of patients with T1DM, the syndrome 'dead in the bed' was proposed, where hypoglycemia was considered the main cause lethal outcome [4], and the development of the so-called 'disruption of autonomous regulation associated with hypoglycemia' was deemed a pathogenetic link.

Modern research with the parallel use of long-term monitoring of CGM glycemia and long-term ECG monitoring has shown prolongation of the QT interval, the occurrence of ectopic rhythms, and a decrease in heart rate variability during hypoglycemic events. These results impose certain conditions for insulin therapy. Thanks to the development of basal insulin analogs (Glargine, Detemir), modern endocrinology has commenced to solve several important issues at the same time: reducing the risk of hypoglycemia, ease of administration due to the duration of action. In this regard, data on new basal insulins are of interest, one of the latest representatives of which is insulin Degludec, whose efficacy and safety have been extensively studied in the BEGIN □ clinical trials program (9 international multicenter, randomized, phase 3a controlled trials with a duration of 26-52 weeks involving about 9,000 patients with T1DM and T2DM, both receiving and not previously receiving insulin therapy) [5]. The use of basal insulin alone, both Degludec and Glargine for T2DM, as well as the use thereof in combination with oral antihyperglycemic drugs (OAD) have been the cause of the development of severe hypoglycemic states very rarely (no more than in 2% of patients) [6].

In this article, we highlighted our own results on the use of basal insulin Degludec in combination with other antihyperglycemic drugs in patients with type 2 diabetes using long-term ECG monitoring and FreeStyle Libre glycemia.

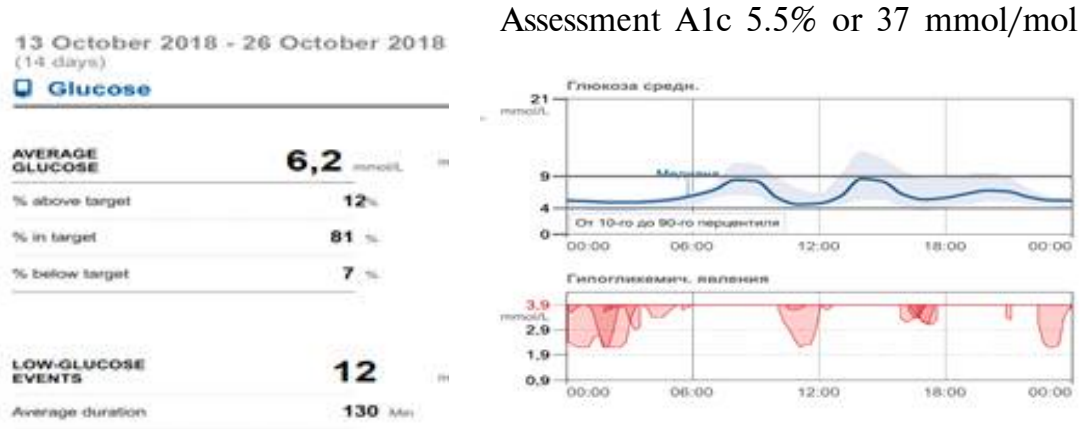
Clinical case 1.

Patient M., 54 years of age; complains of general weakness and periodic rapid heart palpitations. From the anamnesis: has been suffering from T2DM for 15 years. IHD experience is 6 years, that of hypertension (HD) is 10 years.

During the last year, short-term, self-stopping atrial fibrillation paroxysms have been detected.The BMI is 38.8 kg/m2.The patient receives Sitagliptin/Metformin in adaily dose of 100/1000 mg, 40 units of insulin glargine at 8AM, Bisoprolol 2.5 mg per day, Aspirin 75 mg, Valsartan 80 mg, and Rosuvastatin 10 mg per day.

Laboratory data: glycated hemoglobin - 6.7%, fasting venous glucose - 6.2 mmol/L, creatinine - 127 ?mol/L (GFR - 41.5 ml/min), urea - 8.0 mmol/L, microalbuminuria - 336 mg/L, total cholesterol - 145 mg/dl, triglycerides - 180 mg/dl, LDL - 81 mg/dl, HDL - 28 mg/dl.

Assessment of glycemia using CGM showed that during the observation period, when he received the above therapy, the patient has experienced 12 hypoglycemic events with an average duration of 130 minutes.

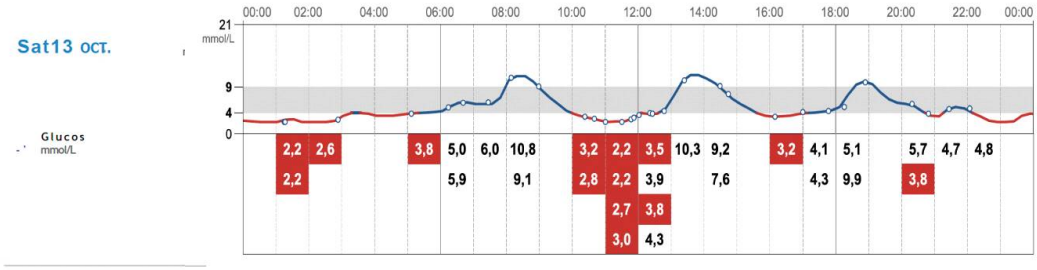


Assessment A1c 5.5% or 37 mmol/mol

Fig. 1 Baseline CGM glycemic profile.

Table 1
Glycemic profile assessed using the Contour Plus meter on 13 October 2018

Time	06-30	08-40 2 hours after meal	14-00 one hour after meal	20-00	21-00
Values	6.4	10.9	11.3	6.8	3.9



13 October, Saturday
Glucose
Fig. 2. Glycemic Profile Assessed by CGM on 13 October 2018

As shown by a comparative analysis of the glycemic profile based on self-monitoring and CGM data, almost all 14 hypoglycemic events were not recognized.

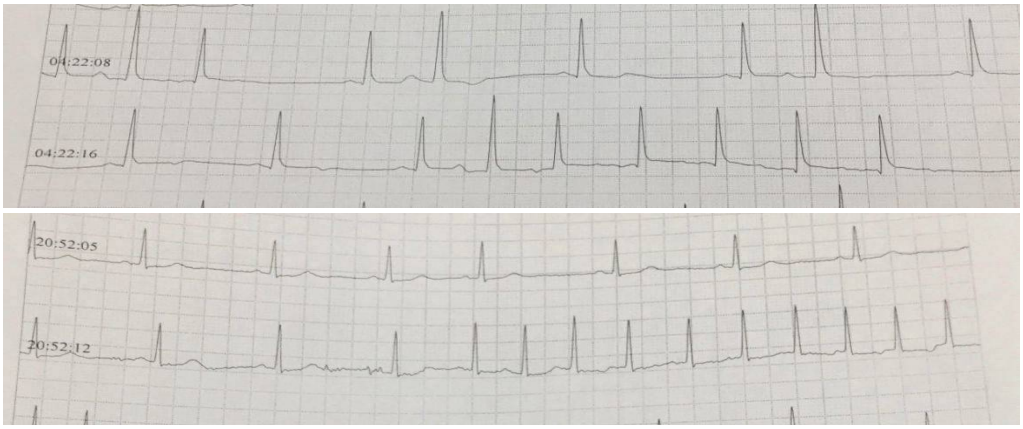


Fig. 3. Atrial fibrillation observed during hypoglycemia

Parallel ECG monitoring showed that hypoglycemia was associated with the development of AF paroxysm.

High blood glucose variability, frequent hypoglycemic events and, at the same time, insufficient compensation of the state on insulin Glargine was an indication for us to replace it with Degludek. However, when switching to insulin Degludec, we subtracted 10% from the initial dose of Glargine, thus the dose of Degludec was 36 units.

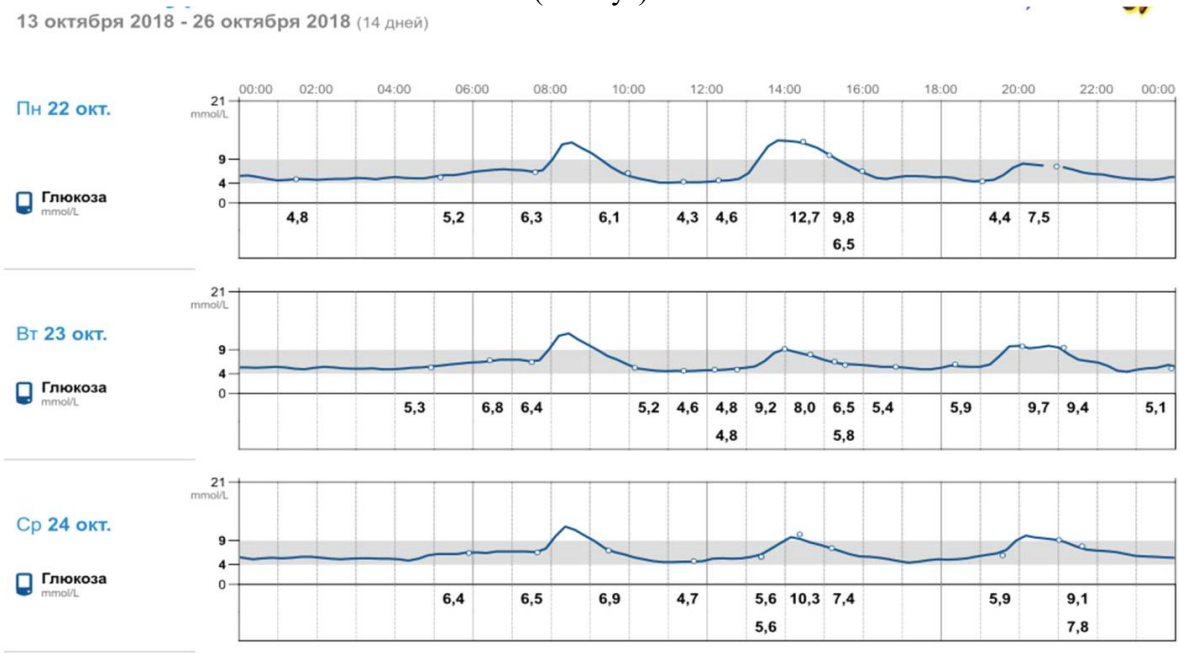
The patient has postprandial glycemia, whereas basal insulin acts primarily on fasting glycemia, therefore, to compensate for this condition we needed a combination of insulin and drugs with incretin mechanism. In the BEGIN study, the subgroup with the addition of GLP-1 receptor agonist Liraglutide to Degludec contributed to the intensification of the decrease glycated hemoglobin, as well as the weight of patients [7].

In our case, the combination of insulin Degludec and Liraglutide (Victoza) at a dose

of 0.6 mg contributed to the complete leveling of hypoglycemic events, which is clearly seen from the CGM data.

It should also be noted that the patient noted the disappearance of arrhythmia symptoms, which was confirmed with ECG monitoring data.

13 October 2018 – 26 October 2018 (14 days)



22 October, Monday
Glucose
23 October, Tuesday
Glucose
24 October, Wednesday
Glucose
Fig. 4. Glycemic profile according to CGM data against the background of insulin Degludek and Liraglutide. 5-6-7th days.

In the Recommendations of the Endocrinologic and Metabolic Drug Advisory Committee, it is advised on the need to titrate the dose of insulin Degludec once a week on a basis of 2 or 3 previous FPG measurements. After 7 months we succeeded in maintaining adequate glycemic control on the insulin Degludec dose up to 12 units, and the dose of Liraglutide was titrated to 1.2 mg.

15 June 2019 – 21 June 2019 (7 days)

Glucose	Assessment A1c 6.3% or 45 mmol/mol	
Average level of gucose	**7.4** mmol/L	
% higher than the target range	4%	**Fig.**
% within the target range	96%	
% lower than the target range	0%	
hypoglycemic events	**0**	
Average duration	0 min	

Fig. 5 Glycemic profile according to CGM data against the background of insulin Degludek and Liraglutide at 7 months of observation.

As can be seen from the above data, in 96% of the time interval, glycated hemoglobin was within target range with no hypoglycemic events at all.

It should also be noted that there was an improvement in filtration capacity of the kidneys with an increase in GFR from 55.2 to 73.7 ml/min and a decrease in BMI from 38.8 to 33.6 kg/m2.

Summarizing the above, it should be noted that, unfortunately, the existing inertia in the management of patients with diabetes, may in the future lead to decompensation of glycemic control and development and progression of vascular complications, which we observed in this patient as nephropathy and IHD. Insulin therapy, providing the best glycemic control, increasing the amount of endogenous insulin, however, has its drawbacks, in particular, the risk of hypoglycemia, which is accompanied by complications such as fatal arrhythmia. It should also be said that a year after the start of therapy, only half of the patients manage to achieve the target

level of glycated hemoglobin [8]. In our patient, judging by the level of glycated hemoglobin, the situation seemed to be under control. But even in this case, the obtained values should be viewed with a critical eye. So, in recent years, the position of glycated hemoglobin has been questioned, and there is more and more evidence in favor of assessing such indicators, obtained during long-term monitoring, as the frequency of hypoglycemic events and glycemic variability. So, our patient with a favorable indicator of glycated hemoglobin, according to the CGM data, had frequent hypoglycemic events, which were associated with paroxysms of atrial fibrillation. Such situation supported resolving the issue of revising the therapy that was being administered. So, we replaced basal insulin Glargin with Degludec, the newer generation insulin, which has a more pronounced effect on variability of glycemia, therefore, its effect is more predictable. It is common knowledge that the relative contribution of fasting blood glucose level and that in fed state varies with different values of HbA1c. With a moderate increase in the level of HbA1c, the greatest contribution is made by postprandial glycemia [9]. The rate of gastric emptying and the hormonal response of islet cells to food intake are the main mechanisms regulating postprandial glycemia. In this case, drugs with incretin effect, affecting gastric emptying, help to reduce its level. Weight gain during insulin therapy contributes to an increase in cardiovascular risk. Therapy based on the incretin effect, minimizing the hypoglycemia risk, prevents an increase in body weight [10], which prompted us to choose the drug aGPP-1R, Liraglutide, as the second drug to insulin Degludec in a patient with obesity.

A special attention should be paid to the effect of liraglutide on kidney function, which are most often affected in patients with diabetes mellitus. Based on the results of studies involving patients with mild to moderate kidney damage, where it did not have a negative effect, Liraglutide was recommended for patients with mild nephropathy [11].

Conclusion:

Today, we have convincing evidence for the developmental impact of hypoglycemia on the electrical instability of the myocardium with the occurrence of fatal arrhythmias. Using synchronous systems of long-term monitoring of glycemia and heart rate will make it possible to more accurately record hypoglycemic events and adjust insulin therapy, thereby reducing the risk of arrhythmias.

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