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Original scientific paper

EVALUATION OF THE GLYCOREGULATION EFFICACY BEFORE AND AFTER TREATMENT WITH INSULIN DEGLUDEC IN PATIENTS WITH TYPE 2 DIABETES MELLITUS IN THE REPUBLIC OF NORTH MACEDONIA

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Abstract

Patients with type 2 diabetes mellitus (T2DM) who have unsatisfactory glycoregulation with concurrent use of basal insulin and oral hypoglycemics, should be switched to a more intensive therapy regime. To evaluate the efficacy of newly available insulin degludec 70/insulin aspart 30 (IDegAsp), we retrospectively analyzed glycoregulation in 131 patients with T2DM treated with this insulin. All 131 patients were with unsatisfactory glycoregulations, and were switched to IDegAsp from other insulins (except basal-bolus insulin regimen). After a mean period of 11.75±5 months of the treatment with IDegAsp, we found statistically significant improvement in fasting and postprandial glucose levels, and HbA1c (12.5±4.4 vs. 8.8±3.9mmol/l, 13.2±4.6 vs. 9.6±4.1mmol/l, 9.7±1.8 vs. 8.1±1.6%, $p<0.01$, respectively). The total average daily dose of insulin units (IU) was the same, and there weren't statistically significant differences in the frequency of hypoglycaemia ($p<0.05$). From the results, we can conclude that patients with T2DM, who switched to IDegAsp from previous antidiabetic insulin treatment (except basal-bolus insulin regimen) had improved glycaemic control without increased insulin units, and without higher risk for hypoglycemia.

Keywords: insulin degludec 70/insulin aspart 30, type 2 diabetes mellitus, insulin units, hypoglycemia.

1. Introduction

Patients diagnosed with type 2 diabetes mellitus (T2DM) who experience inadequate glycoregulation while using a combination of basal insulin and oral hypoglycemic medications may benefit from transitioning to a more intensive treatment approach. This intensified therapy regimen involves the use of basal insulin in conjunction with rapid-acting insulin administered during meals, commonly known as a basal-bolus insulin regimen (Bellido, Suarez, Rodriguez, Sanchez, Dieguez, Riestra *et al*, 2015).

One notable option for basal insulin is insulin degludeg, which is an insulin analog with an extended duration of action lasting approximately 42 hours. This duration significantly exceeds that of insulin glargine (IGlar 100) and detemir, with respective durations of action ranging from 18 to 26 hours and 5.7 to 23 hours (Elizarova, Galstyan & Wolffenbuttel, 2014; Christiansen, Home & Kumar, 2016).

In the Republic of North Macedonia, two commonly used premixed insulin options are biphasic insulin aspart (BIAsp30) and biphasic insulin lispro (lispro mix25). BIAsp30 is composed of 30% soluble insulin aspart and 70% protamine-crystallized insulin aspart, while lispro mix25 comprises 25% soluble insulin lispro and 75% protamine-crystallized insulin lispro. These premixed insulins combine short-acting and long-acting components to provide comprehensive glycemic control. The short-acting component of premix insulin becomes effective within approximately 30 minutes, whereas the long-acting component acts more

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gradually over a span of 5-10 hours. Unlike basal insulin, the combination of short and long-acting insulin regulates postprandial hyperglycemia. The premix insulins are more acceptable for patients with T2DM because the dosage regimen includes two or a maximum of three applications of insulin per day, unlike the basal-bolus insulin dosage regimen which includes up to four applications of insulin per day (Moon, Chung, Kim, Yu, Jeong, Park *et al*, 2021).
Insulin degludec 70/insulin aspart 30 (IDegAsp) represents a unique soluble insulin product, comprising 70% insulin degludec (IDeg) as an ultra-long-acting basal insulin and 30% insulin aspart (IAsp) as a fast-acting mealtime insulin (Kalra *et al*, 2016). IDeg is a basal insulin analogue with a half-life of over 25 hours, while IAsp is an analogue that begins its action after 10 to 15 minutes and compared with the human insulin, has a shorter duration of action (4-5 hours) (Reynolds & Wagstaff, 2004). Patients with T2DM can apply this combination of two insulin analogues once or twice daily with the main meals (Franek, Haluzík, Canecki Varžić, Sargin, Macura, Zacho *et al*, 2016; Woo, Berard & Roscoe, 2020; Kaneko, da Rocha Fernandes, Yamamoto, Langer, & Faurby, 2021). IDegAsp provides a prolonged and stable basal glucose-lowering effect attributable to the IDeg component and reduces the postprandial glucose spikes due to the IAsp component (Heise, Korsatko, Nosek, Coester, Deller, Roepstorff, 2016). The literature data showed that IDegAsp, compared to other premixed insulins, lowers the risk of hypoglycemia and in addition, the fasting glycemia is more stable (Franek, Haluzík, Varzic, Sargin, Macura, Zacho *et al*, 2014; Fulcher, Christiansen, Bantwal, Polaszewska-Muszynska, Mersebach, Andersen *et al*, 2014). However, several studies showed that the conventional insulin regimens are not inferior compared to IDegAsp, thus there is no consensus on switching from conventional insulin regimens to IdegAsp (Kalra 2014; Kalra & Gupta, 2015).
IDegAsp has been available in our country for about two years and there are no data concerning the efficacy of IDegAsp in glicoregulation compared to the conventional insulin regimens. This study aimed to evaluate the efficacy of IDegAsp in patients with T2DM in the Republic of North Macedonia who do not have satisfactory glycoregulation with the existing insulin therapy other than IDegAsp.

2. Materials and Methods

This research was performed in the Diabetes Center at the Shtip Clinical Hospital, Republic of North Macedonia. The current study included 131 patients (63 men and 68 women) with T2DM with a mean age of 63.8±7.7 years. All patients at the beginning received other conventional types of insulin (such as premix analogue insulin; human basal insulin; human insulin and basal analogue insulin) and at some time point, they were switched to a fixed combination of insulin degludec 70/insulin aspart 30.
The glycemic control was retrospectively analyzed. The glycoregulation expressed through the fasting blood glucose (FPG), post-prandial glycemia (PPG), and glycated haemoglobin (HbA1C), as well as the overall antidiabetic therapy was recorded. These parameters were recorded before starting with the therapy with IDegAsp and at the latest control that the patients had had at the Diabetes Center. During the latest follow-up, patients were surveyed about the rate of hypoglycemia before and after starting their therapy with IDegAsp.
The results are presented as mean standard deviation (SD) and as percentages. The t-test for dependent variables was used to assess the statistical significance between the difference in the glycoregulation before and after starting the therapy with IDegAsp. A p-value less than 0.05 was considered statistically significant.

3. Results

This research involved 131 patients with a median duration of T2DM of 15 years, while the duration of the insulin treatment was 6 years. Before the introduction of IDegAsp for the treatment of T2DM 75 patients received premix analogue insulin; 23 patients received human basal insulin; 25 patients were on premixed human insulin and 8 patients received basal analogue insulin. The FPG, PPG, and HbA1c values were retrospectively analyzed before and after the treatment started with IDegAsp.

The results were evaluated after a mean duration of the treatment with IDegAsp of 11.75±5 months. The t-test showed that there was a statistically significant difference between the evaluated parameters before and after the treatment with IDegAsp. Namely, the decrease of the mean values of FPG, PPG, and HbA1c before and after the treatment with IDegAsp was found to be statistically significant (12.5±4.4 vs. 8.8±3.9mmol/l, 13.2±4.6 vs. 9.6±4.1mmol/l, 9.7±1.8 vs. 8.1±1.6%, p<0.01, respectively), (Table 1, Figures 1 and 2).

Table 1. The obtained results for the glycemic control in the analyzed patients

	Before the treatment with IDEgAsp 70/30	After the treatment with IDEgAsp 70/30	p value
Fasting blood glucose (FPG, mmol/L)	12.5±4.4	8.8±3.9	<0.01
Post-prandial glycemia (PPG, mmol/L)	13.2±4.6	9.6±4.1	<0.01
HbA1c (%)	9.7±1.8	8.1±1.6	<0.01
Total number of insulin units (IU)	52.1±13.5	52.1 ±11.5	NS

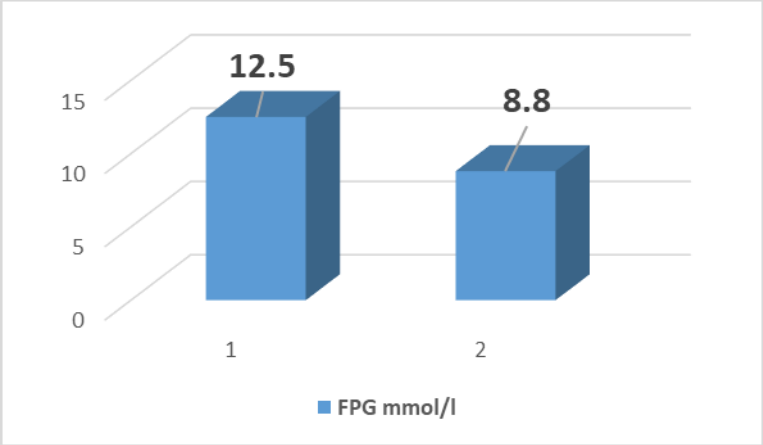

Figure 1. Average values of the fasting glycemia (FPG) (mmol/L): 1. Before the treatment with IDegAsp 70/30, and 2. After the start treatment with IDegAsp 70/30

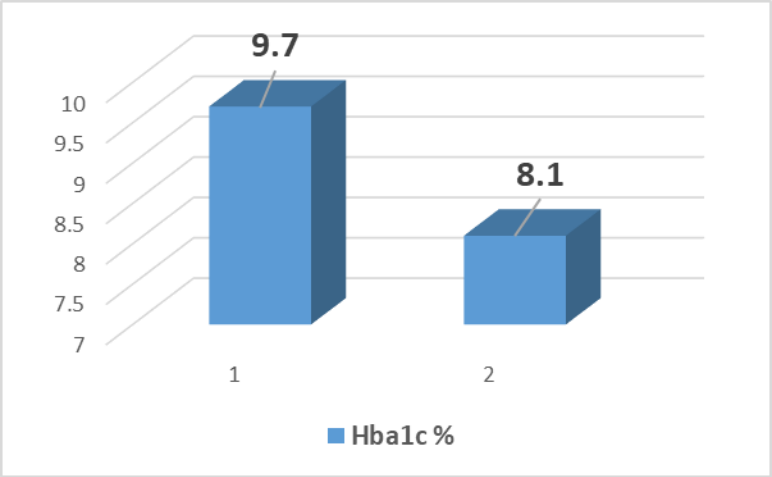

Figure 2. Average values of HbA1c (%): 1. Before the treatment with IDegAsp 70/30, and 2. After the start of the treatment with IDegAsp 70/30

The total average daily dose of insulin units (IU) was the same. The decrease of the IU after the treatment with IDegAsp was found to be statistically insignificant (52.1±13.5 vs., 52.1±11.5 IU). During the evaluation period (before and after the treatment with IDEgAsp), there was no change concerning the other hypoglycemic therapy received by the patients. One hundred and eleven patients received metformin in an average dose of (1390±503 vs., 1375±490 mg), 2 patients received vildagliptin with a total dose of 100 mg, 7 patients received empagliflozin from 10 mg and 4 patients received semaglutide of 1 mg.
Regarding the rate of hypoglycemia, 28 patients reported that before the introduction of IDegAsp, the frequency of the hypoglycemia was at least once a week; whereas at the latest visit, 22 patients reported that the frequency of hypoglycemia was once a week. This difference was not found to be statistically significant.

4. Discussion and Conclusions

The results obtained during this study showed that around one year after the start of treatment with IDegAsp, patients had improved glycemic control without a higher risk for hypoglycemia. Another benefit from the switch from the conventional insulin regimes (premixed insulin and basal insulin) to IDegAsp is that this better glycemic control was achieved with the same insulin units. These findings are in accordance with the results described by Fulcher, Akhtar, Al-Jaser, Medina, Mohamed, Nicodemus *et al*. (2022) where the same glycemic control after switching from basal-bolus regimen was achieved with decreased IDegAsp insulin.
Some physicians prefer not to use fixed-dose insulin preparations because of the belief that the separation of basal and bolus components allows better adaptation of insulin dosages to patients' needs (Home, El Naggar, Khamseh, Gonzalez-Galvez, Shen, Chakkarwar *et al*, 2011). This study compared once-daily IDegAsp with other insulin regiments, but not basal-bolus regimens. So, patients on other insulin regimens (except basal-bolus) who do not meet the glycemic targets statistically significantly decreased FPG, PPG, and HbA1c after 12 months of treatment with IDegAsp.
The American Diabetes Association specifies that longer-acting basal analogues (like degludec) may convey a lower hypoglycemia risk. In a meta-analysis consisting of seven clinical trials, IDegAsp was shown to be associated with equivalent HbA1c control with IGlar and a significantly lower rate of nocturnal hypoglycemia as compared to it (Vora, Christensen, Rana, & Bain, 2014). Other studies (Fulcher *et al*, 2014; Kaneko, Chow, Choi, Taneda, Hirao, Park *et al*, 2015) showed a reduction in the number of hypoglycaemic events with the

introduction of IDegAsp, in comparison to premixed insulins. The conducted study has two limitations. The first is that the patients were not asked to register the hypoglycemic events and the second is that the glycemic control was evaluated only through the FPG, PPG, and HbA1c values without measuring the glycemic variability. However, taking into account the economic status of our country and the unavailability of devices for continuous glucose monitoring (CGM), this study represents real-world results for the patients with T2DM in the Republic of North Macedonia.

In conclusion, patients with T2DM, switching to IDegAsp from previous antidiabetic insulin treatment (except basal-bolus insulin regimen) had improved glycaemic control without increased insulin units, and without higher risk for hypoglycemia.

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