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ORIGINAL INVESTIGATION

Insulin therapy in patients with type 2 diabetes mellitus: An observational study of everyday medical practice in Serbia, Montenegro and Bulgaria (INSU DM2)

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Data Availability Statement: All relevant data are within the paper.

Abstract

Objective: The aim of this study was to evaluate the current insulin management of type 2 diabetes (T2D) in the everyday clinical practice and to assess the proportion of patients achieving target glycemic control according to the international recommendations.

Methods: This was an observational, cross-sectional, multicenter, and multinational study that included 1806 T2D patients on long-term insulin treatment from Serbia (940), Bulgaria (666), and Montenegro (200) from February 2011 to December 2012.

Results: Majority of the patients were overweight and obese with mean age 62.4 ± 9.65 years, mean duration of T2D was 13.6 ± 7.9 years, and mean duration of insulin therapy was 6.8 ± 5.5 years. The proportion of patients achieving target hemoglobin A1c (HbA1c) according to the international recommendations was 27.6% (CI: 25.5–29.7). Poor glycemic control defined as HbA1c ≥7.0% was reported in 72.4% of the patients. This cohort was most commonly treated by biphasic insulin regimen in two daily doses (31.6%), or three daily doses (9.5%), basal insulin alone (36.1%), or basal with three prandial doses (16.3%). Basal insulins were used in 56.7% of patients, prandial in 24.8%, and premixes in 45.3% of patients. Insulin type and regimen affected the rate of hypoglycemia: Patients treated with basal analogs and oral antidiabetic drugs had the lowest risk of hypoglycemia.

Conclusions: Achieving good glycemic control in T2D insulin-treated patients in Serbia, Bulgaria, and Montenegro remains a challenge, with a large proportion of patients not reaching recommended glycemic targets. Basal insulins were the most commonly used insulin regimen; however, the use of premixed insulins was much higher compared to other observational studies, performed in Europe. The use of human insulin is high representing 45% of all insulin therapies used. Our findings suggest that inadequate insulin titration is still frequent as well as the risk of hypoglycemia with currently available insulin options and those remain major barrier to optimal insulin therapy and glycemic target achievement in clinical practice.

Key words: INSU DM2; insulin therapy; observational study; type 2 diabetes

1. Introduction

Incidence of diabetes, especially type 2 diabetes (T2D) is significantly increased worldwide [1]. This dramatic increase in the incidence of T2D and its complications is a great challenge for the health systems, as the diabetic population consumes a disproportionate share of healthcare resources for subsequent microvascular and macrovascular complications. Strategies taken to lessen the disease burden in these patients rely on rigorous treatment of hyperglycemia, dyslipidemia, and hypertension [2].

The results from the landmark study the United Kingdom Prospective Diabetes Study, documented that the reduction of glycosylated hemoglobin A1c (HbA1c) with intensive therapy in patients with T2D, delayed the onset and progression of complications [3,4].

In that context, in 2009 the International Associations - American Diabetes Association (ADA) and European Association for Study in Diabetes, updated their recommendations for management of hyperglycemia in T2D and set the target glycemic goal of HbA1c level <7% [5].

It is well established that progressive decline in beta cell function in T2D leads to worsening of glycemic control in significant number of patients, failed to accomplish the satisfactory glucose regulation on previous therapeutical modalities (lifestyle changes and oral agents), and imply the need for initiation of insulin therapy, considering several insulin regimens: Basal and prandial insulin regimen, conventional treatment with premix insulins and intensified insulin therapy [6].

Despite the consensus guidelines are encouraging intensive glycemic control, achieving HbA1c <7% in clinical practice remains a challenge. Numerous guidelines offer insulin treatment recommendations for T2D patients [7-9], but few studies have been dedicated to investigate how they are implemented in clinical practice.

Therefore, there is a need to better investigate the treatment patterns and achievement of glycemic targets in T2D patients on insulin therapy in real life and to determine physicians' practices for initiation and management of insulin therapy in T2D.

In the context of the previous findings, our observational, cross-sectional, and multicenter multinational study of insulin treatment in patients with T2D in Serbia, Montenegro, and Bulgaria, was aimed to: (a) Describe the current insulin treatment in patients with T2D in everyday clinical practice in these countries, (b) assess the proportion of patients achieving the HbA1c <7% in accordance to the international recommendations, (c) describe the demographic and clinical profile of the insulin treated T2D patients, (d) identify the determinants of the physician's decision for initiation and management of insulin therapy in the T2D, and (e) identify the predictors of achieving target blood glucose values.

2. Methods

2.1. Study design

This was an observational, cross-sectional, multicenter, and multinational study. The primary objective of this study was to describe the current insulin management of T2D in the everyday clinical practice in Serbia, Montenegro, and Bulgaria and to assess the proportion of patients achieving target glycemic control according to the international recommendations.

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice with written informed consent.

The site selection was done based on the number of patients with T2D treated in the center and the geographic distribution of the sites. The initial list of sites represented list of specialists endocrinologists or diabetologists equally geographically distributed across the countries to ensure a good representation of the management of T2D patients on insulin therapy. Participating physicians (final number 134) were randomly selected from this initial list of 200 endocrinologists/diabetologists. Each site enrolled 10 consecutive patients who met the inclusion/exclusion criteria. The number of patients for each site was limited to 20. Patients were enrolled consecutively from the cohort seen by the participating physicians in their daily clinical practice. According to the non-interventional study design, all treatments and procedures were left at the physicians' discretion and did not interfere with everyday clinical practice. The data collected at each visit was part of routine patient care, and no additional diagnostic procedures have been applied.

The inclusion criteria for this study included: T2D outpatients ≥18 years old, on insulin treatment (all regimens were accepted) for more than 6 months and insulin initiated with an intention for a long-term treatment. Respectively, outpatients <18 years old, patients with type 1 diabetes, T2D patients without insulin therapy or with planned short-term insulin therapy (gestational diabetes, pancreatic carcinoma, operation, etc.), patients with secondary diabetes (liver or pancreatic history, steroids therapy, and endocrine diabetes), pregnant women and patients currently participating in a clinical study were excluded from this study.

The characteristics of insulin management of T2D were determined by previous and/or actual oral treatments, as well as the actual insulin treatment - type of insulin and type of regimen, modality of insulin application, reasons for insulinization and distinctive insulin therapy choice. Insulin management of T2D was also evaluated based on the frequency of glycemic laboratory assessments and examinations for different chronic complications of diabetes mellitus during past year.

The clinical characteristics of the T2D patients were determined by anamnestic and physical examination (duration and family burden of T2D), the presence of diabetic complications (retinopathy, neuropathy, micro- or macro-albuminuria, angina, myocardial infarction, heart failure, stroke, peripheral arterial disease, and amputation).

The effectiveness of insulin therapy was determined by the quality of glucose regulation according to ADA recommendations (level of HbA1c <7% and fasting blood glucose concentration FBG <7.2 mmol/L).

The number and severity of hypoglycemic episodes in the past 6 months were used for analysis of tolerability and adverse reactions of insulin therapy.

According to clinical practice and study design, patient's observation and data collection were done once for each patient at the time of the visit and examination in a cross-sectional manner. There was no additional follow-up of the patients. The enrolment period lasted 24 months.

2.2. Statistical methodology

Data were collected on the paper form (CRF and Physician Questionnaire) and then entered into an electronic database (access database application). In case of missing, inconsistent or illegible data, a data clarification form was sent back to the investigator. A double-entry method was used for 5% of the patients to ensure that the data (except comments) were transferred accurately from the CRFs to the database.

All variables are presented as continuous data (scale) or categorical (nominal and ordinal). Continuous data are presented as mean values with standard deviations and 95% CI for means or as medians with interquartile ranges (for skewed data). Categorical data are presented by absolute numbers with percentages and valid percentages.

Depending of the type and number of examined parameters, Chi-square test, Mantel Haenszel test, Student's *t*-test for independent or paired samples and Mann–Whitney test (not Gaussian distribution), and binary logistic regression were used. The control rate in regression analysis was presented as a binary variable indicating whether a patient reached target HbA1c <7.0% (1) or not (0) at the time of visit. The independent variable entered at the first step were: Body mass index (BMI), age, abdominal obesity, obesity grade, waist circumference, gender, demographic data (place of living and physical activity), presence of any of the chronic complications of disease, number of glycemic measurements, number of daily injection, and average daily dose of insulin. In all tests, alpha level at 0.05 ($P < 0.05$) was considered to be statistically significant. Levene's test was used to assume equality of variances.

Sample size calculation was determined on the expected proportion of patients with HbA1c <7%. Real life data from Eastern Europe, Asia, Latin America, and Africa indicates that irrespective of insulin regimen or geographic region, only 18–35% T2D patients reached the A1C goal (<7%) [10].

Assuming that the proportion of treated patients with HbA1c <7 would be around 30%, the inclusion of 1700 patients would allow to calculate this rate with 2.1% precision rate (based on two-sided 95% confidence interval). The precision would be even better if the

proportion is <30%. If we assume that 5% patients will drop out from evaluation due to missing/uncorrected data, the final sample size is corrected to 1785 patients.

3. Results

In this study, a total of 1806 T2D patients on insulin treatment from Serbia (940), Montenegro (200), and Bulgaria (666) were included between February 1, 2011 and December 10, 2012. There were no excluded patients from the analysis, no violation of inclusion criteria and no withdrawal of the patient's informed consent to participate in the study. A total of 134 physicians participated in the study (90 from Serbia, 9 from Montenegro, and 35 from Bulgaria).

3.1. Demographic and clinical characteristics of the study population

There were 918 (50.8%) females and 867 (48.0%) male patients. Males included in the study (61.4 ± 10.0 years) were younger than females (63.2 ± 9.1 years) ($P < 0.01$), while mean age of the whole cohort was 62.4 ± 9.65 years. The overall patients' mean BMI was 29.4 ± 4.9 kg/m^2. The females in INSU DM2 cohort had significantly higher BMI (30.0 ± 5.2 kg/m^2) compared to males (28.7 ± 4.5 kg/m^2), ($P < 0.01$). There was a predominance of overweight (BMI 25–29.9 kg/m^2) and obese Grade I (BMI 30–34.9 kg/m^2) in the study population. There were significantly more obese females (50.6%) than males (38.5%), ($P < 0.01$). Mean waist circumference values for males were 101.1 ± 11.9 cm and for females 98.3 ± 12.8 cm. Central obesity (the waist for men ≥102 cm and for women ≥88 cm) was registered in 1356 (75.1%) patients and was more common in females (93.9% vs. 73.5%) ($P < 0.01$).

The mean ± SD duration of T2D in this cohort was 13.6 ± 7.9 years. There was a predominance of patients with duration of T2D over 15 years (34.9%) and 6–10 years (27.5%). Duration of T2D less than a year was registered in only 1.7% of patients. A positive family history of T2D was reported in 816 (45.2%) of study patients. Clinical data related to chronic complications of T2D showed the significantly higher proportion of microvascular complications, compared to macrovascular complications (Figure 1).

In INSU DM2 study arterial hypertension was registered in 1442 (79.8%) and dyslipidemia of any type in 1049 (58.1%) patients. Active smoking was found in 260 (14.4%) of patients. Arterial hypertension was treated in 1429 (79.1%) of patients. Therapy of dyslipidemia was registered in 878 (48.6%) and antithrombotic therapy was registered in 838 (46.4%) patients. Mean systolic blood pressure was 135.3 ± 15.4 mmHg and diastolic was 81.5 ± 8.9 mmHg. The ACE inhibitors (53.2%), beta-blockers (33.1%), calcium channel blockers (24.6%), and diuretics (20.0%) were the most frequently used antihypertensive drugs, followed by ACE inhibitor and diuretic combinations (16.2%), vasodilators (10.4%), and Angiotensin II receptor blockers (7.1%). The most commonly used antiaggregation drug was the acetylsalicylic acid, in 41.8%, and clopidogrel in 3.1% of the patients. Statins were the most commonly used hypolipidemics in 42.7% of the patients, followed by the fibrates (8.0%).

3.2. Treatment of diabetes mellitus

Out of 1806 insulin-treated patients included in the study 995 (55.1%) were treated with oral anti-diabetic drugs (OAD). Of all prescribed OAD drugs biguanides were the most used (53.9%), followed by the sulfonylureas (SU) (8.99%) and the least used were acarbose (0.4%) and gliptins (0.2%). The mean daily dose of metformin was 1685 ± 601 mg. Most patients used metformin twice a day (62.7%) while 22.6% used it 3 times a day and 14.7% used it once a day. Glimepiride was the most commonly used SU, in 4.7% of study patients, followed by gliclazide in 2.3%, glibenclamide in 1.4%, and glipizide in 0.5% of study patients. The daily dose of SU derived oral anti-diabetics is shown in Table 1.

Mean duration of insulin therapy for patients with T2D was 6.8 ± 5.5 years. Out of 1806 study patients, 56.7% were

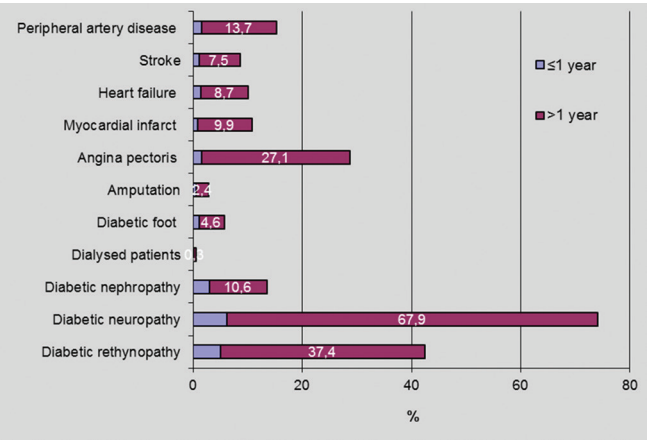

Figure 1. Prevalence (%) of diabetes mellitus chronic complications

treated with a regimen including basal insulin (basal oral, basal plus, or basal-bolus) and 45.3% were treated with premixed insulins. Prandial insulins were used in 24.8% of the patients. Analog insulins were more commonly used compared to human insulins for all insulin types - basal, prandial, and premixed (Figure 2).

Basal insulins (analog or human) were mainly used without prandial insulin (36.1%). The basal-bolus insulin regimen - basal application with three prandial doses, was used in 16.3% of the patients. The basal-plus regimen was not commonly used: Basal application with one prandial dose was only reported in 1.1% of the patients, and basal with two prandial doses was reported in 0.8% of the patients. Basal insulins were also used with one biphasic application in a small number of patients (1.7%). Among the 652 patients treated with basal insulins, 411 (22.7%) patients took concomitant oral anti-diabetics (biguanides or/and SUs) while 241 (13.3%) patients had only basal insulin. Premixed insulins (analog or human) were most frequently applied in two daily doses (in 31.6% of the patients) or three daily doses (in 9.5% of the patients). Once-daily application of premixed insulins has been reported only in 1.7% of the study population.

The isophane insulin was the most frequently used basal insulin type, in 468 (25.9%), followed by insulin glargine, in 453 (25.1%), and insulin detemir, in 103 (5.7%) patients. Among prandial insulins the human rapid-acting insulin was used in 185 (10.2%), glulisine in 126 (7.0%), aspart in 121 (6.7%), and lispro in 13 (0.7%) patients. Among biphasic insulins, human biphasic insulin was used in 380 (21.0%), biphasic aspart in 336 (18.6%), and biphasic lispro in 103 (5.7%).

The mean daily dose of human basal insulin (isophane insulin) was 26.3 ± 13.0 U, which was significantly lower than the mean dose of basal insulin analogs (detemir and glargine) 30.0 ± 12.5 U ($P < 0.01$). The mean daily dose of detemir (31.7 ± 14.9 U) did not differ significantly from the mean dose of glargine (29.6 ± 11.9 U). Data are shown in Table 2.

The mean daily dose of human rapid-acting insulin (30.38 ± 13.76 U) and prandial insulin analogs (aspart 31.76 ± 13.49 U, glulisine 30.53 ± 13.76 U, and lispro 38.38 ± 14.03 U) did not differ significantly ($P = 0.19$) (Table 3).

There was a significant difference in mean daily doses between different types of premixed insulins ($P < 0.01$). The mean daily dose of human biphasic insulin (41.97 ± 15.03 U) was significantly lower than the mean daily doses of biphasic aspart (51.04 ± 17.01 U) and biphasic lispro (59.64 ± 17.03 U), ($P < 0.01$). Mean daily dose of biphasic insulin aspart was significantly lower than biphasic lispro ($P < 0.01$) (Table 4).

One daily application was seen in 92.0% of patients with glargine, 76.7% with detemir and 64.3% with isophane insulin. Mann–Whitney U test showed the significantly fewer number of daily applications for basal insulin analogs compared to isophane insulin, as well as a fewer number of daily applications for glargine compared to detemir ($P < 0.01$) (Figure 3).

Table 1: The mean daily dose of sulfonylurea-derived oral anti-diabetics

Sulfonylurea	N	Mean±SD
Glibenclamide	25	3.72±1.45
Gliclazide	42	74.00±39.70
Glimepiride	85	3.06±1.33
Glipizide	9	9.39±4.10
Total	161	

SD: Standard deviation

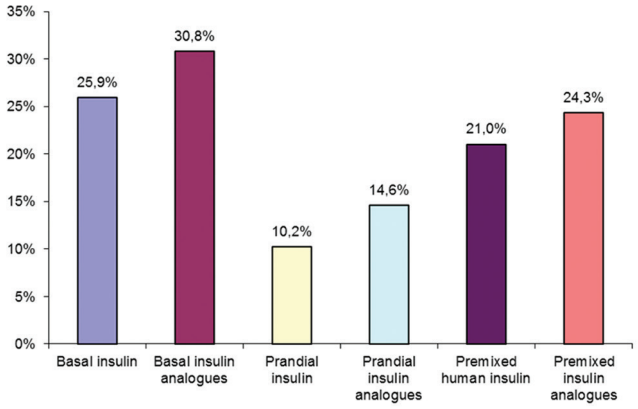

Figure 2. Actual types of insulin treatments for type 2 diabetes mellitus

Three daily applications were seen in 85.2% of patients with human rapid-acting insulin, 87.1% with aspart, and 92.6% with glulisine, and in 100.0% of patients with lispro. Mann–Whitney U-test did not show a significant difference in number of daily application between prandial human insulin and prandial insulin analogs (P = 0.92).

Majority of patients were treated with two daily applications of biphasic insulin - 84.4% for human biphasic, 58% for biphasic aspart, and 68.0% for biphasic lispro. The human biphasic were more often applied in two daily doses than premixed insulin analogs which were sometimes applied in three daily doses (P < 0.01) (Figure 4).

The most often used type of application device was the reusable pen (56.2%) followed by disposable pens (42.5). Mostly insulin application was done by the patient himself, in 94.8% of patients. The self-adjustment of the insulin dose was registered in 965 (55.4%) of study patients.

3.3. Proportion of patients achieving target glycemic control according to the international recommendations

A total of 1748 (96.8%) patients had documented HbA1c measurement in the past year. The mean value of HbA1c at the last laboratory measurement was 8.1 ± 1.6%. The proportion of patients achieving target HbA1c according to the international recommendations (HbA1c <7%) was 27.6% (CI: 25.5–29.7). Poor glycemic control defined as HbA1c ≥7.0% was reported in 72.4% of the patients.

Laboratory assessment of fasting glycemia was registered in 1706 (94.5%) of patients. The mean value of the laboratory measured fasting plasma glucose (FPG) was 8.36 ± 2.98 mmol/l. Target FPG as per ADA recommendations was

Table 2: Mean daily doses of basal insulins

Basal insulins INN	N	Mean±SD	Minimum (U/per day)	Maximum (U/per day)
Isophane insulin	466	26.36**±13.05	6	70
Basal insulin analogs	556	30.01±12.55	6	100
Detemir	103	31.72±14.98	6	100
Glargine	453	29.62±11.92	8	94

**P<0.01 versus basal insulin analogs. SD: Standard deviation

Table 3: Mean daily doses of prandial insulins

Prandial insulins INN	N	Mean±SD	Minimum (U/per day)	Maximum (U/per day)
Human rapid acting	183	30.38±13.76	4	72
Aspart	121	31.76±13.49	4	78
Glulisine	126	30.53±13.76	6	78
Lispro	13	38.38±14.03	20	60

NS for all parameters. SD: Standard deviation

Table 4: Mean daily doses of premixed insulins

Premixed insulins INN	N	Mean±SD	Minimum (U/per day)	Maximum (U/per day)
Human biphasic	380	41.97±15.03	12	92
Biphasic aspart	333	51.04**±17.01	10	138
Biphasic lispro	103	59.64**&&±17.03	20	110

**P<0.01 versus human biphasic; &&P<0.01 versus biphasic aspart. SD: Standard deviation

achieved in 45% of the patients, and in 55% FPG was poorly regulated (FPG over 7.2 mmol/L).

3.4. Frequency of evaluation of blood glucose control and examinations for chronic complications

Almost half of the patients with documented laboratory assessment of HbA1c had two measurements (49.0%) during the past year, 18.2% of the patients had three measurements, 15.8% had only one measurement, and 15.3% had four measurements during the year. Five and more measurements, as well as no measurements, were found in only 0.7% and 1.0% of patients, respectively. Among the patients with documented laboratory assessment of fasting glycemia, the great majority had one to five laboratory measurements (64.2%) per year.

Self-control of FPG concentration by glucometer was registered in 90.6% of the patients. The mean number of fasting self-monitoring plasma glucose measurements was 10.1 ± 7.9 times per month. Self-control of postprandial glycemia was registered in 75.6% of patients.

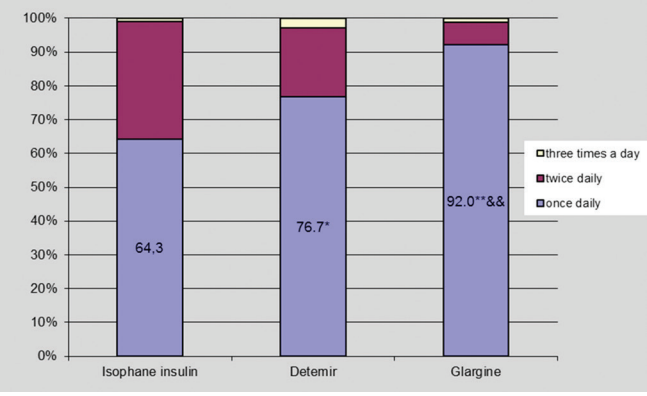

Figure 3. Basal insulins - frequency of daily doses. *P < 0.05, **P < 0.01 versus isophane insulin; &&P < 0.01 versus detemir (Mann–Whitney U test)

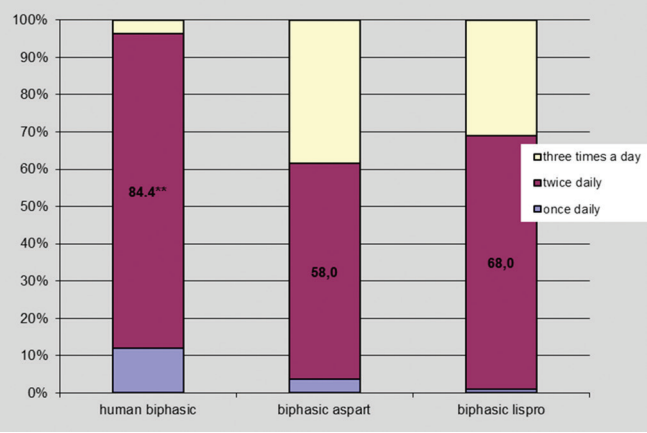

Figure 4. Premixed insulins - frequency of daily doses. **P < 0.01 versus biphasic aspart and biphasic lispro

The total of 1806 patients was evaluated on the frequency of examinations for chronic complications. The most evaluated chronic conditions associated with T2D during the past year were cardiovascular disease (87.3%) and dyslipidemia (77.6%). Examinations for neuropathy were performed in 75% of the patients, for retinopathy in 74.7%, for microalbuminuria in 68.4%, and for diabetic foot in 50.5% of the patients. The mean number of examinations for cardiovascular disease was 1.73 ± 1.7, for retinopathy 1.15 ± 1.0, for neuropathy 0.9 ± 0.6, for microalbuminuria 0.9 ± 0.7, for diabetic foot 0.7 ± 0.9, and for dyslipidemia 1.6 ± 1.2/year.

3.5. Determinants of the physician's decision for initiation and management of particular insulin therapy in the T2D

The main criteria for the selection of insulin therapy for the physicians were patients characteristic (HbA1c, BMI, etc.) (69.0%), simplicity of use and dosing (56.7%), treatment recommendations for T2D (50.7%), risk of hypoglycemia (47.9%), fast reaching of optimal insulin dose (27.9%), and drug price and availability (6%).

3.6. Predictors of achieving target blood glucose values

Increased BMI and older age showed slightly negative association with reaching target HbA1c OR 0.92, 95% CI (0.86–0.98) (P < 0.05). Other anthropometric and demographic data, as well as chronic complications of disease, arterial hypertension, and dyslipidemia, did not show significant association with HbA1c target reaching. Number of daily injections and mean daily dose did not show significant association with reaching target HbA1c, but self-adjustment of daily dose showed significant positive association with reaching HbA1c target (OR 4.8; 95% CI [1.4–16.1]). The frequency of HbA1c measurements also showed significant positive association with reaching target HbA1c: 1.19 (1.06–1.34).

3.7. Hypoglycemic episodes

Symptomatic hypoglycemic episodes in the past 6 months were reported in 712 (39.4%) of patients, of which 97 (5.4%) had severe hypoglycemic episodes and 100 (10.6%) patients had nocturnal hypoglycemic episodes.

The mean number of symptomatic hypoglycemic episodes for the past 6 months was 5.3 ± 6.5, the mean number of severe hypoglycemic episodes was 2.5 ± 2.7, and mean number of nocturnal hypoglycemic episodes was 3.7 ± 3.9.

Insulin therapy regimens and rate of adverse effects are shown in Table 5. The occurrence of symptomatic hypoglycemia was lower in patients treated with basal insulins and OAD. The occurrence of severe hypoglycemia was also lower in patients with basal insulins but without OAD. Basal human insulins with three prandial doses and OAD and biphasic insulins once a day with OAD had less reported nocturnal hypoglycemia (7.3% and 7.4%) compared to other regiments and insulin types.

4. Discussion

This observational study on the insulin management of T2D in the everyday clinical practice in Serbia, Bulgaria, and Montenegro gives an overview of the profile of insulin-treated T2D patients, the characteristics of insulin treatment in the countries and the proportion of patients achieving target glycemic control according to the international recommendations.

The basic characteristics of T2D patients in INSU DM2 cohort were similar to those in other observational studies performed in France. In the present study, there were more female than male patients, and the proportion of the enrolled women was comparable to IDAHO 2 study [11]. As expected, patients with T2D were older (mean age of 62.4 ± 9.65 years) with significantly younger males than females. They were mostly overweight and obese Grade I, with significantly higher BMI in females. Similar data were obtained from another observational study in France [12], where T2D patients were aged 64.8 ± 11.2 years (mean±SD), they were also mostly overweight and obese (mean BMI was 30.1 ± 5.4 kg/m^2). The INSU DM2 cohort of patients showed significantly higher proportion of microvascular and macrovascular complications than the French cohort, which could be an indicator of more complex patients with poor metabolic control despite their somewhat younger age and lower BMI. Presence of risk factors in INSU DM 2 cohort (arterial hypertension, dyslipidemia, and smoking) was very similar to those observed in the French study [12].

The mean duration of T2D in the examined INSU DM2 cohort was somewhat longer than the T2D duration in the IDAHO 2 cohort in France (11 years), while the proportion of patients with a positive family history of T2D was lower compared to the referenced study [11].

T2D is a chronic and progressive disease. Previously, it has been shown that β-cell function deteriorates, during the course of diabetes. In that context, T2D management should begin with lifestyle modifications and OADs treatment, in particular, metformin but, as the disease progresses, insulin may become necessary in 50% of T2D patients for adequate glycemic control [5]. Metformin and SUs are conventional first-line OADs, although second-line OADs with different mechanisms of actions are now available.

Out of 1806 included patients in INSU DM2 cohort, the majority (91.0%) was using OAD before the visit and during a year of treatment of diabetes. Furthermore, at the time of visit more than one half was treated with OAD. Duration of OAD therapy was less than a year in negligible number of patients, while OAD therapy was longer than a year in most of the patients. The analysis of distribution of OAD use in insulin-treated patients showed that the majority of patients was treated with metformin alone (47.2%), 2.2% were treated with SUs alone, and combination of these two oral hypoglycemic agents was used in 6.8% of patients. This is not in concordance with results from the IDAHO 2 study, where the majority of insulin-treated patients was on combination therapy of two OADs or more, and less patients were treated with metformin alone [11]. In general, the proportion of patients treated with OADs in our cohort was lower compared to the French cohort which suggests lower usage of OADs in combination with insulin in Serbia, Bulgaria, and Montenegro.

In our observational, cross-sectional, multicenter, and multinational study the average duration of insulin therapy was about 6.5 years. Basal insulins were used in 56.7% of patients, prandial in 24.8%, and premixes in 45.3% of patients. Basal insulin use was much lower compared to the ADHOC study conducted in France in 2007 and 2008, where basal insulin was used in 87.9% of all cases (12). In addition, the use of premixed insulins was much higher compared to the ADHOC cohort, where premixed insulins were used only in 12.8% of patients [12].

Table 5: Distribution of hypoglycemia episodes per type of insulin therapy

Type of insulin therapy	n	Symptomatic n (%)		Severe n (%)		Nocturnal n (%)	
Basal analog+OAD	224	75	33.5	9	4.0	23	10.3
Basal analog	90	38	42.2	3	3.3	16	17.8
Basal analog+three prandial+OAD	79	37	46.8	8	10.1	12	15.2
Basal analog+three prandial	128	69	53.9	10	7.8	21	16.4
Basal human+OAD	200	70	35.0	8	4.0	28	14.0
Basal human	138	53	38.4	4	2.9	20	14.5
Basal human+three prandial+OAD	41	17	41.5	5	12.2	3	7.3
Basal human+three prandial	49	24	49.0	8	16.3	5	10.2
Biphasic insulins twice a day+OAD	299	123	41.1	13	4.3	51	17.1
Biphasic insulins twice a day	272	100	36.8	13	4.8	36	13.2
Biphasic insulins three times a day+OAD	107	39	36.4	5	4.7	10	9.3
Biphasic insulins three times a day	65	21	32.3	5	7.7	7	10.8
Biphasic insulins once a day+OAD	27	8	29.6	2	7.4	2	7.4
Biphasic insulins once a day	4	3	75.0	0	0.0	0	0.0
Other	83	35	42.2	4	4.8	14	16.9
Total	1806	712	39.4	97	4.0	246	13.6

In the ADHOC French study, about two-thirds of the patients (67.3%) received single insulin injection and, respectively, only one-third of patients (32.7) received multiple insulin injections [12]. Different distribution of insulin's regimens was reported in the present INSU DM2 study. Even though the most commonly used insulin regimen was basal insulin alone (36.1% of patients in one or two applications), much bigger proportion of patients was treated with "multiple-injection" regimens: 41.1% had 2 or 3 injections per day of biphasic insulin, and 16.3% were on basal-bolus insulin regimen. Basal insulin with one or two prandial doses was extremely rare (1.9%).

For many years, the non-physiologic time-action profiles of conventional human insulins remained a barrier to achieving tight glycemic control for many patients. However, the adventure of recombinant DNA technology has allowed modification of the insulin molecule to produce insulin analogs with improved pharmacokinetic parameters. In the present INSU DM2, there is a moderately higher administration of insulin analogs compared to human insulins for all insulin types in INSU DM 2 study. However, the use of human insulins is still high representing 45% of all insulin therapies used.

The most often used type of insulin administration device was the reusable pen, followed by disposable pens, which is in line with data from other countries where the injector pen was preferred. There was a higher proportion of self-application in INSU DM 2 cohort than in other studies. The French study presented results that most patients (73%) were able to do their injections themselves, in the other cases, mainly in patients over 80 years; a nurse or a family member performed the injections [11].

The average time from onset of T2D to initiation of insulin therapy for INSU DM2 patients was about 6 years, which is shorter compared to results from other studies [11] where this period was about 10 years. This indicates good compliance with recommendations for early insulinization of T2D patients in Serbia, Montenegro, and Bulgaria.

The main criteria for the selection of insulin therapy, specified by the participating physicians in INSU DM2,

were patient characteristic (HbA1c, BMI, etc.) in 68.9%, ease of use and dosing in 56.6%, T2DM treatment recommendations in 50.7%, and risk of hypoglycemia in 47.9%.

Treatment of T2D is primarily aimed to maintain optimal glycemic control. It is generally recognized that maintaining HbA1c at target levels can substantially reduce the risk of developing diabetes-related complications [7]. Accordingly, ADA, AACE, and IDF have recommended target HbA1c levels of <7.0%, ≤6.5%, and ≤6.5%, respectively [7-9], but taking into account individualized approach. They recommended FPG concentrations between 5.0–7.2, <6.1 and ≤6.0, mmol/L, respectively [7-9].

Having in mind the great prevalence of comorbidities and the older patients' age in the INSU DM 2 cohort, the individual targets were determined on an individual basis. The physicians were in line with current patient's cantered approach guidelines before initiation of insulin treatment by patient characteristics and needs.

The mean value of last laboratory measured HbA1c was 8.1 ± 1.6%, the mean value of last laboratory measured FPG was 8.3 ± 2.9 mmol/L, and the mean value of self-measured fasting blood glucose was 7.9 ± 2.7 mmol/L. Frequency of poor glycemic control in patients in INSU DM2 cohort (HbA1c ≥7.1%) was 72.4% which is comparable with the International Diabetes Management Practice Study [10]. The target FPG according to ADA in laboratory settings was achieved in 45% of patients. Other published studies presented a higher proportion of poor regulated diabetics on insulin therapy. The ADHOC study in France showed that, after more than 6 months of insulin treatment, almost 80% of T2D still had HbA1c levels >7% and 35% of patients had levels >8% [12]. Lower proportion of poor controlled patients and higher mean values of HbA1c in INSU DM2 cohort compared to other mentioned studies suggest the presence of very poor regulated subgroup of T2D who need additional evaluation and attention in everyday clinical practice. This is of particular interest if we assume that the most common reasons for failure to reach target fasting blood glucose in INSU DM2 study were poor compliance with actual recommendations for lifestyle change in 33.5% of patients.

The number of daily injections and mean daily insulin dose did not show significant association with reaching target HbA1c. However, the self-adjustment of daily dose showed significant association with reaching target HbA1c. This could indicate a possible need for more optimal titration of the insulin dose. Frequency of HbA1c measurements also showed significant positive association with reaching target HbA1c, which once again confirmed that more frequent evaluation of blood glucose control leads to better overall glycemic control.

In clinical practice, fear of hypoglycemia is a common barrier to optimal titration, adherence and achieving glycemic targets with insulin [13]. Moreover, hypoglycemia is a common complication of the pharmacological treatment of diabetes which is highly costly [14]. Especially in aging T2D patients, severe hypoglycemia can be very harmful: For example, fall and seizures are typical complications. Recovery from hypoglycemic coma is slower in older subjects and, in complicated T2D patients, hypoglycemia can precipitate an acute coronary syndrome, through the potent adrenergic burst, which occurs in response to low plasma glucose levels [15].

Symptomatic hypoglycemic episodes during the past 6 months were registered in less than half of patients. Among the registered events, one-quarter was nocturnal hypoglycemic events. Severe hypoglycemic episodes were rare. Insulin type and regimen affected the rate of hypoglycemia in the INSU DM2 study: Patients treated with basal analogs and OADs had lowest risk of hypoglycemic events.

5. Conclusions

The INSU DM2 study showed the current management of type 2 insulin-treated patients in standard clinical settings in Serbia, Montenegro, and Bulgaria. Achieving good glycemic control remains a challenge, with a large proportion of patients not reaching recommended glycemic targets. Basal insulins were the most commonly used insulin regimen; however, the use of premixed insulins was much higher compared to other observational studies, performed in Europe. There was a moderately higher administration of insulin analogs compared to human insulins for all insulin types; however, the use

of human insulins was still high, representing 45% of all insulin therapies used. Our findings suggest that inadequate insulin titration is still frequent as well as risk of hypoglycemia with currently available insulin options and those remain major barrier to optimal insulin therapy and glycemic target achievement in clinical practice.

Author's contributions

All authors contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, critical revision and final approval of the version to be published.

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