ORIGINAL STUDY

Сравнительный анализ эффективности гликемического контроля и частоты развития микроангиопатий у пациентов с сахарным диабетом 1 типа, получающих терапию генноинженерными инсулинами человека или аналогами инсулина человека: данные 10-летнего ретроспективного наблюдения

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В лечении сахарного диабета (СД) используются как генноинженерные инсулины человека (ГИЧ), так и генноинженерные аналоги инсулина человека (АИЧ) ультракороткого и длительного действия, которые, в отличие от ГИЧ, имеют более физиологичный профиль действия, максимально приближенный к профилю действия эндогенного инсулина. Исходя из этого, логично было бы предположить, что длительное (многолетнее) применение АИЧ приводит к меньшей частоте развития поздних осложнений СД по сравнению с ГИЧ. Однако до настоящего времени нет данных долгосрочных наблюдений, позволяющих сравнить оба класса препаратов инсулина не только в отношении эффективности гликемического контроля, но и в отношении частоты развития микрососудистых осложнений в отдаленном периоде у пациентов с СД 1 типа (СД1).

***Цель**. Ретроспективно сравнить эффективность контроля гликемии и частоту развития микрососудистых осложнений (нефропатии и ретинопатии) у пациентов с СД1, получавших в течение 10 лет терапию ГИЧ или АИЧ.*

***Материалы и методы**. На основе данных электронных баз «Регистра сахарного диабета» нескольких регионов РФ была сформирована выборка больных СД1 (n=260), которые на протяжении 10 лет получали либо ГИЧ (n=130), либо АИЧ (n=130). Пациенты обеих групп были попарно сопоставлены по базовым клиническим характеристикам (полу, возрасту дебюта диабета, длительности заболевания и значению HbA_{1c}). Все пациенты наблюдались врачами-эндокринологами в условиях рутинной клинической практики.*

***Результаты**. Через 10 лет наблюдения HbA_{1c} снизился на достоверно большую величину по сравнению с исходным значением у больных, получающих АИЧ по сравнению с больными на ГИЧ (на 1,30% и на 0,81% соответственно; p<0,05). К концу наблюдения распространенность диабетической ретинопатии (любой стадии) увеличилась в обеих группах и достоверно не различалась между группами; распространенность диабетической нефропатии также увеличилась в обеих группах, но ее прирост оказался достоверно ниже у пациентов, получавших АИЧ, в сравнении с больными, получавшими ГИЧ (+20,5% и +33,9% соответственно; p<0,05). В группе пациентов, получавших ГИЧ, получен достоверно более высокий риск развития микрососудистых осложнений (ОР (отношение рисков): 1,84; 95% ДИ: 1,37–2,48) и, в частности, развития диабетической ретинопатии (ОР: 1,37; 95% ДИ: 0,98-1,90).*

***Выводы**. 10-летний ретроспективный анализ лечения больных СД1 в рутинной клинической практике показал достоверно более эффективное снижение HbA_{1c} и более низкую частоту развития диабетической нефропатии у пациентов, получавших АИЧ, в сравнении с пациентами на терапии ГИЧ.*

***Ключевые слова:** сахарный диабет 1 типа; регистр сахарного диабета; ретроспективное исследование; аналоги инсулина человека; генноинженерные инсулины человека; ретинопатия; нефропатия*

Comparative analysis of glycemic control effectiveness and microvascular complications in patients with type 1 diabetes mellitus, treated with genetically engineered human insulin or human insulin analogues: A 10-year retrospective observational study

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Background. *The treatment of diabetes mellitus generally involves genetically engineered human insulin (GICH) or genetically engineered analogues of human insulin (AIC). Compared to GICH, AIC better physiologically mimics endogenous insulin functionally. It would thus be logical to assume that long-term (multi-year) application of AIC leads to a lower incidence of diabetic angiopathy compared to GICH. To date, however, no long-term comparisons of both classes of insulin preparations (in terms of efficacy of glycemic control or incidence of microvascular complications in patients with type 1 diabetes) have been performed.*
Aims. *To retrospectively compare the efficacy of glycemic control and incidence of microvascular complications (nephropathy and retinopathy) in patients with type 1 diabetes treated for at least 10 years with either GICH or AIC.*
Materials and methods. *Based on data from electronic databases (diabetes registry) from several regions within the Russian Federation, the following patient samples were examined (n=260): group 1 received GICH for 10 years (n = 130) and group 2 received AIC for 10 years (n = 130). Patients in both groups underwent pairwise matching for baseline clinical characteristics (sex, age of diabetes onset, duration of disease and HbA_{1c} level). All patients were observed by endocrinologists in the clinic.*
Results. *After 10 years of follow up, HbA1c levels declined more significantly in group 2 than in group 1 (1.30% vs. 0.81%, respectively, P < 0.05). By the end of the observation period, the presence of diabetic retinopathy (any stage) increased in both groups and was not significantly different between groups; the presence of diabetic nephropathy was also increased in both groups, but the increase was significantly lower in group 2 than in group 1 (20.5% vs. 33.9%, respectively, P < 0.05). Overall, the risk of microvascular complications was significantly higher in group 1 than in group 2 [HR (hazard ratio): 1.84; 95% CI: 1.37–2.48), specifically, the risk of diabetic retinopathy (HR: 1.37; 95% CI: 0.98–1.90).*
Conclusions. *A 10-year retrospective analysis of patients treated with AIC for type 1 diabetes in the clinic showed a significantly more effective reduction in HbA1c levels and a lower incidence of diabetic nephropathy, compared with patients treated with GICH.*
Keywords: *type 1 diabetes mellitus; diabetes register; retrospective study; human insulin; insulin analogues; retinopathy; nephropathy*

Background

In recent times, significant progress in the treatment of type 1 diabetes mellitus (DM) was made, allowing patients to manage the chronic disease better. Meanwhile, the problem of diabetes vascular complications has been the major cause of disability and premature death for type 1 DM patients. According to various estimates, the life expectancy of type 1 DM patients with disease onset prior to 18 years of age is 20 years shorter compared to the general population [1], which is due to the development of acute complications and the progression of diabetic micro- and macroangiopathy. The main cause for microvascular complications is poor glycaemic control, especially in young patients who cannot reach the target values of glycaemia with the increase of the disease duration [2, 3]. The causes of poor glycaemic control can be due to poor patient compliance or the pharmacokinetics and pharmacodynamics of the insulin used.

Nowadays, in the treatment of type 1 DM both genetically engineered human insulin (GEHI) and more modern drugs are used, such as genetically engineered analogues of human insulin (AHI) with ultrashort and long action. The disadvantages of GEHI are variability of its absorption from the tissue at the injection site, significant intra- and inter-individual differences in pharmacokinetics, delayed onset of action of prandial insulin and prominent peaks of action of basal insulin. These issues cause instability of glycaemia during the day and the alternating of hyper- and hypoglycaemic conditions [4, 5]. Compared to GEHI, modern AHIs with ultrashort and long-term action have a maximum action similar to endogenous insulin. AHIs of ultrashort action (Lispro, Aspart, Glulisin) begin to act almost immediately after the injection, which ensures the best indicators of glycaemic control in the postprandial period. AHI of long and ultralong action (Glargine, Detemir, Degludec) are characterized by a peakless action profile, significantly reducing the risk of hypoglycaemic states compared to GEHI, especially at night [4, 5]. AHI's pharmacokinetics characteristics allow to achieve better glycaemic control and also may contribute to lower development of micro- and macrovascular complications in the long-term period.

AHIs with ultrashort action have been used in clinical practice since 1995 when Russia became the first country in the world to register the new generation of insulin, which was the insulin Lispro (Humalog®). This was followed by the registration of Aspart (NovoRapid) in 2000 and Glulisin (Apidra) in 2004. The first long-acting AHI Glargine (Lantus) was registered in 2000, and then in 2005 the Detemir (Levemir) was approved for clinical use. Thus, the opportunity to jointly use ultrashort and long-acting AHIs in the treatment of type 1 DM has existed for more than 15 years. However, studies analysing the long-term microvascular complications development differences in AHI and GEHI in type 1 DM patients have rarely been performed.

Aims

To compare the efficacy of glycaemic control and the incidence of microvascular complications (nephropathy and retinopathy) between type 1 DM patients who used GEHI or AHI therapy for 10 years.

Methods

Study design

This retrospective cohort study was performed using data of the state diabetes register of the Russian Federation.

Study methods

The diabetes registry data of seven regions of Russia was used (the Moscow Region, the Republic of Bashkortostan, the Republic of Tatarstan, the Omsk region, the Rostov region, the Sverdlovsk region, the Nizhny Novgorod region). In 2003, according to these databases, the number of type 1 DM patients with the onset of the disease at young age was 765 people. A total of 486 of these patients consistently received only GEHI (regular insulin coupled with neutral protamine Hagedorn insulin (NPH insulin)) or only AHI (ultrashort acting and long peakless acting insulin analogs) during the 10-year period (from 2003 to 2013) and were included in the analysis. Those patients who received insulin of different classes (e.g. ultrashort AHI coupled with NPH insulin, or regular insulin coupled with long-acting AHI) were excluded, and also those patients who alternated GEHI and AHI therapy over the 10-year follow-up period.

It should be noted that the GEHI group received their insulin at the onset of disease, and the patients of the AHI group were transferred to the insulin analogs for 2.6 ± 1.8 months prior to their inclusion in observation period of this retrospective study.

The examination of patients during the entire follow-up period was performed as routine clinical practice by endocrinologists according to methodological recommendations approved by the Ministry of Health of the Russian Federation 'Federal Target Program, Diabetes Mellitus (2002) [6], and was recorded on paper (The register card form number 40-99 approved by order number 193 of 31/05/2000 by the Ministry of Health of the Russian Federation).

We have analyzed collected in the register database information of participant's medical history, yearly dynamic of the HbA_{1c}, the data from the fundoscopy and the urine albumin (protein) excretion. In cases of multiple measurements of HbA_{1c} concentration per year, the annual average HbA_{1c} value was used for the analysis. In the absence of a certain studied indicator, the actual indices were taken in the registration cards within one year as the data recorded in the previous or the subsequent year. Patients without the necessary data in the register in 2 consequent years were excluded.

Pairs of type 1 DM patients were formed out of the remaining patients for matching by gender to determine the onset age of DM, the duration of DM, and the level of HbA_{1c}; there were 260 people in total (130 patients in each AHI and GEHI group).

The results of the annual examination performed as routine clinical practice were determined as follows:

1. HbA_{1c} concentration was determined using high performance liquid chromatography (HPLC) with BioRad analysers (D-10) and standard kits (the BioRadD-10 devices were delivered to medical institutions in the seven regions within the Federal Target Program 'Diabetes Mellitus').
2. Determination of albumin in the morning urine sample was performed using various standard analysers and diagnostic kits. If the test result was positive (the urine albumin concentration exceeded 20 mg/L, or albuminuria in the morning urine portion exceeded 20 mg/min), the test was performed again. If the repeated test was also positive, then diabetic nephropathy (DN) was diagnosed. The stage of microalbuminuria, proteinuria and chronic renal failure was determined according to the results of an additional examination). Since the study started in 2003, when the classification of chronic kidney disease stages was not accepted in Russia, we adhered to the previously accepted classification of DN.
3. The examination of the fundus was performed by an ophthalmologist using the standard method after pupil dilation without photographing. The diagnosis of diabetic retinopathy (DR) was determined based on the presence of microaneurysms and/or haemorrhage (bleeding in the retina) in the paramacular zone, solid or soft exudates, macular edema, proliferation of retinal blood vessels and retinal detachment. The stage of non-proliferative, preproliferative or proliferative was determined for the DR patients.

The data from the annual examination are presented in the regional register databases.

The local ethics committee at Endocrinology Research Centre of the Russian ruled on 12.05.2016 (Protocol №11A2) that is was unnecessary to perform a detailed ethical review of the study protocol due to the nature of the planned study (processing of retrospective data from a registry of patients in the depersonalized form).

Statistical processing

Processing of the results was carried out using the software StatSoft© STATISTICA® 6.0. Normally distributed quantitative traits in groups are presented in the dispersed analysis form (mean ± standard deviation (M ± σ)). The intra-group changes in the indicator were verified using the paired Student's t test, or using the Wilcoxon test in the case of abnormal data distribution. The dependent groups were compared on qualitative characteristic by nonparametric method of comparing the binary characteristic frequencies using the McNemar's test. The analysis of disease course without complications was performed using the Kaplan-Meier curve and the log-rank test. To determine the risk of microvascular events in AHI and GEHI groups, the model of proportional hazards (Cox regression) was used. The differences were considered statistically significant at $p < 0.05$.

Results

Analysis of glycaemic control efficacy

The baseline characteristics of the type 1 DM patients are presented in Table 1. The patients receiving GEHI or AHI were matched by gender, onset age of diabetes, duration of type 1 DM, and magnitude of HbA_{1c}.

After 10 years, the patients in both groups did not achieve the target glycaemia values (HbA_{1c} <7%), but the

Table 1

Clinical characteristics of patients at baseline

Indices	AHI [1] (n=130)	GEHI [2] (n=130)	Total group(n=260)	P[1-2]
Gender, m/f	69/61	57/73	126/134	>0.05
Onset age of diabetes, years	10.9 ± 1.3	11.03 ± 1.3	10.9 + 0.3	>0.05
Duration of diabetes, years	4.0 ± 0.5	4.8 ± 0.6	4.5 + 1.9	>0.05
HbA_{1c}, %	9.38 ± 1.4	9.31 ± 1.2	9.34 + 1.9	>0.05
Retinopathy (any stage), %	6.2	13.8	10.0	>0.05
Nephropathy (any stage), %	6.2	9.2	7.7	>0.05

HbA_{1c} index in patients on AHI was significantly lower ($p < 0.05$) compared to patients on GEHI (8.08 and 8.50%, respectively) (Fig. 1). The significant differences between groups became noticeable at the 4th year of follow-up (Fig. 1). The decrease in HbA_{1c} level from baseline in patients on AHI was 1.3%, while in patients on GEHI – 0.81% ($p < 0.05$) after 10 years of observation.

Incidence of diabetic microangiopathy

The cumulative part of patients who developed microvascular complications within 10 years of the follow-up was 58.4% in the AHI group and 81.5% in the GEHI group. Fig. 2 represents the analysis of outcomes for the development of microvascular complications in these groups. In the group of patients receiving AHI therapy, the risk of microvascular complications was significantly reduced, and the curves for disease course without complications shows the significant difference between groups (log-rank test: 20.79, $p < 0.001$).

The risk ratios from the Cox regression model are shown in Table 2. The risk of developing microvascular complications was significantly lower in the AHI group ($p < 0.01$). A statistically significant reduction in the risk of nephropathy was revealed in the AHI group ($p < 0.02$).

Diabetic retinopathy (DR). It was found that the risk of DR at the onset of type 1 DM in paediatric patients was correlated with the disease duration. According to the WESDR study, the incidence of DR (any stage) is 8% with a duration of diabetes of 3 years or more, 25% with a duration of 5 years or more, 60% with a duration of 10 years or more and 80% with a duration of 15 years or more [7].

In our study, the baseline prevalence of DR (any stage) in the AHI and GEHI groups did not differ significantly and amounted to 6.2% and 13.8%, respectively, with an average disease duration not exceeding 5 years, which corresponds with the worldwide data. According to the conclusion of ophthalmologists, the reported DR cases corresponded to the nonproliferative stage in both groups (Table 2). By the end of the 10-year follow-up period, the prevalence of DR (any step) increased by 48.5% and 59.2% in AHI and GEHI groups, respectively, and was not significantly different between the groups ($p = 0.11$) (Fig. 3).

The prevalence of DR at various stages in both groups at baseline and after 10 years as shown in Table 3.

The findings suggest that the development and progression of DR over the 10 years of routine clinical follow-up occurred in both GEHI and AHI groups. The groups did not differ in prevalence of any of the stages. However, it can be argued that the progression of DR to the preproliferative and proliferative stages occurred less frequently in the AHI group than in the GEHI group.

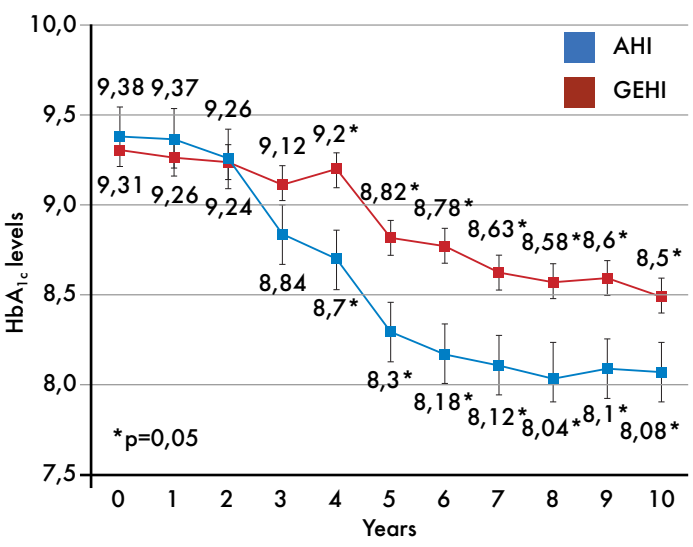

Fig. 1. Dynamics of the content of HbA_{1c} in groups of type 1 DM patients receiving treatment with AHI or GEHI for 10 years.

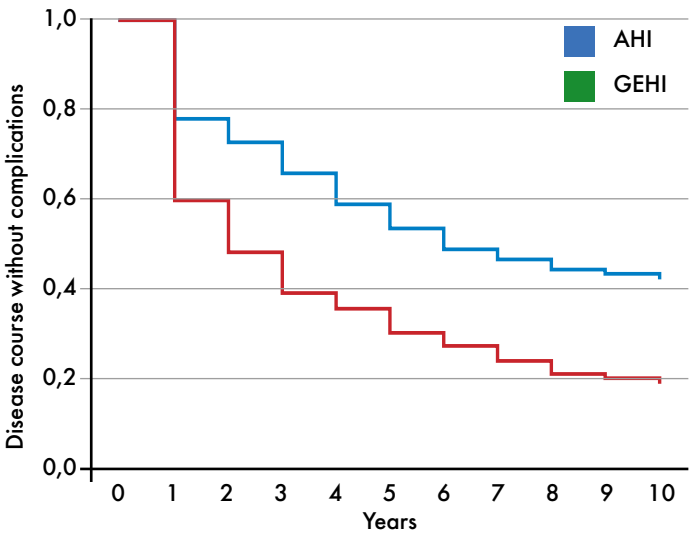

Fig. 2. The Kaplan-Meier curves for the determination of disease course without complications (outcomes on microvascular complications) in type 1 DM patients in groups receiving AHI or GEHI for 10 years.

Table 2

Association of AHI and GEHI use with the incidence of microvascular complications: the Cox regression

Outcomes	AHI (event/patient)	GEHI (event/patient)	Risk ratio (95% CI)	P
Microvascular complications	76/130	106/130	1.84 (1.37- 2.48)	<0.01
Diabetic retinopathy	64/130	77/130	1.37 (0.98-1.90)	<0.64
Diabetic nephropathy	47/130	72/130	1.76 (1.22-2.54)	<0.02

Notes: AHI - analogs of human insulin; GEHI - genetically engineered human insulin.

Diabetic nephropathy (DN). The incidence of DN in type 1 DM is also dependent on the duration of the disease. According to the EURODIAB study, which examined the incidence of DN in 26 European countries, microalbuminuria was found in 13% of type 1 DM patients with a diabetes duration of approximately 7 years [8]. The proteinuric stage of DN was revealed in 5–6% of patients with a duration of type 1 DM of up to 10 years, 25–30% with a duration of up to 20 years and approximately 40% with a duration of more than 30 years [9].

In our study, the prevalence of DN (any stage) at the onset of the follow-up period was 6.2% and 9.2% in the AHI and GEHI groups, respectively, with an average disease duration not exceeding 5 years, which is consistent with global trends. After 10 years the prevalence of DN (any stage) increased to 32.3% and 52.3% in the AHI and GEHI groups, respectively. These differences were statistically significant ($p < 0.05$) (Fig. 4).

The prevalence of DN at various stages in both groups at baseline and after 10 years period is shown in Table 4

As follows from the data presented, after 10 years the prevalence of DN and its severity were significantly higher in the group of patients treated with GEHI compared to the patients treated with AHI. In 8 patients treated with GEHI after 10 years renal failure developed, including renal failure that required substitutive renal therapy with hemodialysis (1 patient). There were no cases of chronic renal failure with AHI treatment. In contrast, microalbuminuria regressed to normoalbuminuria in 4 patients, due to which at the 10th year of follow-up period the incidence of DN was lower than in the previous 2 years (Fig. 4).

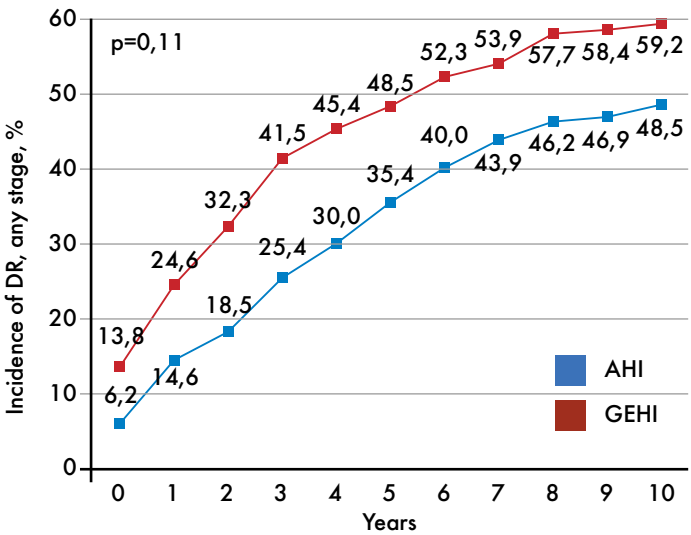

Fig. 3. The dynamics in the incidence of any DR stage in groups of type 1 DM patients receiving AHI or GEHI treatment for 10 years.

Discussion

AHI has been used in routine clinical practice for over 15 years, and it enables the evaluation of not only the efficacy and stability of glycaemic control but also the long-term risks of the development and progression of DM vascular complications compared to traditional human insulin. It was not possible to find a full analogue of our study in foreign sources. Only a few publications analyse micro and macrovascular complications in type 2 DM patients receiving chronic AHI of ultrashort action compared to short-acting GEHI [10, 11], or analyse the basal AHI Glargine compared to NPH insulin [12]. The studies represented either a retrospective analysis of the registries [10, 11] or observational prospective studies in routine clinical practice [12, 13]. In these studies, the authors found no significant difference in the incidence of microvascular complications (retinopathy and nephropathy) in patients with type 2 DM [10, 11], but registered a significantly lower incidence of macrovascular events in patients receiving therapy with basal AHI

Table 3

Prevalence of DR at various stages in AHI or GEHI groups after 10 years of the follow-up period

DR stage	AHI group (n=130)		GEHI group (n=130)	
	Baseline	After 10 years	Baseline	After 10 years
No DR, n (%)	122 (93.8)	67 (51.6)	112 (86.2)	53 (40.8)
Nonproliferative, n (%)	8 (6.2)	54 (41.5)	18 (13.8)	55 (42.3)
Preproliferative, n (%)	0	6 (4.6)	0	19 (14.6)
Proliferative, n (%)	0	3 (2.3)	0	3 (2.3)*

Notes: AHI - analogs of human insulin; GEHI - genetically engineered human insulin; DR - diabetic retinopathy; * of them in 1 patient - total loss of sight

Table 4

Prevalence of DN at various stages in the AHI or GEHI groups after the 10 year follow-up period

DN stage	AHI group (n=130)		GEHI group (n=130)	
	Baseline	After 10 years	Baseline	After 10 years
No ND, n (%)	122 (93.8)	87 (66.9)	118 (90.8)	62 (47.7)
Microalbuminuria, n (%)	7 (5.4)	34 (26.2)	11 (8.4)	46 (35.4)
Proteinuria, n (%)	1 (0.8)	9 (6.9)	1 (0.8)	14 (10.8)
Chronic renal failure, predialysis stage, n (%)	0	0	0	7 (5.3)
End-stage renal disease (dialysis), n (%)	0	0	0	1 (0.8)

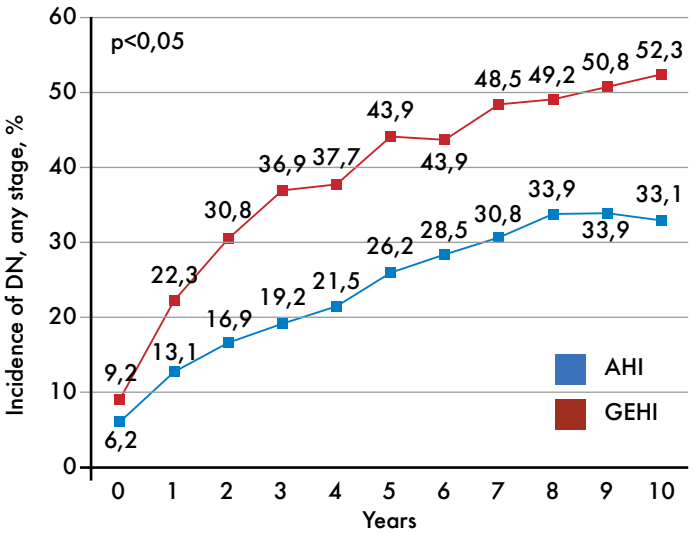

Fig. 4. Dynamics of the incidence of any DN stage in AHI or GEHI groups for 10 years.

Glargine compared with basal GEHI [13], and a lower incidence of later development of macroangiopathy in patients receiving the AHI therapy of ultrashort action compared to the short-acting GEHI [10].

Our study differed from those described above in the fact that for the analysis we have chosen a cohort of young patients with type 1 DM with the onset of the disease at an early age, a small duration of the disease at the study initiation, and no severe concomitant diseases or complications. This selection of patients assured us that for the 10-year comparative analysis of GEHI and AHI the outcome of the treatment and the development of microvascular complications will not be affected by other risk factors, such as hypertension, dyslipidemia and obesity that occur in type 2 DM patients. In addition, we deliberately included only those patients who received independent therapy with either AHI (analogue of ultrashort action coupled with the basal analogue), or GEHI (prandial short-acting insulin coupled with the basal NPH insulin) only. This was done to estimate all the pharmacokinetic advantages of AHI of ultrashort action and long action together. The pairwise comparison of the enrolled patients by gender, onset age, duration of the disease, and HbA_{1c} indicators enabled the avoidance of the effect of these factors on the study results.

Limitations of the study

It should be emphasized that the retrospective design does not allow for a cause-and-effect conclusion; therefore, the link between the HbA_{1c} indicator, incidence of complications and any factor evaluated in this study requires a randomized controlled trial for definitive causality. The retrospective design of the study performed also did not enable an exhaustive analysis of all possible factors that could influence the results of treatment.

The differences in glycaemic control may be explained not only by the above-described pharmacokinetic characteristics of AHI action, but also other factors and indirect effects that were not accounted for when planning the study, which cannot be excluded in a retrospective design. Retrospective cohort observational studies generally demonstrate the superiority of new medications (AHI) over the current medications (GEHI). The patients were enrolled in the groups without randomization, which could lead to both false overestimation of the effect of new medications and distortion of the real effect. However, the absence of randomization should not significantly affect the results, as the patients were enrolled in the study by selecting pairs matched by gender, onset age, duration of DM, and initial HbA_{1c}.

However, we can assume that the groups were not matched for many other factors that could potentially affect the efficacy of the treatment and the development of microvascular complications, such as the level of knowledge and motivation of patients, compliance, social status, etc. It is likely that among the patients treated with the AHI there were significantly more patients actively seeking good glycaemic control. Thus, in the AHI group there could be study participants more compliant and attentive to glycaemic control (usually they have a higher level of education and social level, as the relation of compliance with these parameters is well known). This sampling bias could significantly affect the results, and regardless of the AHI pharmacokinetics to determine lower HbA_{1c} indicators in the group of patients treated with AHI.

This assumption cannot be considered unreasonable, given the data on the average age at which the groups of patients started to differ significantly in HbA_{1c}, which was 4 years from study initiation when the patients were on average 18–20 years of age. This is exactly the age when, after graduating from high school the social and lifestyle differences increase. Therefore, the difference in

HbA_{1c} emerging at this age may reflect the divergence of the educational and social level of the patients. It is also noticeable that the majority of patients in both groups did not achieve the target level of glycaemic control, which was previously achieved in the DCCT study conducted using only GEHI.

In turn, the difference between the groups for the incidence of microvascular complications may also be caused by confounders. The relatively low incidence of microvascular complications in the AHI group may be the result of the pharmacokinetic advantages of AHI, which, as it was shown by numerous studies, cause lower glycaemic variability [14, 15]. More and more studies decisively demonstrate the relationship between glycaemic variability and the development of late diabetic complications [16, 17]. In our study, glycaemic variability was not evaluated as a whole or as preprandial and postprandial glycaemic control alone, which does not enable us to confirm this explanation

A lower incidence of complications in the group of patients receiving AHI may be a direct consequence of better glycaemic control in general; the groups differed for HbA_{1c} at year 4 of the study, and the relationship between HbA_{1c} and the development of microvascular complications is well known [18, 19]. Also, when evaluating the relationship of complications directly with HbA_{1c}, in our study we found that on year 10 of the study, the patients with microangiopathy had a significantly higher value of HbA_{1c} (8.4 ± 1.4% and 7.9 ± 1.2% in patients with and without microangiopathy, respectively, $p = 0.0085$). The same regularity is observed for retinopathy only (HbA_{1c} in 2012 was 8.5 ± 1.5% and 8.0 ± 1.2% in patients with and without DR, respectively, $p = 0.0057$) and nephropathy (HbA_{1c} in 2012 was 8.5 ± 1.5% and 8.1 ± 1.2% in patients with and without DN, respectively, $p = 0.0448$). Thus, it can be argued that the development of microvascular complications in our study should be associated not only with the type of the insulin used, but also with the level of glycaemic control directly. In that respect, the use of AHI for treatment of DM may influence the development of late complications indirectly, allowing better glycaemic control in routine clinical practice.

It is notable that in the analysis we found statistically significant differences in the development of diabetic retinopathy depending on the baseline value of HbA_{1c} at the time of enrollment. Thus, the patients who had retinopathy diagnosis (any stage) by the end of the 10-year follow-up period initially had higher HbA_{1c} ($p = 0.0011$). Furthermore, when assessing the impact of various factors on the development of microvascular complications, a very paradoxical relationship was found; the patients with diabetic retinopathy diagnosed during the follow-up period had a significantly greater decrease in HbA_{1c} from baseline (HbA_{1c} decreased by 0.87 ± 1.75 % and 1.15 ± 1.96% in patients without retinopathy and with retinopathy by 2012, respectively, $p = 0.039$). Also, these patients had a higher HbA_{1c} value at the time of enrollment (HbA_{1c} at the time of enrollment was 8.90 ± 1.89% and 9.66 ± 1.99% in patients with and without DR diagnosis, respectively, $p < 0.00003$).

All these considerations do not allow us to draw the conclusion that the use of AHI itself, compared with GEHI, in the routine clinical practice provides better compensation and inhibits the development of nephropathy, retinopathy and microangiopathy. The findings need to be confirmed using prospective, randomized controlled trials.

Conclusions

As a result of a 10-year retrospective analysis of regional registers of diabetes it was found that in type 1 DM patients:

- the use of AHI in routine clinical practice is associated with lower HbA_{1c} values than the use of traditional GEHI;
- prolonged use of AHI is associated with a lower incidence of progression of DN;
- prolonged use of AHI is not associated with the incidence of DR (any stage).

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Conflict of interest

All authors declare the absence of explicit and potential conflicts of interest related to the study and publication of this article.

Author contribution

M.V. Shestakova — concept, study design, data analysis, interpretation of results and manuscript writing; N.V. Efremova — data collection, processing and analysis, manuscript writing; L.L. Bolotskaya — data analysis and manuscript writing; I.A. Sklyanik — statistical data processing and manuscript writing; Y.I. Philippov — data interpretation and text editing; I.I. Dedov — concept and study design, manuscript editing.

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