

The PROROK project results after 6 months of intervention (Prospective observation project focusing on the relevance of the difference between fasting blood glucose levels and postprandial blood glucose for estimation of success of type 2 diabetes therapy)

Denisa Janičková-Žďárská¹, Pavlína Piřhová¹, Tomáš Pavlík^{2,3}, Milan Kvapil¹

¹ Department of Internal Medicine, 2nd Faculty of Medicine, Charles University, Prague, and Motol University Hospital, Praha, Head Prof. MUDr. Milan Kvapil, CSc., MBA

² The Institute of Biostatistics and Analyses MU, Brno, Head doc. RNDr. Ladislav Dušek, Ph.D.

³ The Institute of Health Information and Statistics of the Czech Republic, Praha, Head doc. RNDr. Ladislav Dušek, Ph.D.

Summary

Introduction: The PROROK project (Prospective observation project focusing on the relevance of the difference between fasting and postprandial blood glucose levels for the estimation of success of type 2 diabetes therapy) had a character of non-interventional, prospective, multicentric observation study lasting 6 months, whose goal was to quantify the relevance of the difference between fasting and postprandial blood glucose levels to the success of the treatment with GLP1 receptor agonists, resp. the treatment with basal, premixed insulin, or a combination of basal-bolus insulin. Physicians chose a therapy for patients with insufficiently compensated problems as they considered appropriate; 4 972 patients were included. **Goal:** Evaluation of the intervention results for the patients included in the PROROK observation project with a focus on the choice of therapy by the treating diabetologist after 6 months of observation. **Results:** An average improvement of the glycated hemoglobin values in the whole cohort reached 1.6%, the median of the resulting glycated hemoglobin reached 5.9% and 5.8% resp. (basal insulin). Statistically significant was the change in the median weight in the cohort treated with GLP-1 receptor agonists, from 105 kg to 100 kg; this did not significantly change in the other cohorts. The change of waist circumference over time in all patients and in the individual cohorts was consistent with the change of weight. The median change of fasting blood glucose levels in the whole cohort was -1.7 mmol/l after 3 months and -2.4 mmol/l ($p < 0.001$) after 6 months. The greatest absolute decrease was recorded in the cohort treated with basal insulin (-2.8 mmol/l). The median change of postprandial blood glucose levels was -2.4 mmol/l after 3 months and -3.3 mmol/l ($p < 0.001$) after 6 months. The greatest absolute decrease was recorded in the branch treated with a combination of prandial and basal insulin (-3.9 mmol/l). All differences $p < 0.001$. **Conclusion:** The choice of therapy in the PROROK project is in agreement with the basic findings in pathophysiology of type 2 diabetes and with the options of an individually chosen targeted intervention involving antidiabetic therapy. The results of the six-month observation have proven the individual choice of therapy correct. In the cohort of diabetic patients differing at the beginning in weight, waist circumference, fasting blood glucose and the difference between fasting and postprandial glucose levels, an individually chosen therapy led to the same final result, while an absolute change in the followed parameters differed in the individual groups.

Key words: therapy for type 2 diabetes mellitus – GLP1 receptor agonists – insulin – intensified insulin regimen – basal insulin – premixed insulin

Introduction

The classes of antidiabetic drugs now available affect with different intensity the individual defects occurring in type 2 diabetes, and consequently they improve fasting glycemia or postprandial glucose excursions in different ways[4]. Basal insulin analogues primarily decrease fasting glycemia [5–7]. GLP-1 receptor agonists (GLP1R agonists) primarily reduce postprandial glucose levels (exenatide, lixisenatide) [7–10], GLP1R agonists with prolonged half-lives also significantly reduce fasting glycemia (liraglutide)[11]. GLP1R agonists also stimulate decrease in body weight [12]. Premixed insulins decrease fasting glycemia as well as postprandial glucose excursions [13]. The basal insulin regimen with prandial bolus doses has similar effects, its advantage is some possibility of individual setting of doses of insulin [14].

The aim of the study was to evaluate the intervention results in the patients included in the PROROK observation project with a focus on the choice of therapy by the treating diabetologist after 6 months of observation.

The project description

The PROROK project (Prospective observation project focusing on relevance of the difference between fasting glucose levels and postprandial blood glucose for estimation of success-rate of type 2 diabetes therapy) had a character of non-interventional, prospective, multicentric observation study lasting 6 months, whose goal was to quantify the relevance of the difference between fasting glucose levels and postprandial blood glucose for success of the treatment with GLP1R agonists (cohort EG), or the treatment with basal insulin (cohort EB), premixed insulin (cohort EP), or a combination of basal-bolus insulin (cohort EIIT).

The project comprised 77 diabetes outpatient clinics. The patients included in the project had glycated haemoglobin higher than 6 % (according to IFCC – International Federation of Clinical Chemistry) and their treating physician decided to intensify their therapy with one of the aforementioned methods. Basic anthropometric and laboratory data was recorded, fasting glycemia (FG) and postprandial glycemia (PPG), glycated haemoglobin (HbA_{1c}) and the treatment method. Control data was recorded after 3 and 6 months [15].

A cohort of patients

There were 4 972 patients included in the PROROK project. Based on the completed data on the type of diabetes, fasting and postprandial glycemia during an entry visit and on the values of glycated haemoglobin during an entry visit, and validation was performed on the follow-up visits after 3 and 6 months.

Only the patients meeting these 4 criteria were included in the analysis:

1. Patients with type 2 diabetes mellitus (DM2T)
2. Patients with the values of fasting and postprandial glycemia within a range of 2 mmol/l – 40 mmol/l

3. Patients with an HbA_{1c} value $\geq 6\%$ and $< 20\%$ on the entry visit
4. Patients with an HbA_{1c} value $< 20\%$ on the follow-up visit after 3 and 6 months

These criteria were satisfied by 4 561 patients consequently included in the analysis (Table). The remaining 411 patients were not included in the analysis for the following reasons, while more than 1 criterion may have been not satisfied in 1 patient:

- 68 patients without DM2T, or DM type not specified
- 70 patients without a recorded fasting or postprandial glycemia on the entry visit
- 15 patients with fasting or postprandial blood glucose levels $< 2\text{ mmol/l}$ or $> 40\text{ mmol/l}$
- 122 patients without a HbA_{1c} initial value or with HbA_{1c} value $\leq 6\%$, or HbA_{1c} $\geq 20\%$
- 163 patients without a specified glycated hemoglobin value on a follow-up visit after 3 and/or 6 months

Table 1 . Numbers of patients in different branches based on used therapy

Project branch	n (%)
PROROK – EG	1 049 (23,0)
PROROK – EB	1 378 (30,2)
PROROK – EIIT	1 448 (31,7)
PROROK – EP	686 (15)

EG – GLP-1 receptor agonist treatment EB – basal insulin therapy
EP – premixed insulin therapy EIIT – basal-bolus insulin therapy

The detailed description of the whole cohort and individual subcohorts, or the differences between the groups of patients, is presented in the basic study concerning this project [15].

Statistical methods

The data collected within PROROK was first subjected to validation with regard to the data critical for evaluation of the primary goal of the study. The cohort of patients for analysis was defined based on the data validation. The cohort was described using the basic descriptive statistics: frequency, average, standard deviation, median, minimum and maximum. The differences in demographic characteristics and laboratory parameters between the followed patient cohorts were assessed using non-parametric tests – χ^2 test for categorical data and a Kruskal-Wallis test for continuous data. A value of 0.05 was considered as a statistical significance level.

Results

An average improvement in glycated haemoglobin values in the whole cohort reached 1.6 %, the median of the resulting glycated haemoglobin reached 5.9 % or 5.8 % (EG), Chart 1. Although within the whole cohort of the followed individuals the median body weight did not change, in the cohort of individuals treated with

GLP-1 receptor agonists the median body weight decreased from 105 kg to 100 kg, reaching statistical significance (Chart 2). The change in waist circumference over time in all patients and in the individual cohorts was consistent with the change in weight (Chart 3).

The development of fasting glycemia over time in all patients and in the individual cohorts is shown in (Chart 4). Although the cohorts differ at the outset (see [15] for details, $p < 0.001$), the therapy chosen by diabetologists reached the same final result. The median change in fasting blood glucose levels in the whole cohort was -1.7 mmol/l after 3 months, and -2.4 mmol/l ($p < 0.001$) after 6 months. The greatest absolute decrease was recorded, as expected, in the cohort treated with basal insulin (EB). A similar result was recorded for the development of glycemia after meals over time in all patients and individual cohorts (Chart 5). The median change after 3 months equalled -2.4 mmol/l, the median change after 6 months equalled -3.3 mmol/l. The greatest absolute decrease was recorded in the branch treated with a combination of prandial and basal insulin (IIT).

Discussion

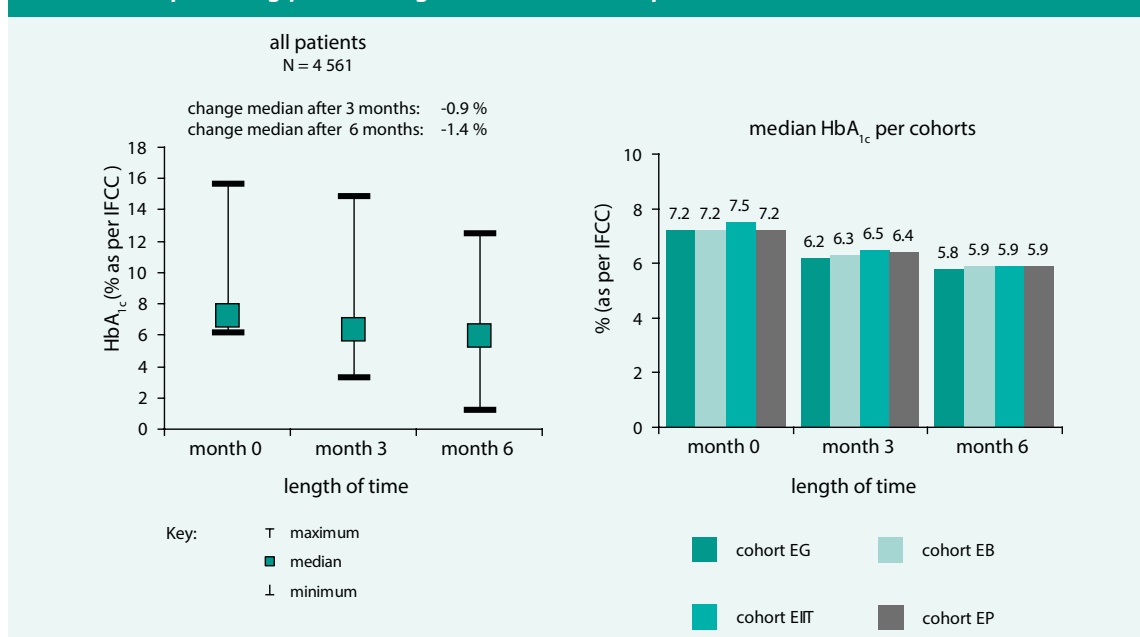
The PROROK project (Prospective observation project focusing on the relevance of the difference between fasting glucose levels and postprandial blood glucose for estimation of success-rate of type 2 diabetes therapy) had a character of non-interventional, prospective, multicentric observation study lasting 6 months, whose goal was to quantify the relevance of the difference between fasting glucose levels and postprandial blood glucose for the success of the treatment with

GLP1R agonists (cohort EG), or the treatment with basal insulin (cohort EB), premixed insulin (cohort EP), or a combination of basal-bolus insulin (cohort EIIT). Physicians chose therapy for unsatisfactorily compensated patients as they considered appropriate [15]. Thereby the project moves closer to the real practice, where a physician can choose a therapy based on an individual patient profile, as opposed to randomized clinical studies. The reason why observation studies are coming to the fore is because the aspects of individual choice of an antidiabetic drug [16] come to be incorporated into recommended procedures.

Basal insulin primarily decreases fasting glycemia [5–7]. This therapy led to the greatest decline in fasting glycemia. In the Czech Republic GLP1R agonists are covered from public health insurance based on the indication limit “P”. One of the limiting conditions is a body mass index (BMI) higher than 35 kg/m². Of course this condition affects the selection of patients, it correlates with the highest BMI in this cohort. Therefore the body weight as well as BMI were considerably higher in the cohort EG [15]. GLP1R agonists reduce the patients’ body weight, as shown by the decrease in median weight by 5 kg in our cohort. The change in body mass corresponds with the change in waist circumference.

With gradual progression of type 2 diabetes, in particular the postprandial insulin secretion decreases [1]. The correlate is a higher postprandial glucose excursion [17]. The most efficient intervention in this phase is prandial insulin. This therapy (EIIT and EP) was chosen by physicians just for the individuals with the greatest difference between fasting and postprandial blood

Chart 1. Development of glycated hemoglobin over time for all patients and for individual cohorts



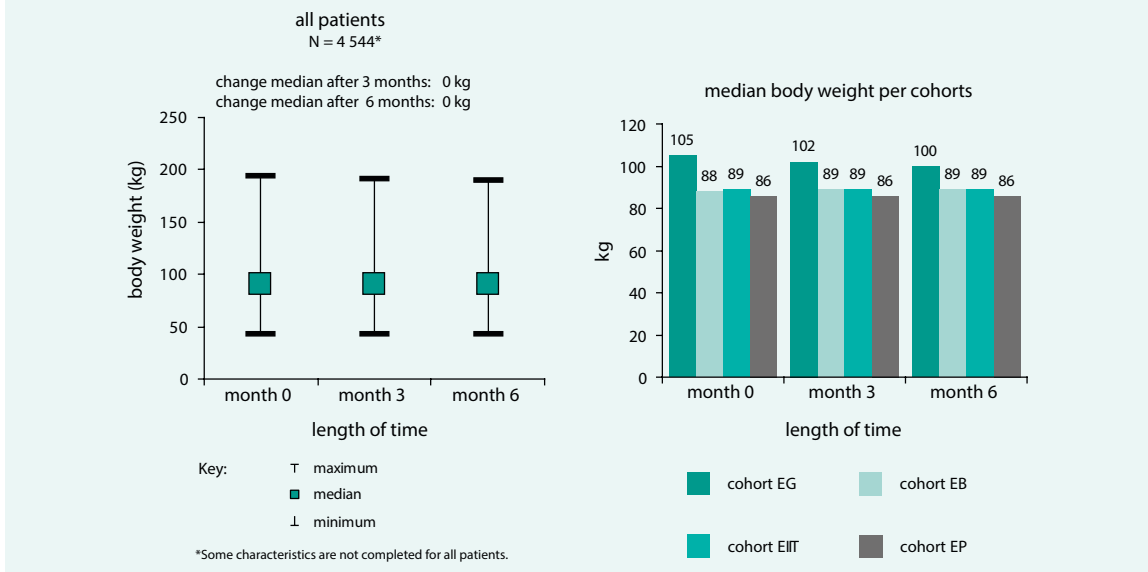
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glucose levels [15]. After 6 months of therapy these individuals reached the greatest absolute decrease in the median difference between fasting and postprandial glycemia.

Primary analysis of the choice of a therapy [15] shows that the choice of the therapy in the PROROK project is in agreement with the basic findings on pathophysiology

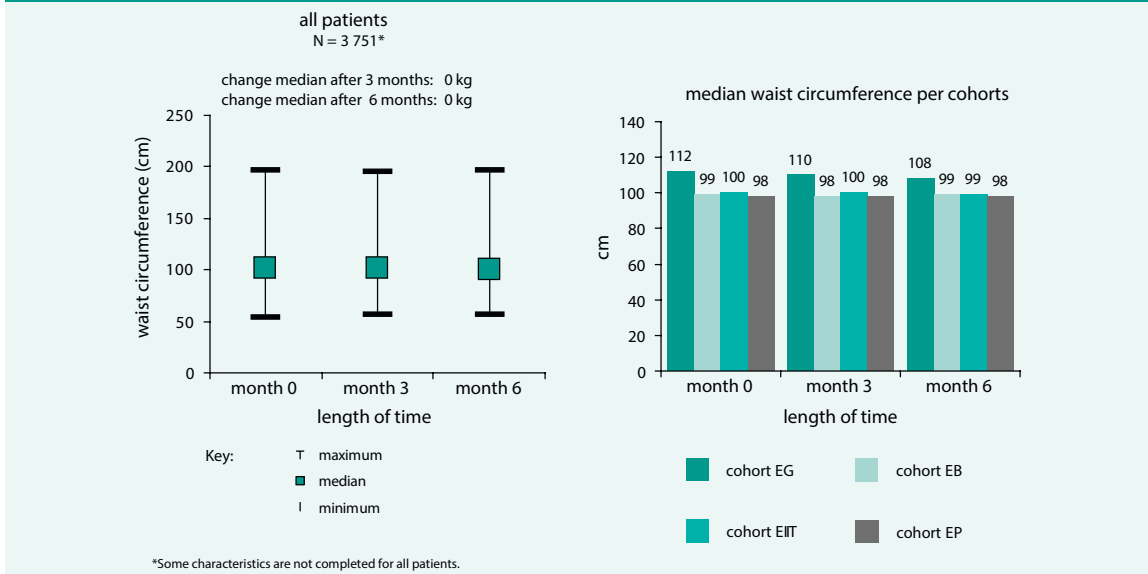
of DM2T and possibilities of an individually chosen targeted intervention through antidiabetic therapy. The physicians participating in PROROK chose the therapy predominantly on the rational grounds. The results of the six-month observation have proven their choice of therapy correct. In the cohort of diabetic patients differing at the beginning in weight, waist circumference,

Chart 2. Development of body weight over time for all patients and individual cohorts: although the median body weight in the whole cohort of followed individuals did not change, the decrease in body weight in the cohort treated with GLP-1 receptor agonists reached statistical significance



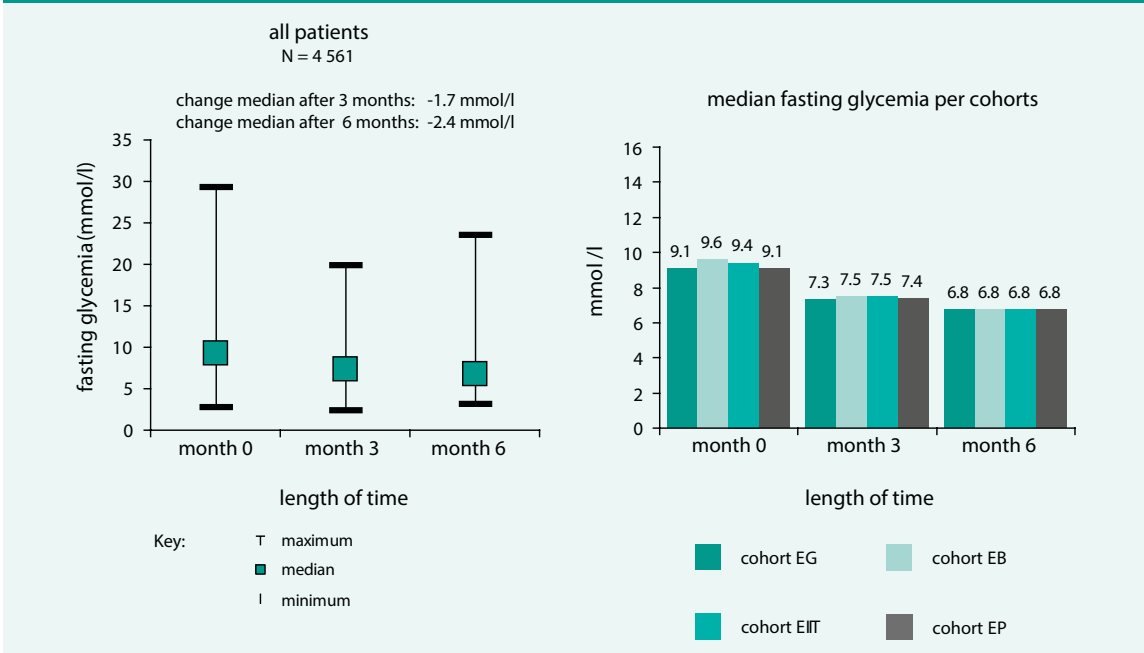
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Graf 3. Development of waist circumference over time for all patients and individual cohorts: change of waist circumference corresponds with change of body weight



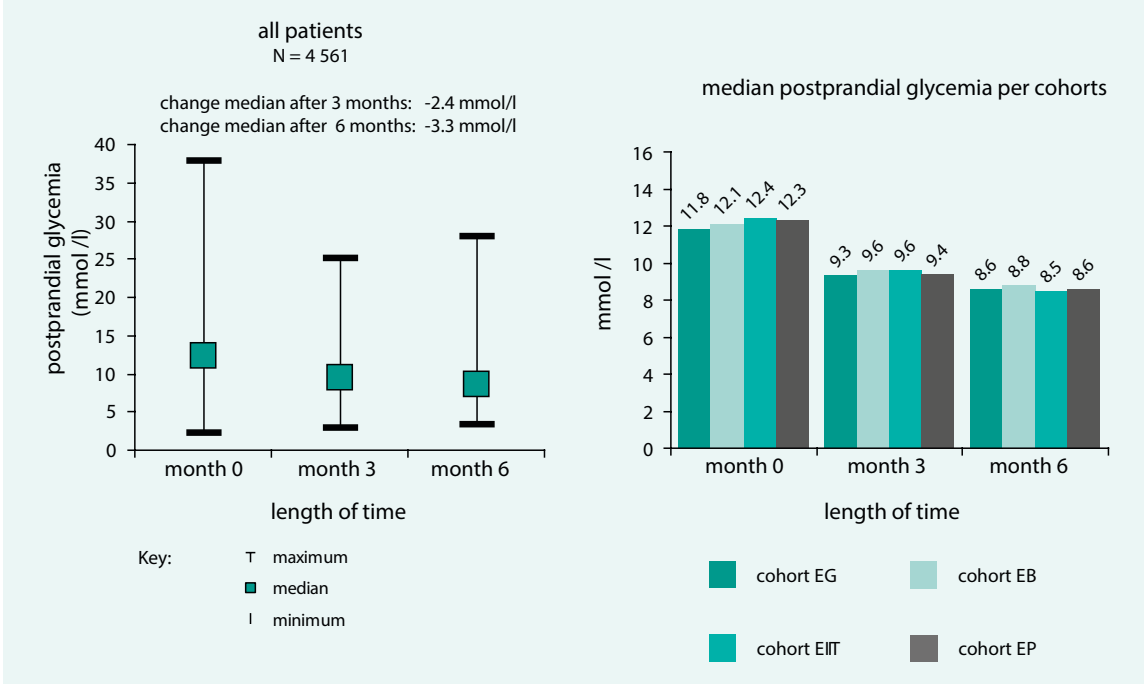
EG – GLP-1 receptor agonist treatment EB – basal insulin therapy EP – premixed insulin therapy EIIT – basal-bolus insulin therapy

Chart 4. Development of fasting glycaemia over time for all patients and for individual cohorts: although cohorts differ at the outset (see [15] for details, $p < 0.001$), the therapy chosen by diabetologists reached a similar final result



EG – GLP-1 receptor agonist treatment EB – basal insulin therapy EP – premixed insulin therapy EIIT – basal-bolus insulin therapy

Chart 5. Development of postprandial glycaemia over time for all patients and individual cohorts: although cohorts differ at the outset (see [15] for details, $p < 0.001$), the therapy chosen by diabetologists reached a similar final result



EG – GLP-1 receptor agonist treatment EB – basal insulin therapy EP – premixed insulin therapy EIIT – basal-bolus insulin therapy

fasting blood glucose and the difference between fasting and postprandial glucose levels, an individually chosen therapy led to the same final result, while an absolute change in the followed parameters differed in the individual groups.

Note: The values of glycated hemoglobin HbA_{1c} are specified in % (according to IFCC– International Federation of Clinical Chemistry), since the project was commenced at the time when laboratories specified the result in these units, values in mmol/mol will be obtained through multiplication by 10.

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Prof. MUDr. Milan Kvapil, CSc., MBA

✉ milan.kvapil@fnmotol.cz

Department of Internal Medicine, 2nd Faculty of Medicine, Charles University, Prague, and Motol University Hospital, Prague

www.fnmotol.cz

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