Tomasz Klupa[1, 2], Bartlomiej Matejko[1, 2], Przemyslaw Witek[1, 2], Malgorzata Grzanka[1], Malgorzata Masierek[3], Pawel Gronowski[4], Magdalena Szopa[1, 2], Maciej T. Malecki[1, 2]

[1]Department of Metabolic Diseases, Jagiellonian University Medical College, Krakow, Poland
[2]University Hospital, Krakow, Poland
[3]Bioton Pharmaceutical Company, Warsaw, Poland
[4]Catermed Enterprise, Krakow, Poland

Dietary carbohydrate content and glycaemic control in type 2 diabetes patients treated with pre-mixed human insulins

Podaż węglowodanów w diecie i kontrola glikemii u pacjentów leczonych za pomocą mieszanek insuliny ludzkiej

ABSTRACT

Introduction. The treatment with pre-mixed human insulins (PMHI) is globally one of the most popular models of insulin therapy. Achieving good glycaemic control on PMHI may, however, be difficult, mostly due to inconsistent calorie and carbohydrate intake. The aim of the study was to examine the impact of dietary modification on glucose levels in patients with type 2 diabetes mellitus (T2DM) treated with PMHI.

Materials and methods. In this prospective cross-over analysis we studied 8 T2DM PMHI treated individuals (mean HbA_{1c} 8.4%). We exposed patients to 2 diets, both based on steady calorie/carbohydrate content: „A" — 50% calories from carbohydrates, 30% from fat, 20% from protein, „B"— 40% from carbohydrates, 30% from fat and 30% from protein. The study was performed in home settings, all the meals were delivered to the patients. Each patient was exposed to diet A for 9 days, than after 7 days of wash-out to 9 days of diet B. Glucose patterns were assessed with continuous glucose monitoring system (CGMS, iPro, Medtronic, USA).

Results. Switching from diet A to diet B resulted in a decrease in mean glucose levels (CGMS data) from 145 mg/dL to 133 mg/dL (p = 0.0001), SD reduction from 51 to 42 mg/dL (p = 0.0429), and a decrease in time spent above the target of 180 mg/dL from 18% to 11% (p = 0.0006).

Conclusions. The study demonstrates that consistent and repeatable carbohydrate (CH) and calorie intake with moderate restriction of CHs helps to improve glycaemic control in this group of patients. (Diabet. Klin. 2015; 4, 4: 127–131)

Key words: type 2 diabetes, insulin, carbohydrates, glycaemic control, pre-mixed human insulins

STRESZCZENIE

Wstęp. Leczenie mieszankami insuliny ludzkiej (PMHI, *pre-mixed human insulin*) jest na całym świecie jednym z najpopularniejszych modeli insulinoterapii. Jednak osiągnięcie dobrej kontroli glikemii u osób stosujących PMHI może być trudne, głównie ze względu na zmienne spożycie węglowodanów i podaż kalorii. Badanie

Address for correspondence:
Tomasz Klupa M.D., Ph.D.
Department of Metabolic Diseases
Jagiellonian University, Medical College
15 Kopernika Street, 31–501 Krakow, Poland
Phone: +48 (12) 424 83 05
Fax: +48 (12) 421 97 86
e-mail: tomasz.klupa@uj.edu.pl
Diabetologia Kliniczna 2015, tom 4, 4, 127–131
DOI: 10.5603/DK.2015.0012
Received: 24.06.2015 Accepted: 29.07.2015

przeprowadzono w celu oceny wpływu modyfikacji diety na stężenia glukozy u chorych na cukrzycę typu 2 (T2DM, *type 2 diabetes mellitus*) stosujących PMHI.
Materiał i metody. Do tego prospektywnego badania przeprowadzonego w układzie naprzemiennym włączono 8 chorych na T2DM leczonych PMHI (średnie stężenie HbA_{1c} 8,4%). U chorych zastosowano 2 diety, obie cechujące się stałą zawartością kalorii/węglowodanów: dieta A — 50% kalorii pochodzi z węglowodanów, 30% — z tłuszczów, 20% — z białek; dieta B — 40% kalorii pochodzi z węglowodanów, 30% — z tłuszczów i 30% — z protein. Badanie prowadzono w warunkach domowych, dostarczano chorym wszystkie posiłki. Każdy chory stosował dietę A przez 9 dni, a następnie po 7-dniowym okresie wypłukiwania przez 9 dni stosował dietę B. Profile glukozy oceniano przy użyciu systemu ciągłego monitorowania glikemii (CGMS, *continuous glucose monitoring system*, iPro, Medtronic, USA).
Wyniki. Zmiana z diety A na dietę B spowodowała zmniejszenie średnich stężeń glukozy (dane z system CGMS) ze 145 mg/dl do 133 mg/dl (p = 0,0001), redukcję SD z 51 do 42 mg/dl (p = 0,0429) oraz skrócenie czasu, w którym glikemia utrzymywała się powyżej progowej wartości 180 mg/dl z 18% do 11% (p = 0,0006).
Wnioski. W badaniu wykazano, że zapewnienie odpowiedniej i powtarzalnej podaży węglowodanów i kalorii z umiarkowanym ograniczeniem węglowodanów umożliwia poprawę kontroli glikemii u chorych na cukrzycę typu 2. (Diabet. Klin. 2015; 4, 4: 127–131)

Słowa kluczowe: cukrzyca typu 2, węglowodany, mieszanki insuliny ludzkiej

Introduction

Achieving and maintaining good glycaemic control is a key objective in type 2 diabetes mellitus (T2DM) management. The progressive nature of the disease, related mainly to continuous deterioration of endogenous insulin secretion, requires a stepwise intensification of the pharmacological treatment [1, 2]. Most T2DM patients will eventually need insulin therapy to maintain glycaemic control. In such a situation, premixed formulation is a common treatment option — in some countries almost half of the patients with T2DM diabetes use this model. Pre-mixed human insulins 30 (PMHI 30), one of the popular premixed preparations, contains a fixed soluble human insulin component, which makes 30% of the formulation, whereas Neutral Protamine Hagedorn (NPH) insulin constitutes the remaining 70%. When PMHI is injected before a meal, the former lowers postprandial glucose excursions, while the latter provides basal insulin coverage.

Treatment with premixed insulin is recommended by most clinical guidelines for T2DM patients as one of the options for initiation and intensification of insulin therapy [3]. However, many T2DM patients do not achieve recommended glycaemic goals even when treated with insulin [1]. This may be caused by a lack of detailed dietary recommendations for T2DM patients, which should be tailored to specific insulin therapy, for example PMHI injections. Since there is a general agreement that nutritional intervention is essential for diabetes management, defining an optimal dietary composition may be helpful in reaching therapeutic targets [4, 5]. Carbohydrates (CHs) are the most potent modifier of glycaemic patterns in patients with T2DM [4–9]. The aim of this study was to examine if repeatable CHs intake improves glycaemic control in T2DM patients treated with PMHI.

Materials and methods

Eight consecutive T2DM patients treated with PMHI who agreed to participate were enrolled. Their mean age was 68.9 years, mean T2DM duration — 9.8 years, mean body mass index — 28.48 kg/m^2 and mean HbA_{1c} — 8.4%. These patients were free from advanced microvascular complications. On the basis of clinical assessment their pre-study compliance was satisfactory. Patients with severe hypoglycaemic episodes over the last 6 months before the study or with hypoglycaemia unawareness were excluded. All the study patients were treated with two injections of PMHI 30 with an average daily dose of 44.5 IU; in 7 cases insulin was combined with metformin (dose range 1000–2550 mg). The patients were exposed to two types diet, defined as A and B. Both diets were based on steady calorie and CH content: A — 50% calories from CH, 30% from fat (F), 20% from protein (P), B — 40% from CH, 30% from F, and 30% from P. The calorie content was based on declared pre-study consumption (mean 1475 calories a day) and remained the same for the whole intervention period. The CH content was repeated for each day of the study and for each meal for a diet A and a diet B, respectively. The total daily consumption of calories from fat and protein was also fixed; however, the fat/protein proportions for individual meals could have changed from day to day. The study was performed in home settings and all the meals were delivered to the patients. The subjects were allowed to drink water and other CH free drinks without restrictions. Each patient was exposed to the following diet pattern: diet A — 9 days, the wash-out — 7 days, diet B — 9 days (Fig. 1). At study entry, the memories of the patients' own blood glucose meters were downloaded for further analysis. The patients were asked to per-

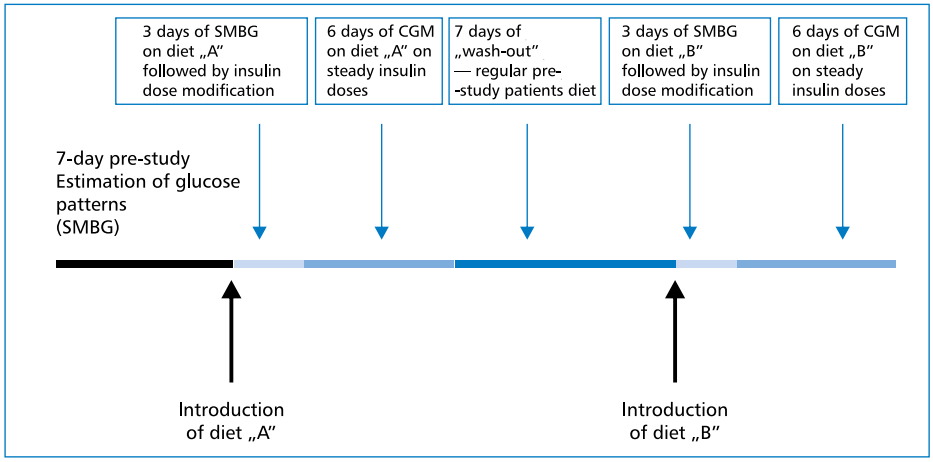

Figure 1. Schematic presentation of the study design. SMBG — self blood glucose monitoring; CGM — continuous glucose monitoring

form self-monitoring of blood glucose with their own blood glucose meters for the whole study period. The following daily pattern for taking blood glucose levels was recommended: fasting, 2 hours after breakfast, 2 hours before and after lunch and 2 hours before and after dinner. Glucose patterns during days 4 to 9 when on diet A and diet B were assessed with the blinded continuous glucose monitoring (CGM) system (iPro2, Medtronic, USA). For the purpose of the study the Enlite Sensors (Medtronic) were used. All the patients submitted informed consent. The study was approved by the Bioethical Committee of the Jagiellonian University.

Results

In comparison to pre-study glucose patterns, the implementation of diet A resulted in a decrease of mean glucose levels (glucometer data) from 187 to 153 mg/dL ($p = 0.0001$). Blood glucose variability as measured with standard deviation (SD) was reduced from 84 mg/dL to 44 mg/dL. Switching from diet A to diet B resulted in a decrease of mean glucose levels (CGMS data) from 145 mg/dL to 133 mg/dL ($p = 0.0001$), SD reduction from 51 to 42 mg/dL ($p = 0.0429$), and a decrease of time spent above the target of 180 mg/dL from 18% to 11% ($p = 0.0006$). One of the patients' Continuous Glucose Monitoring (CGM) records on a diet A and a diet B is shown in Figure 2. There were no episodes of severe hypoglycaemia.

Discussion

The prandial insulin requirement is mostly driven by the meal CH amount and its quality. Treatment with PMHI implies fixed insulin doses as well as a steady proportion of both basal and prandial insulin components. Thus, for fixed prandial insulin, a repeatable, steady CH meal content also seems to be needed. This clinical experiment shows that such an approach helps to achieve satisfactory glycaemic control (as assessed here by a CGM system) in patients with T2DM on PMHI. There is a significant number of insulin treated T2DM patients for whom allowance for wide modifications of daily insulin doses may be not only difficult but also dangerous due to limited compliance and co-operation abilities [10]. It seems that easy to understand diet modification may be easier for them to implement, repeatable and steady CH meal content may be a solution of choice for this group of patients. The need for consistent carbohydrate intake with respect to time and amount which can result in improved glycaemic control and reduced risk for hypoglycaemia in T2DM patients treated with pre-mixed insulins was recognized in the recommendations by American Diabetes Association (ADA) (evidence rating „B") [11].

It has to be added that a moderate reduction in CH content produced further improvement in the patients' glycaemic control. It has recently been shown that carbohydrate restriction according to baseline HbA1c levels may improve glycaemic control in T2DM patients [12]. Of interest, moderate reduction in carbohydrate content with time led also to the reduction of total energy intake [12]. It is important, however, to place greater emphasis on the role of various types of carbohydrate foods for glycaemic control, which was not a subject of investigation in present study [13].

Unfortunately there is no general agreement concerning the ideal proportion of carbohydrates in diet recommended for patients with diabetes [1, 3, 5, 6]. The recommendations by ADA state that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people with diabetes; therefore, macronutrient distribution should be based on individualized

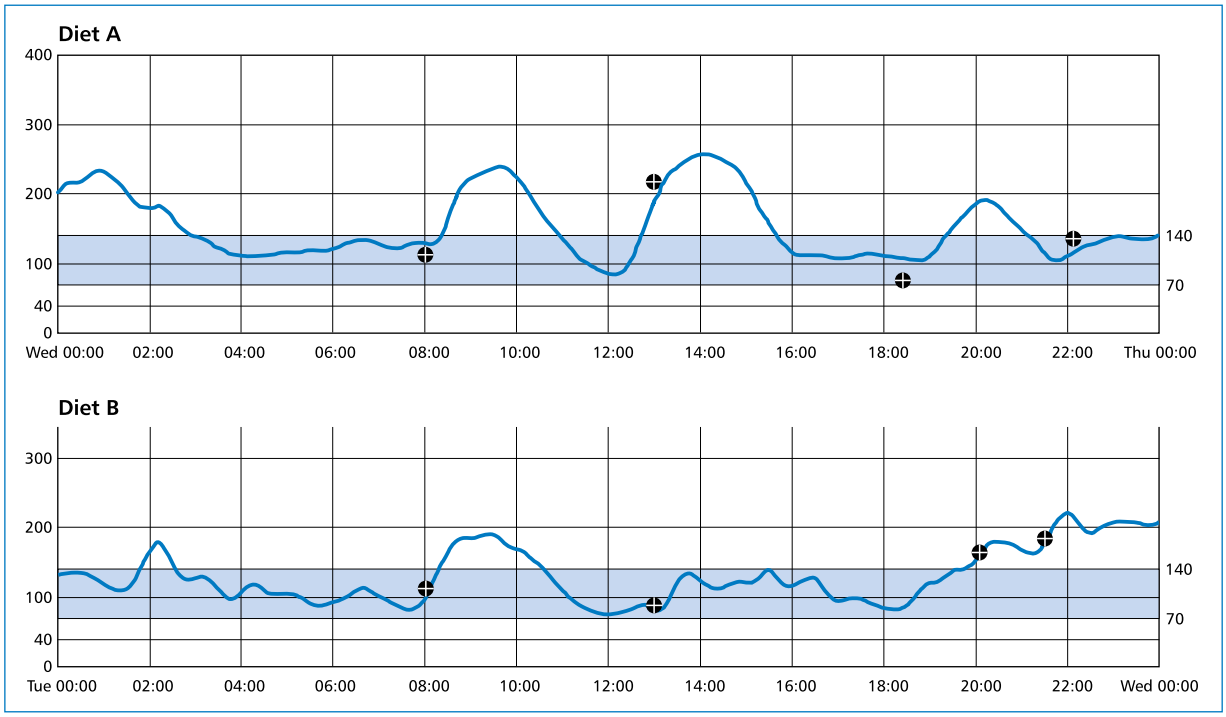

Figure 2. An example of a 24-hour CGM record on diet A (upper graph) and diet B (lower graph) in one study patient is shown. Bullets represent consumed meals

assessment of current eating patterns, preferences, and metabolic goals [11].

Although this study was performed in an artificial environment of pre-prepared and ready to use meals, its results simply suggest that dietary education in T2DM patients treated with PMHI should include information on how to maintain a repeated amount of CH in their diet on a daily basis. Focusing on this aspect of dietary intervention may improve patients' diet acceptance and compliance [14]. The individual content of other food components, such as fat and protein, seems to be of less importance as long as their total summarized proportion is fixed.

Conclusions

Consistent and repeatable CH with their moderate restriction along with steady calorie intake allow to improve glycaemic control in T2DM patients treated with PMHI as manifested by a significant reduction of mean glucose levels and decreased blood glucose variability. We postulate that in T2DM patients treated with PMHI an emphasis is put on education how to maintain a recommended pattern of CHs intake.

The study was supported by unrestricted grant from Bioton Company.

Conflict of interest

MTM and TK gave lectures for Bioton
MM is a Bioton employee

REFERENCES

1. International Diabetes Federation. Global guideline for type 2 diabetes. Brussels: International Diabetes Federation; 2012. http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf.
2. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2012; 55: 1577–1596.
3. European Diabetes Policy Group 1999. A desktop guide to Type 2 diabetes mellitus. Diabet Med 1999; 16: 716–730.
4. Pastors JG, Warshaw H, Daly A et al. The evidence for the effectiveness of medical nutrition therapy in diabetes management. Diabetes Care 2002; 25: 608–613.
5. Mann JI1, De Leeuw I, Hermansen K et al. Diabetes and Nutrition Study Group (DNSG) of the European Association Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. Nutr Metab Cardiovasc Dis 2004; 14: 373–394.
6. American Diabetes Association, Bantle JP, Wylie-Rosett J, Albright AL et al. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care 2008; 31 (Suppl 1): 61–78.
7. Freckmann G, Hagenlocher S, Baumstark A et al. Continuous glucose profiles in healthy subjects under everyday life conditions

and after different meals. J Diabetes Sci Technol 2007; 1: 695–703.
8. Khoury D, Anderson GH. Recent advances in dietary proteins and lipid metabolism. Curr Opin Lipidol 2013; 24: 207–213.
9. Nilsson M., Stenberg M, Frid AH et al. Glycemia and insulinemia in healthy subjects after lactose equivalent meals of milk and other food proteins: the role of plasma amino acids and incretins. Am J Clin Nutr 2004; 80: 1246–1253.
10. Sorli C, Heile MK. Identifying and meeting the challenges of insulin therapy in type 2 diabetes. J Multidiscip Healthc 2014; 7: 267–282.
11. Evert AB, Boucher JL, Cypress M et al. Nutrition Therapy Recommendations for the Management of Adults with Diabetes. Diabetes Care 2013; 36: 3821–3842.
12. Haimoto H, Sasakabe T, Kawamura T et al. Three-graded stratification of carbohydrate restriction by level of baseline hemoglobin A1c for type 2 diabetes patients with a moderate low-carbohydrate diet. Nutr Metab (Lond). 2014; 28; 11: 33.
13. Breen C, McKenzie K, Yoder R. A qualitative investigation of patients' understanding of carbohydrate in the clinical management of type 2 diabetes. J Hum Nutr Diet 2015 Jan 26.
14. Asante E. Interventions to promote treatment adherence in type 2 diabetes mellitus. Br J Community Nurs 2013; 18: 267–274.