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The Impact of Medical Nutritional Therapy on the Efficacy of Premix Insulin in Glycemic Control in Patients with Type 2 Diabetes

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ABSTRACT

Background: Medical nutritional therapy (MNT) is a key component in the treatment of Diabetes mellitus (DM). MNT is completely individual and should be present in the treatment of diabetes from the very beginning, continuously with pharmacological therapy, taking into account lifestyle, dietary habits and the type of antidiabetic therapy. Mistakes that are made when planning the diet are the absence of individual adjustment of the diet, which means that the number and time of meals, as well as the amount of UH per meal, is not adjusted to the patients' oral or insulin therapy according to their pharmacokinetics and pharmacodynamics. **Objective:** This study investigated the effect of MNT with reduced carbohydrate content (MNT M-ADA) on the efficacy of human and analogue premix insulin in patients with T2DM. **Methods:** Subjects were randomized into two groups (human and analog premix insulins), and then each group into two subgroups of 30 subjects each. One subgroup each on therapy with human and analog biphasic insulins was educated about MNT and learned to count UH, and then they applied MNT M-ADA for 24 weeks, unlike the other two subgroups. In this review, we present only the subgroup analysis on human and analog premix insulins that applied MNT M-ADA (200 g UH/day). Efficacy outcomes in the analysis of these subgroups were estimated changes in each subgroup from baseline to end point (week 24) and differences between subgroups at the end of the study in levels of glycated hemoglobin (HbA1c), self-measured glucose values (SMBG) and frequency of hypoglycemia. **Results:** Both subgroups of subjects with MNT M-ADA improved glycemic control, which was assessed by improvements in HBA1C, SMBG levels, without an increase in the frequency of hypoglycemia, but at the end of the study there was no statistically significant difference in the mentioned parameters between the subgroups. **Conclusion:** The effectiveness of MNT M-ADA in people with T2DM did not depend on the type of insulin, both insulin regimens are effective if the amount of ingested UH is taken into account.

Keywords: medical nutritional therapy, carbohydrates, Hba1C, biphasic insulins.

1. BACKGROUND

Despite modern drugs used in the treatment of diabetes, about 50% of patients still do not achieve satisfactory glycemic control and other metabolic parameters (1). Although most diabetes guidelines recommend starting pharmacotherapy only after lifestyle, dietary and physical activity changes, this is not generally applied in practice. When type 2 Diabetes mellitus (T2DM) is diagnosed, the patient often leaves the clinic with a list of new medications and without adequate education about medical nutrition therapy (MNT), which, regardless of the modern drug therapy used in the treatment of diabetes, is a factor of utmost importance. in the treatment and prevention of T2DM. The advice and instructions that patients receive regarding nutrition often read "beware of food", "watch what you eat" "you must be on a diet", which in fact patients did not receive any instructions re-

lated to proper nutrition and lifestyle. This is because most doctors are not trained in MNT. In addition, talking to patients about nutrition requires a lot of time that most doctors do not have. Numerous studies have attempted to identify the optimal ratio of macronutrients in dietary plans for people with diabetes. Evert et al. (2) conclude that there is no ideal ratio that would be widely applied and that macronutrient ratios should be individualized. People with diabetes have been found to eat, on average, about the same proportions of macronutrients as the general public: ~45% of calories from carbohydrates, ~36–40% of calories from fat, and the rest (~16–18%) from protein (2).

2. OBJECTIVE

The aim of the study was to determine the efficacy and safety of MNT with reduced carbohydrate content in glycemic control in patients with T2DM treated with human and analog biphasic insulins. To compare, based on glycemic control parameters, whether MNT with reduced carbohydrate content (MNT M-ADA) is equally effective and safe with both insulin regimens.

3. MATERIAL AND METHODS

The study was a 24-week open, prospective, randomized study designed and monitored in accordance with the Good Clinical Practice guidelines, the International Conference on Harmonization and the Declaration of Helsinki. The study included men and women older than 30 years who had been diagnosed with T2D at least 3 years prior to screening, treated with metformin (at least 1500 mg or maximum tolerated dose) in combination with other oral antidiabetic agents, or basal insulin with oral therapy, or biphasic with human and analog insulin, they had inadequate glycemic control 7.0-10.0% and the will to change their condition, willingness and ability to adhere to the research protocol, the prescribed diet and to measure glycemia according to the established protocol.

Subjects were excluded from the study if they had diabetes other than T2D, renal insufficiency (eGFR ≤30 ml/min/1.73m²), congestive heart failure (NYHA III/IV), liver cirrhosis, uncontrolled hypertension, any disorder for which the investigator considers that it may endanger the safety or compliance of subjects, women who are pregnant, subjects with T2D previously treated with GLP-1 RA, if they do not cooperate with the study, do not comply with the study protocol, subjects who are illiterate and those who voluntarily decided to stop further participation in the study .

Study design

After screening, in the preparatory phase, patients who were on oral therapy or basal insulin with OAD were transferred to therapy with human or analog biphasic insulin and educated about the administration and titration of the insulin dose. All insulins are prescribed via foam, twice a day before breakfast and dinner (human insulins 30 minutes before breakfast and dinner and analogue insulins immediately before breakfast and dinner or during the said meals). Of the total daily dose of insulin, subjects received 2/3 of insulin in the morning and 1/3 of insulin in the evening. For all patients in this phase, the dose of metformin was titrated to a stable dose of 1700 mg. Subjects who at the end of the preparatory phase had HbA1≥7.0 and ≤10.0% were randomized into two groups (human and analog premix insulins), and then each group into two subgroups, a total of four subgroups of 30 subjects each. One subgroup each on therapy with human (BHI) and analog (BIA) biphasic insulins was educated about MNT and calculation of UH using ADA nutrition tables, and then for 24 weeks they applied MNT with a reduced proportion of UH (200 g UH/day). We called this diet MNT M-ADA and the subgroups that used this diet were labeled as BHI: M-ADA and BIA: M-ADA. The daily dose of UH was divided into different number of meals and planned hourly meals, which depended on the type of insulin, taking into account its

	Group BHI (n=60)	Group BIA (n=60)
Age distribution (years)	65.32±8.30	64.30±8.51
Sex Male/Female (n, %)	19/41 (31.7 / 68.3)	9/51 (15 / 85)
Body mass (kg)	81.25 (71.12-95.25)	79.68 (75.00-89.75)
BMI (kg/m²)	29.25 (26.00-31.00)	28.50 (26.47-33.00)
Daily dose of insulin (i.j.)	42 (34.50-57.50)	54 (44.00-65.00)
Fasting Plasma glucose (FPG) mol/L	10.10 (7.30-14.07)	9.95 (8.30-13.57)
HBA1C %	9.50±1.69	9.80 ±1.43

Table 1. Baseline characteristics . Parameters are expressed as median (range, Q1-Q3 interquartile range); mean mean value (standard deviation SD); n-absolute number; % relative number; BHI - biphasic human insulin: BIA biphasic analog insulin; BMI-Body Mass Index; HbA1c- Glycosylated hemoglobin;

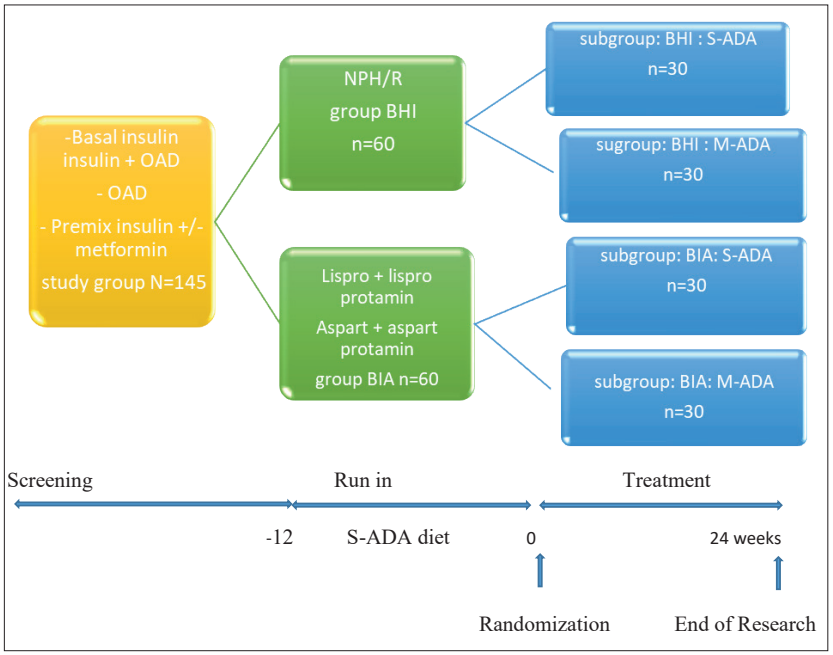

Figure 1. Research design

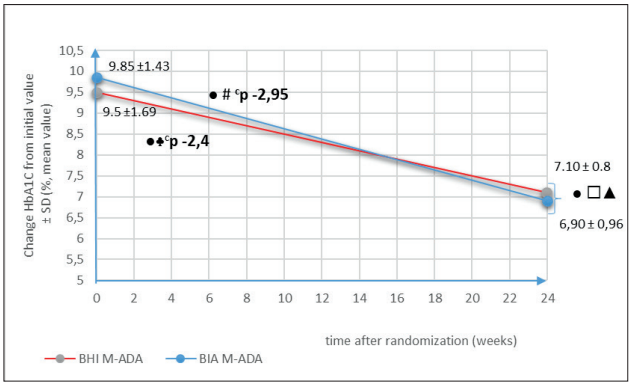

Figure 2. Mean change from baseline in HBA1C levels in T2D participants with MNT M-ADA Legend: parameters are expressed as mean (standard deviation SD); BHI-biphasic human insulin: BIA – biphasic analog insulins; HbA1c- Glycosylated hemoglobin; M-ADA-Medical nutritional therapy, modified diet according to ADA tables with a reduced dose of carbohydrates; ADA-American Diabetes Association; ●=Independent samples t-test; ▲ –no significance; ap < 0.05; bp< 0.01; cp < 0.001; ♣ =Hba1c: BHI S-ADA basal vs. BHI M-ADA at the end of the study; #= Hba1C: BIA S-ADA basal vs BIA M-ADA at the end of the study; • = Hba1C at the end of the study: BHI M-ADA vs. BIA M-ADA

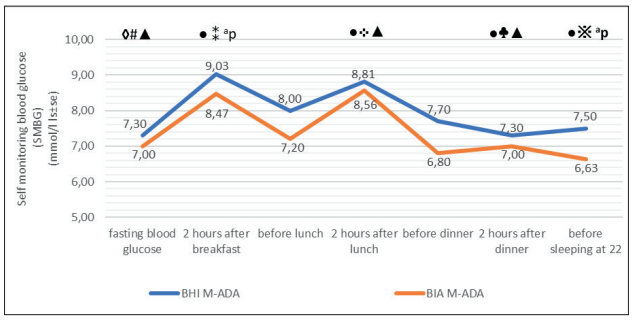

Figure 3. Comparison of mean values of self-monitored blood glucose levels (SMBG) between subgroups of human and analogue biphasic insulins after administration of MNT M-ADA. Legend: parameters are expressed as median (range, Q1-Q3 interquartile range); mean value (standard deviation SD); PGN – fasting plasma glucose; M-ADA-Medical nutritional therapy, modified diet according to ADA tables with a reduced dose of carbohydrates; ADA-American Diabetes Association; BIA - biphasic analog insulins; BHI-biphasic human insulins; ◊=Two-Independent-Samples-Test (Mann-Whitney U); ● =Independent samples t-test; ▲ –no significance; ap < 0.05; bp< 0.01; cp < 0.001; #=Guk on mother-in-law according to M-ADA:BHI and BIA; ⁑=guk 2h after breakfast according to MADA: BHI and BIA ⁘=guk 2h after lunch according to M-ADA: BHI and BIA; ♣ = guk 2h after dinner according to M-ADA: BHI and BIA; ※= guk at 22h according to M-ADA: BHI and BIA.

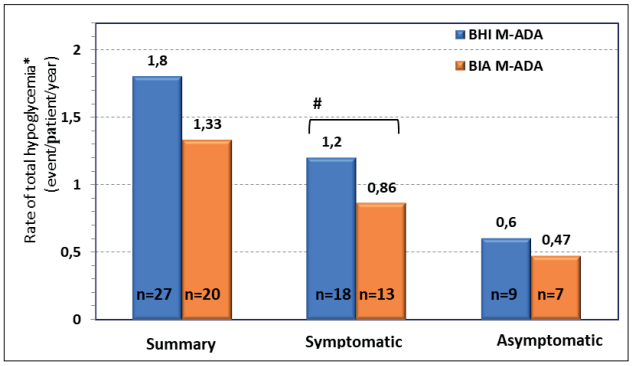

Figure 4. Rate of hypoglycemia. Legend: # P=1, OR=1.08 (95%CI: 0.26, 4.27) *Total hypoglycemia was defined as a plasma glucose level ≤3.9 mmol/l which may or may not be accompanied by symptoms; n-absolute number; BHI - biphasic human insulin: BIA - biphasic insulin analogs; M-ADA- Medical nutritional therapy, modified diet according to ADA tables with a reduced dose of carbohydrates; ADA-American Diabetes Association;

pharmacokinetics and pharmacodynamics. The other two subgroups (one on human and the other on analogue premix insulins) continued the standard diet with a higher carbohydrate content of 200 g/day. We named this way of eating MNT S-ADA nutritional therapy and the subgroups that used this eating pattern were marked as BHI: S-ADA and BIA: S-ADA. In this review, we only present subgroup analysis on human and analog premix insulins that applied MNT M-ADA (Figure 1).

Efficacy and safety-endpoints

Efficacy outcomes in the analysis of these subgroups were estimated changes in each subgroup from baseline to endpoint (week 24) and differences between subgroups at the end of the study in HbA1c, self-measured glucose (SMBG) levels. The safety of insulin was assessed through the rate of occurrence of hypoglycemia during 24 weeks of using the diet, which the patients recorded in a self-monitoring diary. Also, at each visit, patients were asked about the occurrence and number of hypoglycemias (symptomatic and asymptomatic).

Statistical analysis

Statistical processing was done with application software (Statistical Package for Social Sciences for Windows, version 22.0 SPSS Inc., Chicago, IL, USA). Statistical hypotheses were tested at alpha=0.5 level, i.e. the difference between groups was considered significant if p<0.05.

4. RESULTS

Out of 145 subjects who entered the screening, 120 subjects were randomized into 4 subgroups. In total, n=60 patients received NPH/R and n=60 analog biphasic insulin. The basic characteristics of the subgroups are in Table 1

After 24 weeks of MNT M-ADA administration, the estimated mean change in HbA1c from the beginning to the 24th week was -2.4% in the BHI subgroup and -2.95% in the BIA subgroup. At the end of the study, there was no statistically significant difference in the Hba1C value between the BHI M-ADA and BIA M-ADA subgroups (7.10 vs. 6.90 p= 0.386) (Figure 2) .

Participants in both groups with MNT M-ADA achieved a reduction in SMBG, but there was no statistically significant difference at the end of the study between the BIA and BIH subgroups with M-ADA MNT in fasting glucose (p=0.118), 2 hours after lunch (p= 0.373), 2h after dinner (p=0.990). Subjects of the BIA subgroup only had a statistically significantly better result in the blood glucose, 2 h after breakfast compared to the BHI subgroup (p=0.048) (Figure 3).

The overall rate of hypoglycemia (plasma glucose less than 3.9 mmol/l) was 1.8 episodes/patient-year of exposure (PYE) in the BHI subgroup and 1.33 episodes/PYE in the BIA subgroup. The OR of the occurrence of symptomatic and asymptomatic hypoglycemia in any comparison is not statistically significantly different from 1 (OR=1.08; 95% CI: 0.26;4.27 p>0.05) (Figure 4).

5. DISCUSSION

In this study, both BHI M-ADA and BIA M-ADA subgroups improved glycemic control using MNT with reduced UH intake as assessed by improvements in HbA1c and SMBG levels. Our results support the idea that glycemic control depends more on the amount of UH in the diet than on the type of premix insulin used. These results agree with the results of other studies, that UH contributes the most to the excursion of postprandial glycemia (PPG) (3). Reports by Kirkpatrick et al. (4), and Wang et al., (5) also show the effectiveness of a low-US diet in improving glycemic control. A decrease in PPG when reducing the amount of UH at a meal (6) was also observed in our study because PPG with M-ADA diet was reduced in both insulin regimens.

Other studies favor premixed analogs over human premixed insulins because they achieved better control of postprandial glycemia (7). In a study by Shestakov, Sharma, et al. (8) and Das, et al. (9), glycemia improved when T2DM patients poorly controlled on BHI were switched to BIAsp30. These studies mainly followed the effects of different insulins on glycemic control without taking into account the influence of diet. The BIA subgroup had slightly better PPG after breakfast compared to the BHI subgroup. It is possible that slightly better post-breakfast glycemic values are the result of improved, more physiological pharmacodynamics and pharmacokinetics of analogue premix insulins compared to human insulin and because they have a faster onset of action and achieve better control of postprandial glycemia (7). Subjects did not receive insulin before lunch and there was no difference in PPG value after lunch with both insulin regimens. Although analog premix insulins are preferred over human pemix insulins (7), in our study both insulin regimens, with M-ADA nutritional therapy, were comparably effective.

The indicator of long-term glycemic control is Hba1C, whose value depends on fasting glycemia (FPG) and PPG. In our study, subjects on both human and analog premixes with M-ADA MNT achieved lower FPG and PPG glycemia values on average, so that at the end of the study, their HbA1C decreased by an average of 2.4%, while Tucker (10) recorded a decrease HbA1c, of 2.6% in the group on a low UH diet and 1.9% in the group with high UH. Gannon et al had similar experiences with a diet with low UH on HbA1C (3). Haimoto et al. (11) reported that a diet with a 45% UH content reduced the HbA1c level more than a 60% UH diet.

HbA1C values at the end of our study were comparable with both insulin regimens, which shows that the efficacy of human premix insulins is comparable to analog premix insulins when taking into account the amount of UH administered. Also, in most other studies, the HBA1c value was comparable for analog and human premix insulins. Nabrdalik et al. (12) showed that patients treated with analog premix insulins had better results in terms of reducing FPG, PPG values, but analog and human premix insulin regimens were comparably effective in reducing HbA1c. No analog premix is better than human premix insulin for lowering HbA1c (pooled difference = -0.05% is the conclusion of the Qayyum, Bolen, et al. (13) and Garber (14) studies).

From the results of our research, it can be concluded that the reduction of UH in the diet was effective in improving the values of SMBG and HbA1C in both human and analog premix insulins, and that at the end of the research both insulin regimens were comparable in glycemic control and that human premix insulins can be equally effective as analog premixes if the amount of UH taken in is taken into account, which is a key factor for achieving better glycemic control.

The frequency of hypoglycemia during the intervention period did not depend on the type of premix insulin, it was similar for human and analog premix insulins (OR, 1.08; 95%CI, 0.26-4.27; p>0.05), and both insulin regimens were safe because the incidence of hypoglycemia was similar.

Garber (14) and Garber et al. (7) reported that the frequency of minor hypoglycemic episodes during treatment with analog and human premix insulins was comparable, while major hypoglycemia was rare with either insulin formulation. Similar rates of major and minor hypoglycemia (OR = 0.6; 95% CI = 0.2 to 1.3; OR = 1.0; 95% CI = 0.6 to 1.5) in analog and human premix of insulin was recorded in the study by Qayyum, Bolen et al. (13).

However, there are studies that favor analogues over human premix insulins, as a lower rate of hypoglycemia was observed when patients with T2DM who were poorly controlled on BHI were switched to BIAsp30 (8). Giugliano et al (15) reported that tighter glycemic control increased the risk of severe hypoglycemia compared with less intensive glycemic control. In our study, better glycemic control did not increase the incidence of hypoglycemia. This could partly be explained by the increase in protein intake (16, 17) and on the other hand by the fact that the subjects of both insulin regimens were well educated about nutrition, had an adjusted number and timing of meals in accordance with the pharmacokinetics of the administered insulin, had more frequent glycemic control, promptly reduced the dose of insulin, thus reducing the risk of hypoglycemia and its frequency.

6. CONCLUSION

This study showed that nutrition with a reduction of UH is effective and safe, and that it can improve glycemic control regardless of the insulin regimen, and that if the amount of UH ingested is taken into account, human premix insulins are not inferior to analog premixes in glycemic control and the incidence of hypoglycemia.

Limitation of the study

A limiting factor of our study is that the study did not last longer than 24 weeks to assess the long-term impact of a reduced-dose UH diet on glycemic control.

- **Author's contribution:** All authors were involved in all steps of preparation this article. Final proofreading was made by the first author.
- **Conflict of interest:** None declared.
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