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RESEARCH PAPER

Meal replacement reduces insulin requirement, HbA1c and weight long-term in type 2 diabetes patients with >100 U insulin per day

K. Kempf,* N. C. Schloot,†‡ B. Gärtner,* R. Keil,§ P. Schadewaldt¶ & S. Martin*

*West-German Centre of Diabetes and Health, Düsseldorf Catholic Hospital Group, Düsseldorf, Germany
†NutriVista GmbH, Köln, Germany
‡Lilly Deutschland GmbH, Bad Homburg, Germany
§Post-Apotheke, Grevenbroich, Germany
¶Institute for Clinical Biochemistry and Pathobiochemistry, German Diabetes Center, Düsseldorf, Germany

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Correspondence
K. Kempf, West-German Centre of Diabetes and Health, Düsseldorf Catholic Hospital Group, Hohensandweg 37, 40591 Düsseldorf, Germany.
Tel.: +49 (0)211 56 60 360 16
Fax: +49 (0)211 56 60 360 72
E-mail: kerstin.kempf@wdgz.de

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Abstract

Background: Despite high insulin doses, good glycaemic control is often lacking in type 2 diabetes patients and new therapeutic options are needed.
Methods: In a proof of principle study, an energy-restricted, protein-rich meal replacement (PRMR) was examined as a means of reducing insulin requirement, HbA1C and body weight. Obese type 2 diabetes patients (n = 22) with >100 U insulin per day replaced, in week 1, the three main meals with 50 g of PRMR (Almased-Vitalkost) each (= 4903 kJ day^{-1}). In weeks 2–4, breakfast and dinner were replaced, and, in weeks 5–12, only dinner was replaced. Clinical parameters were determined at baseline, and after 4, 8 and 12 weeks, as well as after 1.5 years of follow-up. The Wilcoxon signed-rank test was used for the intention-to-treat analysis and the Mann–Whitney U-test for subgroup analyses.
Results: The 12-week-programme was completed by 15 participants (68%). After 1 week, the mean insulin dose was reduced from 147 (75) U to 91 (55) U day^{-1} (P = 0.0001), and to 65 (32) U (P < 0.0001) after 12 weeks of study. Over a period of 12 weeks, HbA1c decreased from 8.8% (1.4%) to 8.1% (1.6%) (P = 0.048) and weight decreased from 118.0 (19.7) kg to 107.4 (19.2) kg (P < 0.0001). Moreover, body mass index, waist and hip circumference, fasting blood glucose, triglycerides and high-density lipoprotein cholesterol improved significantly. After 1.5 years, insulin requirement and weight remained significantly lower than baseline. Participants who continued PRMR further reduced their HbA1c, weight and insulin dose. Two patients were able to stop insulin therapy altogether.
Conclusions: Energy-restricted PRMR was effective in reducing insulin requirement of type 2 diabetes patients with intensified insulin therapy accompanied by a reduction of HbA1c, weight and other cardiometabolic risk factors. With the continuous use of PRMR, glycaemic control might be improved in the long term.

Introduction

Insulin therapy is an integral part of type 2 diabetes therapy today (UK Prospective Diabetes Study Group, 1998). Current diabetes guidelines (Matthaei *et al.*, 2011) recommend measures for changes in lifestyle, education, diet and physical therapy, as well as Metformin as the initial therapy and, subsequently, if HbA1c cannot be reduced

below 6.5% within 3–6 months, the use of oral anti-diabetes medication. If these measures do not result in a satisfactory blood glucose adjustment, insulin therapy is often the only option. Generally, half of diabetes patients were treated with insulin 10 years after type 2 diabetes was diagnosed (UK Prospective Diabetes Study Group, 1995). This often results in additional weight gain, which requires a further increase of the insulin dosage (Yki-Jarvinen *et al.*, 1997). The reasons for the weight gain are multifactorial: (i) insulin is an anabolic hormone and promotes fat storage; (ii) patients on insulin therapy feel hungrier; and (iii) although intensified insulin therapy prevents patients from post-meal blood glucose increase, additional energy further increases weight. This weight gain promotes the existing insulin resistance and also negatively affects blood pressure, cholesterol and triglyceride levels, inflammation markers, and mortality risk (Aas *et al.*, 2005, 2006; Whitlock *et al.*, 2009), and results in a vicious cycle in which patients who cannot achieve satisfactory metabolic adjustment are treated with >100 U insulin per day.

It has been shown that substitution of dietary carbohydrate for protein supports weight loss (Parker *et al.*, 2002), improves insulin sensitivity (Piatti *et al.*, 1994) and reduces risk factors for cardiovascular disease (Wycherley *et al.*, 2010). Furthermore, a meta-regression analysis demonstrated that, independent of energy intake, high-protein diets favourably affect body mass and composition (Krieger *et al.*, 2006). The aim of the present proof of principle study was to examine whether an energy-restricted protein-rich meal replacement (PRMR) can help to reduce the insulin requirement in patients with type 2 diabetes using >100 U insulin per day and simultaneously improve HbA1c, weight and other cardiometabolic risk factors.

Materials and methods

Study design

Twenty-two patients with type 2 diabetes [inclusion criteria: body mass index (BMI) > 27 kg m^{-2}, age 35–75 years, insulin therapy with >100 U insulin per day] from a diabetological centre participated in the present study. Laboratory parameters were determined with the same standardised methods at the start of the study, as well as after 4, 8 and 12 weeks. At the first visit, the design and intention of the study were explained to the participants by the attending physician, and participants provided their written informed consent. In addition, they were given a manual, as well as the PRMR (Almased-Vitalkost; Almased-Wellness-GmbH, Bienenbüttel, Germany), a mixture of flaxseed, olive and canola oils, and vegetable juice. Participants carried out a daily eight-point blood glucose profile and noted down these values in the manual, the amount of PRMR taken, the number of meals replaced, as well as their insulin doses. Based on these numbers, insulin therapy was monitored and adjusted by the diabetologist. The study was approved by the ethics committee of the Heinrich-Heine-University Düsseldorf and conducted in accordamce with the Helsinki Declaration. After 1.5 years, participants who completed the 12-week study, received a follow-up phone call and were asked to state their current weight, HbA1c (measured by attending physician), daily insulin requirement and whether they still consumed PRMR.

Diet regimen

Almased is a protein-rich meal replacement available in pharmacies. Almased contains three main ingredients:

Table 1 Table of composition showing the average contents of the product ready for consumption mixed with water (serving size of 50 g)

	Per 100 g
Energy	1507 kJ (360 kcal)
Protein	53.4 g
Carbohydrates of which:	30.6 g
Sugar	30.54 g
Polyols	0.06 g
Starch	0 g
Fat of which:	2.0 g
Saturates	1.0 g
Monounsaturates	0.8 g
Polyansaturates	0.2 g
Fibre	0.4 g
Sodium	0.68 g
Vitamin A	508 µg
Vitamin D	3.2 µg
Vitamin E	7.8 mg
Vitamin C	30.4 mg
Thiamin	0.8 mg
Riboflavin	1.6 mg
Niacin	12.2 mg
Vitamin B_6	1.0 mg
Folic acid	212 µg
Vitamin B_{12}	1.4 µg
Biotin	24 µg
Panthothenic acid	2.6 mg
Potassium	1008 mg
Calcium	434 mg
Phosphorus	628 mg
Magnesium	90 mg
Iron	9.8 mg
Zinc	6.2 mg
Copper	0.72 mg
Manganese	0.66 mg
Selenium	36 µg
Iodine	86 µg

50% soy protein isolates (identity-preserved product), 25% raw enzyme-rich bee honey and 23% skim milk yogurt powder (Table 1). These ingredients are gently processed to make a fine powder. During the first week of the study, breakfast, lunch and dinner were replaced with Almased (50 g per meal dissolved in 120 mL of water, resulting in a total of 150 g day^{-1} = 2223 kJ. Additionally, the participants consumed 45 g of oil (= 1717 kJ) and 750 mL of vegetable juice (= 544 kJ). No additional snacks were permitted, thus lowering the energy intake to 4903 kJ day^{-1}. During weeks 2–4, the participants were asked to replace breakfast and dinner with 50 g of Almased each (= 1465 kJ) and to have a regular lunch. This lunch was to include 150–200 g of fish or meat, 500 g of vegetables and no more than 50 g of carbohydrates from whole grain bread or brown rice (= 2093 kJ). Additionally, they were asked to consume 45 g of oil per day to achieve a daily energy intake of 4600–5300 kJ. In weeks 5–12, only dinner was replaced with 50 g of Almased.

Statistical analysis

The primary endpoint was the reduction of insulin; secondary endpoints were the reduction of weight and HbA1c; data are shown as the mean (SD/SEM). Differences compared to baseline values were determined using the Wilcoxon signed-rank test. For subgroup analysis, the Mann–Whitney *U*-test was used. $P < 0.05$ was considered statistically significant. GRAPHPAD PRISM, version 4.0 (GraphPad Software, San Diego, CA, USA) was used for the analysis.

Results

Significant reduction of daily insulin requirement, HbA1c and body weight during the 12-week study

A total of 22 participants were included in the study (Table 2). Fifteen individuals (68%) completed the entire 12-week course, whereas seven dropped out early. The seven participants dropped out because they were not able to adhere to the study protocol and to substitute the mandated numbers of meals with PRMR. Baseline characteristics of the 22 participants included in the study, the 15 who actually finished it, and the seven drop-outs, did not differ significantly. After 1 week, the intention-to-treat-analysis (i.e. comparison of baseline values of the 22 participants included in the study versus values after 12 weeks from those 15 participants who completed the study) demonstrated that the daily insulin dosage could be reduced from 147 (75) U to 91 (55) U (−56 U; $P = 0.0001$) and further lowered to 65 (32) U day^{-1}

Table 2 Baseline characteristics and improvement of glucometabolic parameters

	All participants start (n = 22)	LOCF end (n = 22)	Completers start (n = 15)	Completers end (n = 15)
Sex (male/female) (n)	14/8		11/4	
Age (years)	64.6 (8.6)		63.6 (9.6)	
Diabetes duration (years)	14.8 (10.2)		13.1 (7.4)	
Weight (kg)	117.0 (19.7)	110.9 (21.1)***	115.2 (17.7)	107.4 (19.2)***
Body mass index (kg m^{-2})	39.2 (6.9)	37.1 (7.3)***	38.7 (7.3)	36.0 (7.7)***
Waist circumference (cm)	128.1 (13.1)	122.8 (15.7)***	127.5 (12.6)	120.5 (15.6)***
Hip circumference (cm)	128.5 (14.2)	125.6 (15.4)**	125.7 (13.9)	122.4 (15.5)*
Systolic BP (mmHg)	142.9 (16.8)	136.6 (18.4)	142.3 (17.9)	133.3 (18.7)
Diastolic BP (mmHg)	81.4 (10.1)	79.1 (12.9)	81.7 (9.9)	77.7 (12.1)
Total cholesterol (mg dL^{-1})	199.7 (50.9)	195.7 (53.9)	193.5 (33.5)	184.6 (36.0)
LDL cholesterol (mg dL^{-1})	107.4 (30.2)	106.9 (31.0)	107.5 (24.9)	109.1 (29.9)
HDL cholesterol (mg dL^{-1})	37.6 (10.4)	38.6 (9.2)	37.3 (8.0)	39.5 (7.4)*
Triglycerides (mg dL^{-1})	279.1 (201.6)	239.6 (208.6)**	246.5 (113.9)	176.3 (64.2)***
HbA1c (%)	8.8 (1.4)	8.8 (1.9)	8.9 (1.6)	8.1 (1.6)*
Fasting blood glucose (mg dL^{-1})	197.7 (60.9)	178.9 (58.8)*	191.0 (52.2)	163.4 (41.1)*
Proinsulin (pM)	10.5 (8.7)	9.5 (7.0)	10.7 (9.0)	9.5 (7.0)
C-peptid (ng mL^{-1})	3.9 (2.8)	3.7 (2.4)	3.7 (2.7)	3.5 (1.8)
Creatinine (mg dL^{-1})	1.1 (0.3)	1.1 (0.4)	1.2 (0.3)	1.1 (0.3)
Urea (mg dL^{-1})	23.2 (10.0)	30.0 (16.1)	20.7 (5.2)	29.8 (16.3)
Uric acid (mg dL^{-1})	5.9 (1.4)	6.1 (1.2)	6.0 (1.2)	6.3 (1.1)

Data are shown as the mean (SD). Differences between 'All participants – start' and 'Intention-to-treat – end', as well as 'All participants – start' and 'LOCF (last-observation-carried-forward) – end', were determined by the Wilcoxon signed-rank test.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

(−82 U; $P < 0.0001$) by week 12. Simultaneously, HbA1c significantly improved from initially 8.8% (1.4%) to 8.0% (1.2%) ($P = 0.004$) after 4 weeks and further to 7.7% (1.1%) ($P = 0.002$) after 8 weeks. At the end of the study, a slight increase of HbA1c to 8.1% (1.6%) was observed, although it remained significantly lower than baseline [−0.8% (1.4%); $P = 0.048$]. Over the course of the study, all participants significantly reduced their weight from 117.0 (19.7) kg to 115.4 (20.9) kg ($P = 0.0003$) after 4 weeks, and to 112.2 (21.4) kg ($P = 0.0003$) after 8 weeks, reaching a final weight of 107.4 (19.2) kg [−7.9 (3.5) kg; range −2.5 to −16.5 kg; $P < 0.0001$] after 12 weeks at the end of the study (Fig. 1). Moreover, the 12 weeks of meal replacement resulted in a mean reduction of BMI by 2.6 (1.3) kg m^{-2} ($P < 0.0001$), waist circumference by 7.1 (6.6) cm ($P = 0.0003$), hip circumference by 3.3 (6.2) cm ($P = 0.035$), improvement of high-density-lipoprotein-cholesterol by 2.2 (3.8) mg dL^{-1} ($P = 0.049$), triglycerides by 70.3 (85.1) mg dL^{-1} ($P = 0.0001$) and a fasting blood glucose level by 27.6 (39.6) mg dL^{-1} ($P = 0.027$). The results (Table 2) also remained stable when baseline and end values of the 15 completing participants were compared or when missing values of the drop-outs were filled in using the last-observation-carried-forward-principle. No statistically significant effects were observed regarding the relationship of muscle to fat mass measured by bioimpedance, energy expenditure measured by indirect caloriemetry and blood concentration of the intestinal hormone glucagon-like peptide-1, which induces glucose-dependent stimulation of insulin secretion (data not shown). In all analyses, we found no effect of sex.

By continuous use of protein-rich meal repacement, improvements can be maintained long-term

After an average of 1.5 years, a follow-up survey was conducted via phone with the 15 participants who completed the entire 12-week study. Generally, they maintained the decrease of insulin requirement, HbA1c and weight that they had achieved during the 12-week study, so that there were no statistically significant differences compared to the values reported at study end. The daily insulin requirement of 94 (71) U ($P = 0.026$) and a weight of 108.2 (18.7) kg ($P = 0.0004$) were still significantly lower after 1.5 years versus the initial values at the beginning of the study. After the end of the study, four participants continued to use PRMR regularly, four used it sporadically and seven stopped using PRMR. The stratified analysis of these three groups showed that insulin requirement, HbA1c and weight further decreased only in the participants who used PRMR continuously (Fig. 2). Two of them were even able to terminate insulin therapy. By contrast, insulin requirement, HbA1c and weight increased again in occasional PRMR users ($P = 0.029$ for each, insulin requirement and weight, compared to continuous users) and the group that no longer used PRMR ($P = 0.024$ for each, insulin requirement and weight).

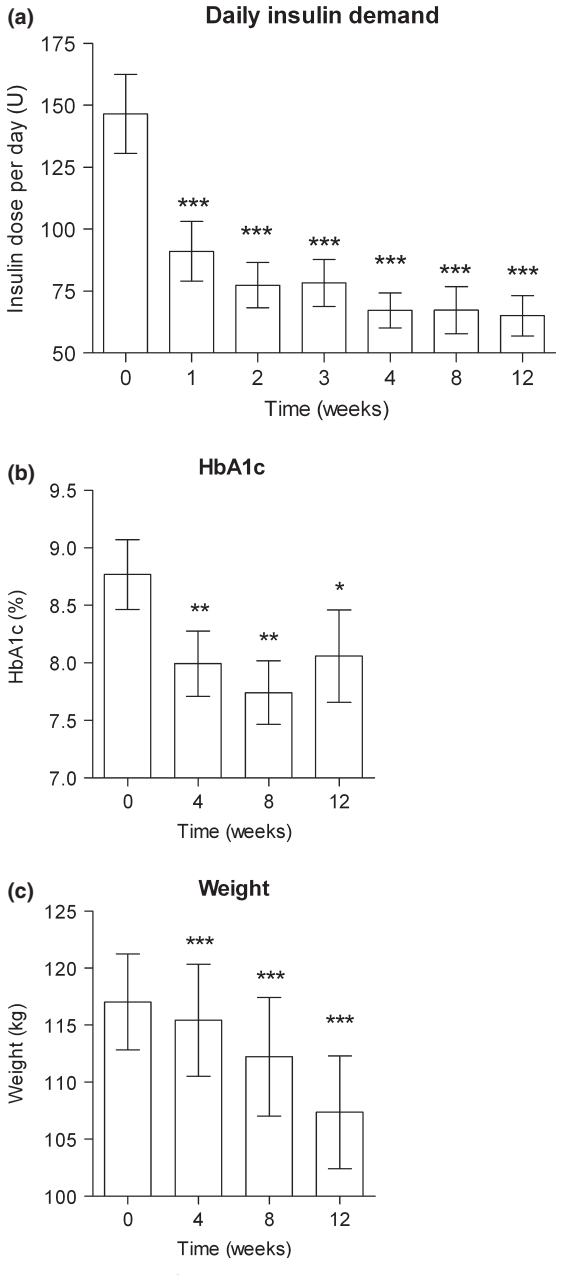

Figure 1 Reduction of daily insulin requirement, HbA1c and body weight. (a) The daily insulin requirement was strictly controlled and adjusted; (b) HBA1c and (c) body weight were measured at the beginning of the study, after 4, 8 and 12 weeks. Data are shown as the mean (SEM). Differences compared to the values at beginning were determined using the Wilcoxon signed-rank test (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

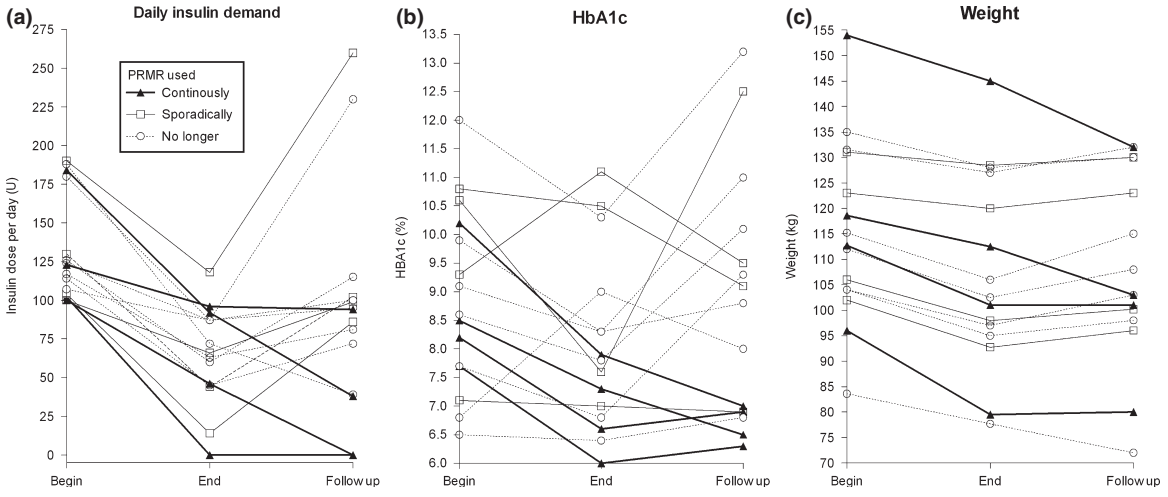

Figure 2 Insulin requirement, HbA1c and body weight after 1.5 years of follow-up. Individual values for (a) daily insulin requirement, (b) HBA1c (c) and body weight at the beginning of the study, after the end of the study and at follow-up after 1.5 years are shown for the three groups that used the meal replacement continuously after the end of the study (n = 4; black triangle), sporadically (n = 4; white square) and no longer (n = 7; white circle). PRMR, protein-rich meal replacement.

Discussion

The pilot study demonstrates that patients with type 2 diabetes who injected more than 100 U insulin per day were able to improve their glucometabolic control, with a significant reduction of insulin requirement, HbA1c and body weight, as well as other glucometabolic risk factors, by using energy-restricted PRMR. There are indications that this success could be maintained long-term with continuous PRMR use.

Change of diet and lifestyle should be a mainstay of treatment for type 2 diabetes patients with high insulin requirement and poor glycaemic control. However, lifestyle interventions including insulin-treated patients are rare. Successful usage of studies of lifestyle and diet intervention for insulin-treated type 2 diabetes patients had been shown by the Look-AHEAD (Action For Health in Diabetes)-Study (Pi-Sunyer *et al.*, 2007; Wing, 2010). Using a combination of an energy-restricted diet, exercise, motivation and self-monitoring of blood glucose within 1 year, patients in the Look-AHEAD study could achieve an 8.6% weight loss, a decrease of mean HbA1c from 7.3% to 6.6% and a significant reduction of anti-diabetic medication. Losing weight was harder to achieve for insulin-treated patients than for patients with oral antidiabetic medication. Insulin-treated patients in the Look-AHEAD study only reduced their weight by 7.6%, which is in line with our patients, who lost 7.1%, by just consuming PRMR. The follow-up of the Look-AHEAD-Study (Wing, 2010) showed that the weight loss was still 6.2% after 4 years, which is almost identical to the results of our follow-up, which showed a weight loss of 6.3% after 1.5 years. However, it needs to be emphasised that the lifestyle intervention in the Look-AHEAD-Study required a significant amount of personal and economical effort. In comparison, the cost for the 12-week long PRMR usage for a total of 12 cans at 500 g was approximately €180. On average, this is a cost of €2.15 per day. Because the insulin requirement was lowered from approximately 150 U per day (approximately €6.70 per day) to approximately 65 U per day (approximately €2.80) during the 12-week study, this equals a daily saving of €3.90 (58%). After subtracting the costs for the meal replacement €1.75 per person and per day could be saved during the study (approximately €150 per person in 12 weeks), without calculating the cost for food that was saved by using the meal replacement. Therefore, it might be speculated that reimbursement of PRMR might be profitable for health insurers to save costs for insulin therapy. Moreover, it might be expected that the achieved weight reduction and improved glycaemic control might also reduce the development of cardiovascular diseases (and associated costs), although a recent prospective cohort study suggested that the incidence of cardiovascular diseases might be increased [incidence rate (95% confidence interval) = 1.05 (1.02–1.08)] with low carbohydrate-high protein diet (Lagiou *et al.*, 2012). Because the incidence rates for cardiovascular diseases in cases of being overweight (BMI 25.0–29.9 kg m^{-2}) and obesity (BMI ≥ 30.0 kg m^{-2}) in the present study were approximately 1.44 (1.27–1.64) and 2.48 (2.09–2.94), weight reduction by a protein-rich diet might be considered as a risk reduction.

Another study including insulin-treated patients with type 2 diabetes was conducted in Norway (Aas *et al.*, 2005). Patients with oral antidiabetic medication and poor glycaemic control were randomised into three

groups: the first group only received lifestyle intervention, the second group received lifestyle intervention and insulin therapy, and the third group was treated with insulin. In all three groups, there was a comparable reduction of HbA1c, although the lifestyle intervention group showed a weight loss of 3.0 (4.0) kg, whereas the other two groups had gained 3.5 (3.4) and 4.9 (6.9) kg. This shows that weight gain could not be avoided during insulin therapy, even with lifestyle intervention. In a second study from England, type 2 diabetes patients were randomised into a lifestyle intervention group and a group with routine treatment immediately after start of insulin therapy (Barratt *et al.*, 2008). After 6 months, both groups demonstrated a comparable improvement of HbA1c but a significant weight gain of 4.9 (3.6) kg in the control group. The intervention group reduced their weight by 0.6 (5.1) kg; however, an intensive diet and motivation regimen and an energy reduction of 2093 kJ day^{-1} was necessary.

The present study has shown a rapid decrease of insulin requirement as a result of PRMR even before a substantial weight loss occurred. This means that mechanisms other than just weight reduction appear to be responsible for the increase in insulin sensitivity. Similar observations have been made for bariatric procedures because insulin doses can often be drastically reduced a few days after surgery (Kashyap *et al.*, 2010). It might be assumed that the secretion of incretin hormones changes. The amount of energy used in the present study, 4600–5300 kJ, falls in the area of a slightly hypocaloric diet. In this context, a recently published study showed that strict energy restriction to 2512 kJ day^{-1} can normalise beta cell function and insulin resistance, demonstrating that the disease is reversible (Lim *et al.*, 2011). However, those diets are hard to apply practically, as indicated by the drop-out rate of 27% for that study, as well as of 26% for another study with a challenging diet regimen (Aas *et al.*, 2005). The drop-out rate of 32% for our study also indicates that changes in diet, even if they are short-term, appear to be harder to apply for the patients than injecting high doses of insulin and achieving insufficient metabolic adjustment.

The present study is limited by the lack of a control group. The purpose of a control group is to discover which part of the success that was achieved is really a result of the intervention, and which is only a result of the better supervision of patients. The present study included patients who had already received intensive treatment during the months before the start of the study as a result of their intensified insulin therapy. The magnitude of insulin reduction (two patients even stopped insulin therapy) and metabolic improvement, as well as their maintenance for 1.5 years after study end, was surely greater than a potential placebo effect. Moreover, participants who continued to use PRMR after study end could be used as an internal control for the follow-up. The comparison with those participants who continued PRMR use also indicates that the effect goes beyond a mere placebo effect.

Type 2 diabetes patients with intensified insulin therapy significantly reduced insulin requirement, HbA1c and weight by using PRMR for 12 weeks. Therefore, PRMR may be an option for patients with poor glycaemic control despite intensified insulin therapy. However, the continuous use of PRMR appears to be necessary for long-term success.

Conflict of interests, source of funding and authorship

P. Schadewaldt has no conflicts of interest concerning this manuscript.

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NCS, RK and SM conceived and designed the study. NCS, BG, PS and SM performed the data collection. KK analysed and interpretated the data. KK drafted the manuscript. KK, NCS, BG, RK, PS and SM approved the final version of the manuscript submitted for publication.

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