Efficacy of the Telemedical Lifestyle intervention Program TeLiPro in Advanced Stages of Type 2 Diabetes: A Randomized Controlled Trial

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OBJECTIVE

Lifestyle interventions are the foundation of treatment in newly diagnosed type 2 diabetes. However, their therapeutic potential in advanced disease stages is unknown. We evaluated the efficacy of the Telemedical Lifestyle intervention Program (TeLiPro) in improving metabolic control in advanced-stage type 2 diabetes.

RESEARCH DESIGN AND METHODS

In this single-blind, active comparator, intervention study, patients with type 2 diabetes (with glycated hemoglobin [HbA_{1c}] ≥7.5% [58.5 mmol/mol]), and BMI ≥27 kg/m^2 and on ≥2 antidiabetes medications) were recruited in Germany and randomized 1:1 using an electronically generated random list and sealed envelopes into two parallel groups. The data analyst was blinded after assignment. The control group (n = 100) got weighing scales and step counters and remained in routine care. The TeLiPro group (n = 102) additionally received telemedical coaching including medical-mental motivation, a formula diet, and self-monitored blood glucose for 12 weeks. The primary end point was the estimated treatment difference in HbA_{1c} reduction after 12 weeks. All available values per patient (n = 202) were analyzed. Analyses were also performed at 26 and 52 weeks of follow-up.

RESULTS

HbA_{1c} reduction was significantly higher in the TeLiPro group (mean ± SD −1.1 ± 1.2% vs. −0.2 ± 0.8%; P < 0.0001). The estimated treatment difference in the fully adjusted model was 0.8% (95% CI 1.1; 0.5) (P < 0.0001). Treatment superiority of TeLiPro was maintained during follow-up (week 26: 0.6% [95% CI 1.0; 0.3], P = 0.0001; week 52: 0.6% [0.9; 0.2], P < 0.001). The same applies for secondary outcomes: weight (TeLiPro −6.2 ± 4.6 kg vs. control −1.0 ± 3.4 kg), BMI (−2.1 ± 1.5 kg/m^2 vs. −0.3 ± 1.1 kg/m^2), systolic blood pressure (−5.7 ± 15.3 mmHg vs. −1.6 ± 13.8 mmHg), 10-year cardiovascular disease risk, antidiabetes medication, and quality of life and eating behavior (P < 0.01 for all). The effects were maintained long-term. No adverse events were reported.

CONCLUSIONS

In advanced-stage type 2 diabetes, TeLiPro can improve glycemic control and may offer new options to avoid pharmacological intensification.

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An increased risk for the development of type 2 diabetes mellitus is associated with a high-caloric diet and lack of physical activity. During the prediabetes stages, lifestyle interventions can prevent or delay the development of the disease (1,2). Furthermore, after the onset of type 2 diabetes, nonpharmacological lifestyle interventions can potentially delay the introduction of pharmacological antidiabetes therapy, reduce the dose of antidiabetes drugs, or even induce remission of the disease (3–6). In the UK Prospective Diabetes Study (UKPDS), one-third of newly diagnosed patients no longer met the fasting plasma glucose inclusion criteria after 3 months of diet treatment (7). However, most lifestyle intervention studies have only included patients in the early stages of type 2 diabetes. In the more advanced stages of the disease, significant improvements in metabolic control have only been demonstrated with bariatric surgery (8).

The Telemedical Lifestyle intervention Program (TeLiPro) is a newly developed 12-week multimodal approach that combines telemonitoring, telemedical coaching, a structured lifestyle intervention program including dietary intervention with a protein-rich meal replacement (PRMR) therapy, self-monitoring of blood glucose, and evaluated mental motivational training (9–11). This telemedical approach allows patients to remain in the routine care of their attending physician. To evaluate the potential impact of TeLiPro on metabolic control in advanced disease stages, we enrolled patients with poorly controlled type 2 diabetes receiving at least two different antidiabetes drugs into a randomized controlled trial. We tested the hypothesis that participation in TeLiPro would be associated with reductions in glycated hemoglobin (HbA_{1c}), body weight and composition, cardiovascular disease (CVD) risk factors, and antidiabetes medication use and improvements in quality of life and eating behavior.

RESEARCH DESIGN AND METHODS

Study Design

This was a randomized, single-blind, active-comparator controlled, intervention trial with two parallel groups. The first participant was enrolled on 20 February 2014; the last participant finished the 52-week follow-up on 16 December 2015. The study was conducted at the West-German Centre of Diabetes and Health in Düsseldorf, Germany, in cooperation with the German Institute for Telemedicine and *Healthpromotion*. The study was conducted in compliance with the principles of the Declaration of Helsinki (1964) and in accordance with Good Clinical Practice guidelines as defined by the International Conference on Harmonization. Approval of the research protocol and any amendments was obtained from the ethics committee of the Ärztekammer Nordrhein (approval no. 2011294). All participants gave written informed consent prior to inclusion into the study. The study is registered on ClinicalTrials.gov (NCT02066831).

Study Population

Patients with type 2 diabetes who were overweight or obese were recruited in Germany via attending physicians or newspaper articles. Male or female patients were eligible if they were between 25 and 79 years of age, had insufficient glycemic control ($HbA_{1c} \geq 7.5\%$ (58.5 mmol/mol)), had a BMI ≥ 27 kg/m^2, and were being treated with at least two different antidiabetes drugs. The exclusion criteria were acute infections, chronic diseases other than type 2 diabetes and hypertension (e.g., cancer, chronic obstructive pulmonary disease, asthma, dementia, chronic gut diseases, psychoses, liver cirrhosis, macronephropathy/nephropathy, kidney insufficiency with glomerular filtration rate <30 ml/min/1.73 m^2), smoking cessation for <3 months and/or planned smoking cessation during study, weight-influencing medication, pregnancy or breast-feeding, known intolerance of any ingredient of the PRMR, and acute chemotherapy or chronic cortisol treatment.

Randomization and Masking

Participants were randomized in a 1:1 ratio using an electronically generated random list (created by trial statistician) into two parallel groups (assigned by study nurse). In detail, each participant was assigned a serial study identification number. For each identification number, there was a closed envelope with the group assignment. The allocation sequence was concealed from the participants, the study nurse, and the outcome assessor. The data analyst was blinded after assignment to the interventions.

Procedures and Interventions

Participants in both groups received a self-management guide, a weighing scale, and a step counter; the TeLiPro group additionally received a blood glucose meter (HMM Holding AG, Dossenheim, Germany). The participants were advised to measure their steps and weight daily. The devices automatically collected, reported, and transferred the measured data into a personalized online portal. By logging in (using a username and password) the participants could monitor the course of their personal weight and step counts, but the system itself did not give any suggestions. The control subjects remained in routine care (quarterly visits with their attending physician for routine health care visits as defined by the Disease Management Programs [DMP] for Type 2 Diabetes in Germany). For the first 12 weeks, the TeLiPro group received dietary intervention to achieve an initial weight reduction (PRMR; Almased-Vitalkost, Almased Wellness GmbH, Bienenbüttel, Germany) and weekly care calls (planned duration 20 min) from trained diabetes coaches. Care calls included information about type 2 diabetes, antidiabetes medication, healthy diet, physical activity, and subjective possibilities for lifestyle changes. Furthermore, measured data were discussed during these calls and participants were encouraged using medical-mental motivation techniques, and target agreements (i.e., behavioral changes concerning physical activity and eating) were fixed (11).

Health parameters (including laboratory variables, weight, BMI, and blood pressure) were measured by the attending physician at baseline, after 12 weeks of intervention, and after 26 and 52 weeks of follow-up. Values at 12 weeks before study entry were derived from medical records. Body weight was measured in light clothing to the nearest 0.1 kg, height to the nearest 0.5 cm, and waist circumference at the minimum abdominal girth (midway between the rib cage and the iliac crest). Blood pressure on both arms was determined using a mean of two measurements after a 5-min rest in a sitting position. Venous blood was collected by inserting an intravenous cannula into the forearm vein after an overnight fast and cessation of medication for at least 10 h. Laboratory variables (HbA_{1c}, fasting blood glucose, total cholesterol, HDL and LDL cholesterol, and triglycerides) were analyzed at local laboratories. Validated self-reporting questionnaires were used to assess quality of life (12-Item

Short-Form Survey [SF-23] and the German version of the Center for Epidemiological Studies-Depression [CES-D] Scale) and eating behavior (German version of the Three-factor Eating Questionnaire [TFEQ]) (12–14). Antidiabetes medication and changes throughout the study were documented, and the medication effect score (MES) based on the potency and dosage of antidiabetes medication was calculated (15). Ten-year CVD risk was assessed according to Framingham Risk Score (16).

Diet Regimen

During the first week of the study, the TeLiPro group replaced breakfast, lunch, and dinner with 1 g PRMR/kg normal body wt (defined as height in cm − 100) per meal (dissolved in 250 mL water) and consumed 45 g oil rich in n-3 fatty acids and 750 mL vegetable juice each day. No additional snacks were permitted. During weeks 2–4, breakfast and dinner were replaced by PRMR, and a low-carbohydrate protein-rich lunch was allowed. This lunch included 150–200 g fish or meat, 500 g vegetables, and not more than 50 g carbohydrates from whole grain bread or brown rice. During weeks 5–12, only dinner was replaced with PRMR (9).

Outcomes

The primary end point was the difference in the change from baseline at week 12 in HbA_{1c} between the two groups. Secondary end points were differences in body weight and composition, antidiabetes medication, CVD risk factors and 10-year CVD risk, quality of life, and eating behavior between the two groups. Adverse events were documented.

Statistical Analysis

Previous data have indicated that a reduction in HbA_{1c} of 0.7% could be achieved using PRMR, whereas an HbA_{1c} reduction of 0.2% was assumed for the control group (9). At least 83 data sets were required to detect these HbA_{1c} reductions with a power of 90% and a level of significance of 5%. Therefore, 100 participants per group were recruited, assuming a drop-out rate of ~20%.

Primary outcome was the estimated treatment difference in HbA_{1c} reduction after 12 weeks between groups (TeLiPro vs. control). It was analyzed using several adjustment models: model 1 = mixed model adjusted for repeated measurements, model 2 = model 1 + adjustment for potential confounders (i.e., sex, age, diabetes duration, and baseline values of excess weight, BMI, fasting blood glucose, and systolic and diastolic blood pressure), model 3 = model 2 + adjustment for HbA_{1c} at time point −12, and model 4 = model 2 + adjustment for HbA_{1c} at time point 0 (baseline). For secondary outcomes, changes from baseline at each time point were evaluated using the Friedman plus Dunn's multiple comparison test, and the between-group differences were compared using the Mann-Whitney test. Dichotomous variables were compared using the Fisher exact test. The Bonferroni correction was used for multiple testing.

If not otherwise stated, all available values per patient (n = 202) were used for the analyses. Single missing values of participants who completed the study were imputed using a last-observation-carried-forward (LOCF) approach. For the intention-to-treat analyses, missing values due to drop-out or loss to follow up were imputed using the following methods: *1*) missing values simulated based on the mean of each group at each time point, and *2*) the lower limit of the 95% CI for the control group versus the upper limit for the TeLiPro group.

The level of significance (α) was 0.05. Data were analyzed using GraphPad Prism, version 6.04 (GraphPad Software, San Diego, CA), and SAS statistical package, version 9.3 (SAS Institute, Cary, NC). The interim analysis after the 12-week intervention demonstrated superiority of the TeLiPro treatments (17).

RESULTS

A total of 202 patients were randomized into the control (n = 100) or TeLiPro (n = 102) (Supplementary Fig. 1) group. Mean duration of care calls in the TeLiPro group was 17 min (range 12–30). Overall, 74 (74%) participants in the control group and 93 (91%) participants in the TeLiPro group completed 12 weeks of intervention; the drop-out rate in the control group was significantly higher than in the TeLiPro group (P = 0.001). For the control and TeLiPro groups, follow-up data were available for 66 and 82 participants after 26 weeks and for 56 and 77 participants after 52 weeks (Supplementary Fig. 1). Baseline characteristics were similar between the two study groups (Table 1) and did not differ significantly between participants who completed the intervention phase and those who dropped out (Supplementary Table 1).

After the intervention phase, only in the TeLiPro group was a significant reduction of mean HbA_{1c} observed (Fig. 1*A*). At 12 weeks, mean HbA_{1c} was reduced by 1.1 ± 1.2% (from 8.4% [68.3 mmol/mol] ± 1.3% to 7.3% [56.3 mmol/mol] ± 1.1%) (Tables 1 and 2) in the TeLiPro group ($P <$ 0.0001) and by 0.2 ± 0.8% (from 8.2% [66.1 mmol/mol] ± 1.2% to 8.0% [63.9 mmol/mol] ± 1.3%) in the control group. The estimated treatment difference in the fully adjusted model (TeLiPro vs. control) was 0.8% (95% CI 1.1; 0.5); $P <$ 0.0001 (Table 3). Treatment superiority of TeLiPro was maintained until 52 weeks of follow-up (at week 26: 0.6% [95% CI 1.0; 0.3]; P = 0.0001; at week 52: 0.6% [0.9; 0.2]; $P <$ 0.001). All sensitivity analyses confirmed this result (Table 3).

In the TeLiPro group, further significant improvements in fasting blood glucose, body weight, BMI, blood pressure, CVD risk factors, quality of life, eating behavior, and antidiabetes medication were observed after 12 weeks of intervention (Table 1). These improvements were maintained until 52 weeks of follow-up (Table 1). No significant changes were seen in the control group (Table 1). Differences between the groups in the changes from baseline at 12 weeks demonstrated significant higher effects in the TeLiPro group compared with the control group (Table 2), with a reduction of 6.2 ± 4.6 kg body wt ($P <$ 0.0001) (Fig. 1*B*), 2.1 ± 1.5 kg/m^2 BMI ($P <$ 0.0001) (Fig. 1*C*), 5.7 ± 15.3 mmHg systolic blood pressure (P = 0.0006) (Fig. 1*D*), 3.4 ± 9.5 mmHg diastolic blood pressure (P = 0.02), and 0.9 ± 1.7% 10-year CVD risk (P = 0.0007). Physical health significantly improved ($P <$ 0.0001), and impairment of quality of life decreased ($P <$ 0.0001) in the TeLiPro group versus the control group at 12 weeks (Table 2). Eating behavior improved as indicated by the increase of cognitive control (P = 0.0002) and reduction in suggestibility (P = 0.002) and hunger (P = 0.0006) (Fig. 1*E*). Medication demand for antidiabetes drugs, measured using MES, was significantly reduced ($P <$ 0.0001), with 53% of participants achieving a reduction of at least 20% in MES and a reduction of almost 50% in insulin demand ($P <$ 0.0001)

Table 1—Glycemic control, body weight and composition, CVD risk factors, physical activity, quality of life, eating behavior, and antidiabetes medication

	Control group (n = 74)	TeLiPro group (n = 93)
Male/female sex	39 (53)/35 (47)	51 (55)/42 (45)
Age (years)	60 ± 8	59 ± 9
Diabetes duration (years)	11 ± 8	11 ± 7

	Control group (n = 74)					TeLiPro group (n = 93)				
	−12 weeks	0 weeks	12 wees	26 weeks	52 weeks	−12 weeks	0 weeks	12 weeks	26 weeks	52 weeks
Glycemic control										
HbA_{1c}, % (mmol/mol)	8.4 ± 1.4 (68.3)	8.2 ± 1.2 (66.1)	8.0 ± 1.3 (63.9)	8.1 ± 1.2 (65.0)	8.2 ± 1.3 (66.1)	8.5 ± 1.4 (69.4)	8.4 ± 1.3 (68.3)	7.3 ± 1.1 (56.3) ****	7.5 ± 1.3 (58.5) ****	7.6 ± 1.2 (59.6) ****
FBG (mg/dL)	185 ± 66	179 ± 54	174 ± 60	171 ± 56	173 ± 67	168 ± 55	168 ± 54	147 ± 46*	147 ± 47**	152 ± 42
Body weight and composition										
Body weight (kg)	111.6 ± 21.0	110.8 ± 21.1	109.8 ± 20.7	109.7 ± 20.1	109.4 ± 20.3*	104.0 ± 19.6	104.3 ± 19.4	98.1 ± 19.1****	97.6 ± 19.2****	97.8 ± 19.2****
Excess body weight (kg)†	38.5 ± 19.5	37.7 ± 19.7	36.7 ± 19.4	36.5 ± 18.9	36.2 ± 19.2*	32.3 ± 17.2	32.6 ± 17.0	26.5 ± 17.0****	26.0 ± 17.5****	26.1 ± 17.5****
BMI (kg/m^2)	37.3 ± 6.6	37.0 ± 6.7	36.7 ± 6.6	36.6 ± 6.5	36.5 ± 6.5*	35.2 ± 6.0	35.3 ± 5.9	33.3 ± 6.0****	33.1 ± 6.1****	33.2 ± 6.1****
CVD risk factors and 10-year CVD risk										
Systolic BP (mmHg)	134 ± 12	134 ± 13	135 ± 12	134 ± 12	133 ± 12	139 ± 16	139 ± 16	133 ± 15*	133 ± 14***	136 ± 17
Diastolic BP (mmHg)	81 ± 9	81 ± 9	80 ± 10	79 ± 9	79 ± 9	83 ± 9	93 ± 10	80 ± 9	80 ± 8	80 ± 10
Total cholesterol (mg/dL)	196 ± 48	194 ± 48	191 ± 46	190 ± 46	189 ± 45	193 ± 45	195 ± 45	187 ± 41	190 ± 41	192 ± 41
HDL cholesterol (mg/dL)	47 ± 11	47 ± 11	48 ± 12	47 ± 13	47 ± 13	46 ± 12	46 ± 12	47 ± 13	48 ± 12	48 ± 13
LDL cholesterol (mg/dL)	115 ± 38	117 ± 36	116 ± 37	115 ± 36	114 ± 36	115 ± 41	115 ± 40	112 ± 36	114 ± 38	117 ± 45
Triglycerides (mg/dL)	192 (139–255)	194 (144–232)	182 (144–225)	182 (143–225)	186 (137–228)	187 (131–250)	197 (132–261)	173 (106–235)**	174 (114–236)**	186 (115–253)
10-year CVD risk (%)‡	15.5 ± 3.3	15.4 ± 3.6	15.3 ± 3.5	15.2 ± 3.7	15.5 ± 3.9	16.4 ± 3.5	16.4 ± 3.6	15.6 ± 3.9***	15.5 ± 3.6***	16.0 ± 4.2
QoL and eating behavior										
Physical health (au)§	nd	41 ± 12	42 ± 12	43 ± 12	43 ± 12	nd	43 ± 11	48 ± 10****	48 ± 10****	46 ± 11***
Mental health (au)§	nd	38 ± 5	39 ± 6	38 ± 6	38 ± 6	nd	38 ± 6	38 ± 5	39 ± 5	39 ± 6
Impairment of QoL (au)‖	nd	14 ± 9	15 ± 11	16 ± 11	16 ± 11	nd	15 ± 9	12 ± 9***	11 ± 8****	15 ± 10
Depression‖	nd	10 (14)	16 (22)	16 (22)	16 (22)	nd	17 (18)	10 (11)	9 (10)*	15 (16)
Cognitive control (au)¶	nd	7.2 ± 3.6	8.1 ± 4.2	7.8 ± 4.0	7.7 ± 3.9	nd	6.9 ± 2.9	9.4 ± 3.5****	9.5 ± 3.5****	9.0 ± 3.4***
Suggestibility (au)¶	nd	5.3 ± 3.4	4.9 ± 3.2	4.8 ± 3.0	4.9 ± 3.1	nd	5.8 ± 3.0	4.4 ± 3.0****	4.4 ± 3.0****	4.7 ± 3.3***
Hunger (au)¶	nd	5.6 ± 3.2	4.8 ± 2.9	5.1 ± 2.9	5.3 ± 3.0	nd	6.7 ± 3.1	4.6 ± 3.2****	4.3 ± 3.1****	4.6 ± 3.4****
Antidiabetes medication										
MES (au)	nd	3.2 ± 4.9	2.5 ± 1.5	2.·5 ± 1.4	2.4 ± 1.3	nd	3.1 ± 4.1	2.1 ± 2.2****	2.1 ± 2.2****	2.1 ± 2.2****
Metformin	nd	66 (89)	66 (89)	64 (86)	66 (89)	nd	84 (90)	81 (87)	81 (87)	80 (86)
DPP-4 inhibitors	nd	25 (34)	25 (34)	24 (32)	20 (27)	nd	41 (44)	38 (41)	39 (42)	40 (43)
GLP-1 analogs	nd	16 (22)	14 (19)	14 (19)	13 (18)	nd	13 (14)	11 (12)	11 (12)	9 (10)
Sulfonylurea	nd	10 (14)	9 (12)	9 (12)	6 (8)	nd	19 (20)	5 (5)	7 (8)	6 (6)
SGLT2 inhibitors	nd	5 (7)	5 (7)	5 (7)	4 (5)	nd	9 (10)	6 (6)	7 (8)	8 (9)
Glinides	nd	4 (5)	4 (5)	3 (4)	1 (1)	nd	6 (6)	1 (1)	2 (2)	2 (2)

Continued on p. 5

Table 1—Continued

	Control group (n = 74)					TeLiPro group (n = 93)				
	−12 weeks	0 weeks	12 weeks	26 weeks	52 weeks	−12 weeks	0 weeks	12 weeks	26 weeks	52 weeks
Glitazones	nd	1 (1)	1 (1)	0 (0)	0 (0)	nd	1 (1)	1 (1)	1 (1)	1 (1)
Insulin therapy	nd	56 (76)	54 (73)	54 (73)	54 (73)	nd	62 (67)	51 (55)*	54 (58)*	54 (58)*
Insulin use (units/day)	nd	52 ± 51	48 ± 47	51 ± 48	50 ± 47	nd	43 ± 45	22 ± 27****	24 ± 29****	26 ± 30***

Data are means ± SD, median (interquartile range), or n (%). Between-group differences were analyzed by the Mann-Whitney test, and within-group differences over time were determined using the Friedman plus Dunn's multiple comparison test. Dichotomous variables were analyzed using the Fisher exact test. au, arbitrary units; BP, blood pressure; DPP-4, dipeptidyl peptidase-4; FBG, fasting blood glucose; nd, not determined; QoL, quality of life; SGLT2, sodium-glucose cotransporter 2. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$. †Excess weight was determined as the difference between body weight and normal weight (normal weight [in kg] = height [cm] − 100). ‡Determined using SF-12 (12). §Determined using the German version of the CES-D (13). ‖Determined using the German version of the TFEQ (14). ¶According to Framingham Risk Score (16).

(Fig. 1*F* and Table 2). These differences remained stable during 52 weeks of follow-up, and no sex-specific effects were observed.

CONCLUSIONS

Our study shows that in patients with advanced stages of type 2 diabetes, metabolic control can be significantly improved by lifestyle intervention. Patients in the TeLiPro group achieved significantly greater reductions in HbA_{1c}, body weight, blood pressure, and other CVD risk factors compared with a control group who did not receive telemedical coaching and remained in routine medical care. The TeLiPro group reported a significant improvement in quality of life and a beneficial change in eating behavior. The improvement in metabolic control was achieved in conjunction with a concomitant decrease in the demand for antidiabetes medication.

The increasing prevalence of type 2 diabetes and the concomitant increase in antidiabetes medication costs are a considerable burden for national health care systems (18,19). Consequently, there is a strong need for alternative lifestyle-based therapeutic approaches. The Look AHEAD (Action for Health in Diabetes) study demonstrated clearly that in the early stages of type 2 diabetes significant improvements in HbA_{1c} and reductions in antidiabetes medication can be achieved with lifestyle intervention (4). TeLiPro combines five components including telemonitoring, telemedical coaching, medical-mental motivation, PRMR, and self-monitoring of blood glucose in a supraregional 12-week intervention program, which can be implemented alongside the standard care provided by general practitioners or diabetologists. The effectiveness of each single component has been previously shown in independent trials (9–11).

The reduction in HbA_{1c} in the TeLiPro group (–1.1% after 12 weeks, –0.9% after 26 weeks, and –0.7% after 52 weeks) is comparable with the therapeutic efficacy of new antidiabetes medications. Two studies of glucagon-like peptide (GLP)-1 receptor agonists either alone or in a fixed combination with the insulin degludec, which included patients with a duration of diabetes similar to that of participants in the current study, reported HbA_{1c} reductions of 0.8% (exenatide), 1.1% (liraglutide), and 1.9% (insulin degludec plus liraglutide [IdegLira]) after 26 weeks of intervention (20,21). In the Liraglutide Effect and Action in Diabetes (LEAD)-6 trial, an HbA_{1c} target of $<$7.0% (53.0 mmol/mol) was achieved by 43% of the exenatide-treated participants and 54% of the liraglutide-treated participants (21), whereas this proportion was 45% after the TeLiPro intervention. However, in the present trial, the decrease in HbA_{1c} was achieved during only 12 weeks of intervention, even though the use of antidiabetes medication was significantly reduced, whereas in the aforementioned drug trials (20,21), the antidiabetes drugs were used continuously for 26 weeks. In addition, while GLP-1 receptor agonists can reduce body weight (–2.7 kg with IDegLira, –2.9 kg with exenatide, and –3.2 kg with liraglutide) (20,21), the TeLiPro program was associated with greater reductions in body weight (–6.1 kg after 12, –6.7 kg after 26, and –6.5 kg after 52 weeks). The combination of TeLiPro and antidiabetes medication with potential for body weight reduction may be the next step for blood glucose and weight control in the studied population.

The intervention in TeLiPro was well tolerated. The drop-out rate in the TeLiPro group during intervention was 9%, and overall no adverse events were reported. Because blood glucose values were telemetrically transferred to the health coaches, the dose of antidiabetes medication was immediately adjusted; consequently, no hypoglycemic events were reported, whereas hypoglycemia incidence ranged from 24 to 34% in antidiabetes medication trials (20,21). The telemedical approach is associated with benefits in terms of cost-effectiveness. The total cost for 12 weeks of TeLiPro intervention and follow-up until week 26 was $1,300 per patient, with a concomitant 50% reduction in the use of antidiabetes medication. The annual drug cost for GLP-1 receptor agonist therapies is between $1,765 and $6,338 (22,23).

In contrast to other intervention trials, the underlying dietary intervention in TeLiPro is believed to reduce carbohydrate supply by using an initial PRMR. Furthermore, patients in the TeLiPro were encouraged to increase their intake of unsaturated lipids. These dietary interventions have been shown to successfully prevent the development of type 2 diabetes and delay the introduction of

pharmacological treatment in newly diagnosed type 2 diabetes (3,24). The speed of the glucose-lowering effect using the TeLiPro approach was comparable with that observed after bariatric surgery (25).

The number of telemedical approaches for lifestyle alterations and chronic disease self-management programs are increasing and encouraging (26,27), although it has been shown that telephone calls alone are not sufficient to sustainably alter behavior (28). Therefore, the TeLiPro combines different interventions; this multifactorial approach does not allow dissection of the effect of the individual components. The initial step of dietary intervention with meal replacement to achieve a fast improvement of blood glucose levels leads to a strong motivational response and probably accounts for the main weight loss. This step was followed by telemedical education and self-monitoring to maintain motivation and improve eating behavior in the long-term. This multistep procedure was effective, as shown by the improvement in several measures of mental health and improvements in blood glucose control, which are higher than to be expected with the dietary intervention alone. However, the multifactorial approach aimed to achieve the maximum capacity of lifestyle intervention on HbA_{1c} reduction, but it would have been overestimated to expect a net additive benefit of the five lifestyle components on the HbA_{1c} reduction itself.

This study has certain strengths and limitations. The major limitation might be the

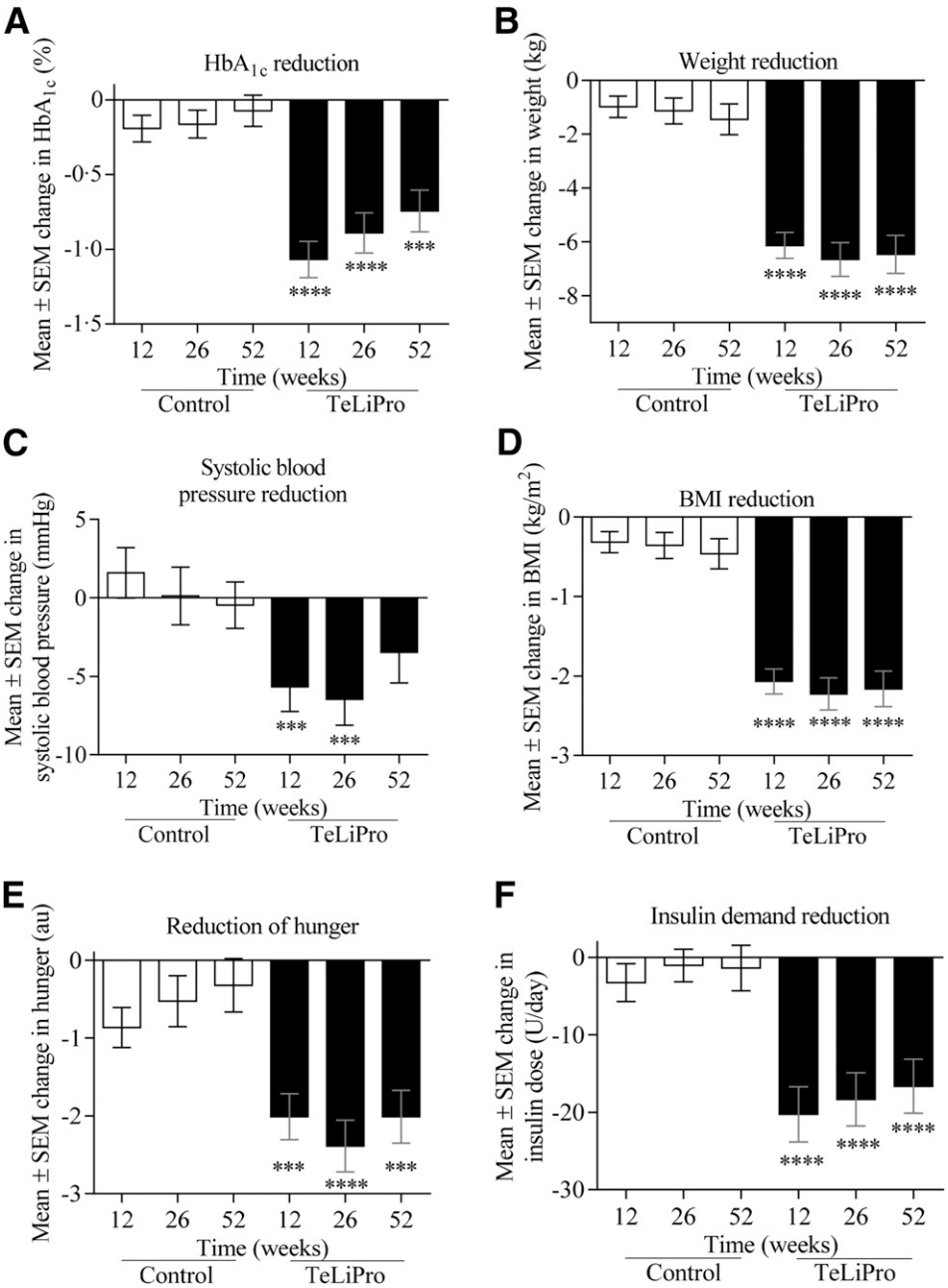

Figure 1—Metabolic effects of TeLiPro. Differences in HbA_{1c} (*A*), body weight (*B*), BMI (*C*), systolic blood pressure (*D*), hunger (*E*), and daily insulin demand (*F*) were compared between the control group ($n = 74$) and the TeLiPro group ($n = 93$) using the Mann-Whitney test. ***$P < 0.001$; ****$P < 0.0001$. U, units.

Table 2—Comparison of the differences between groups

	Control group (n = 74)			TeLiPro group (n = 93)		
	Δ (week 12)	Δ (week 26)	Δ (week 52)	Δ (week 12)	Δ (week 26)	Δ (week 52)
Glycemic control						
HbA_{1c} (%)	−0.2 ± 0.8	−0.2 ± 0.8	−0.1 ± 0.9	−1.1 ± 1.2****	−0.9 ± 1.3****	−0.7 ± 1.3***
Fasting blood glucose (mg/dL)	−5.3 ± 39.4	−8.7 ± 36.2	−17.2 ± 64.7	−21.1 ± 52.4	−21.0 ± 52.5	−24.5 ± 66.4
Body weight and composition						
Body weight (kg)	−1.0 ± 3.4	−1.1 ± 4.2	−1.4 ± 5.0	−6.1 ± 4.6****	−6.7 ± 6.1****	−6.5 ± 6.8****
BMI (kg/m^2)	−0.3 ± 1.1	−0.4 ± 1.4	−0.5 ± 1.6	−2.1 ± 1.5****	−2.2 ± 2.0****	−2.2 ± 2.2****
CVD risk factors and 10-year CVD risk						
Systolic blood pressure (mmHg)	1.6 ± 13.8	0.1 ± 15.9	−0.5 ± 12.8	−5.7 ± 15.3***	−6.5 ± 16.0***	−3.5 ± 18.4
Diastolic blood pressure (mmHg)	−0.4 ± 7.6	−1.4 ± 9.1	−1.7 ± 9.3	−3.4 ± 9.5*	−3.5 ± 9.6	−2.9 ± 11.5
Total cholesterol (mg/dL)	−2.6 ± 19.2	−4.3 ± 27.1	−4.8 ± 29.5	−7.8 ± 25.2	−5.1 ± 31.2	−2.7 ± 26.8
HDL cholesterol (mg/dL)	0.8 ± 7.6	0.4 ± 8.7	0.4 ± 8.9	1.0 ± 5.7	1.8 ± 6.5	2.5 ± 6.8
LDL cholesterol (mg/dL)	−0.9 ± 14.0	−2.0 ± 16.4	−3.3 ± 17.6	−3.0 ± 17.6	−0.9 ± 22.7	1.7 ± 30.4
Triglycerides (mg/dL)	−4.7 ± 93.9	−5.9 ± 90.0	−6.7 ± 85.4	−24.4 ± 90.1	−27.5 ± 91.6	−18.1 ± 126.2
10-year CVD risk (%)†	−0.1 ± 1.6	−0.2 ± 1.9	0.1 ± 2.2	−0.9 ± 1.7***	−0.9 ± 2.0**	−0.4 ± 2.5
Quality of life and eating behavior						
Physical health (au)‡	0.8 ± 6.0	1.3 ± 7.2	2.0 ± 11.1	5.3 ± 8.6****	5.2 ± 9.0**	3.3 ± 11.9
Mental health (au)‡	0.9 ± 5.8	−0.2 ± 6.6	−0.2 ± 6.5	0.1 ± 6.3	0.5 ± 6.3	0.9 ± 7.8
Impairment of quality of life (au)§	0.9 ± 7.3	1.6 ± 8.1	1.7 ± 8.8	−3.7 ± 7.1****	−3.9 ± 7.7****	−0.7 ± 9.2*
Cognitive control (au)‖	0.8 ± 2.7	0.6 ± 3.1	0.5 ± 2.7	2.5 ± 3.4***	2.6 ± 3.3***	2.2 ± 3.2***
Suggestibility (au)‖	−0.4 ± 2.0	−0.5 ± 2.3	−0.4 ± 2.1	−1.4 ± 2.3**	−1.5 ± 2.2***	−1.2 ± 2.4**
Hunger (au)‖	−0.9 ± 2.2	−0.5 ± 2.8	−0.3 ± 3.0	−2.0 ± 2.8***	−2.4 ± 3.2****	−2.0 ± 3.3***
Antidiabetes medication						
MES (au)	−0.7 ± 4.9	−0.7 ± 4.9	−0.8 ± 4.9	−1.0 ± 3.6****	−1.0 ± 3.6****	−1.0 ± 3.7***
20% decrease in MES	8 (11)	13 (18)	17 (23)	49 (53)****	47 (51)****	44 (47)**
Insulin use (units/day)	−3.3 ± 21.1	−1.0 ± 18.2	−1.4 ± 25.2	−20.3 ± 34.2****	−18.3 ± 33.2****	−16.6 ± 33.6****

Data are means ± SD or n (%). Δ values represent values at weeks 12, 26, or 52 minus values at week 0 and were compared between the groups using the Mann-Whitney test. Dichotomous variables were analyzed using the Fisher exact test. au, arbitrary units. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$. †Determined using SF-12 (12). ‡Determined using the German version of the CES-D (13). §Determined using the German version of the TFEQ (14). ‖According to Framingham Risk Score (16).

drop-out rate in the control group. While during the 12 weeks of intervention only 9% of the TeLiPro group dropped out, the drop-out rate in the control group was 26%. The overall feedback of the dropouts in the control group was that they did not perceive any benefit in glucometabolic control during the study and therefore they refused further participation. Therefore, imputation of missing data based on the LOCF principle seems to be a conservative approach. Nevertheless, for the intention-to-treat analysis we also simulated the missing HbA_{1c} values based on the mean of the completers and a model with superior estimations for the control group. Since the sensitivity analyses of all imputation models demonstrate superiority of the TeLiPro group, the high drop-out rate in the control group might, rather, lead to an underestimation of the effect. Clinical variables were measured in local laboratories. However, intraindividual differences were not affected because laboratory measurements were consistently performed at the same laboratory and were reported in written form by the attending physician using the standardized DMP documentation. We did not measure the frequency or the duration of portal usage. However, participants were able to see and, if desired, note their weight, steps, and blood glucose values. The portal just visualizes the course of values over time. A strength of our study is that we included patients from routine clinical practice who were receiving medications from at least two different antidiabetes drug classes including insulin and who had a mean diabetes duration of 11 years. During the trial, patients remained in routine care with their general practitioner or diabetologist. The mean HbA_{1c} reduction was identical in those treated with oral antidiabetes medication in combination with insulin and alone. Thus, the results demonstrate that TeLiPro could be effective in patients with advanced treatment and a long duration of type 2 diabetes.

Actually, several health insurances and companies booked TeLiPro for >1,000 their insured or their staff with chronic diseases, respectively. Owing to its telemedical structure, the TeLiPro application has the potential to be scaled up extensively in order to serve a multitude of patients. In Germany, one strategy might be the combination with the existing DMP for patients with diabetes. Currently, there are >830,000 patients enrolled into these programs run by specific DMP centers. Those call centers that already service diabetes patients could use the TeLiPro application in a franchise system. The call center employees, i.e., educated diabetes nurses in general, would be empowered by a specific training program and supported by the digital TeLiPro portal solution. In other countries, dependent on the health care system, another strategy could be to enhance the usage and functionality of the portal according to the Lorig model (29,30). As a way of optimizing resources at less cost, peer mentors were installed in Diabetes Self-Management Programs (31,32) to support the clinical outcome improvements. If TeLiPro were to be integrated into routine care, long-term

Table 3—Estimated treatment difference (TeLiPro versus control) in HbA_{1c} reduction

	−12 weeks	0 weeks	12 weeks	26 weeks	52 weeks
Analysis using all available values per patient					
Model 1	0.1 (−0.3; 0.5)	0.1 (−0.2; 0.5)	−0.7 (−1.1; −0.4)****	−0.6 (−1.0; −0.2)**	−0.5 (−0.9; −0.2)**
Model 2	0.1 (−0.3; 0.5)	0.1 (−0.2; 0.5)	−0.7 (−1.0; −0.4)****	−0.6 (−0.9; −0.2)**	−0.5 (−0.9; −0.1)*
Model 3		0.1 (−0.1; 0.4)	−0.8 (−1.1; −0.5)****	−0.6 (−0.9; −0.3)***	−0.6 (−0.9; −0.2)**
Model 4			−0.8 (−1.1; −0.5)****	−0.6 (−1.0; −0.2)***	−0.6 (−1.0; −0.2)**
Intention to treat†					
Model 1	0.1 (−0.3; 0.5)	0.1 (−0.2; 0.5)	−0.7 (−1.0; −0.4)****	−0.6 (−0.9; −0.2)**	−0.5 (−0.8; −0.2)**
Model 2	0.1 (−0.3; 0.5)	0.1 (−0.2; 0.5)	−0.7 (−1.0; −0.4)****	−0.6 (−0.9; −0.2)**	−0.5 (−0.8; −0.1)**
Model 3		0.1 (−0.2; 0.4)	−0.7 (−1.0; −0.5)****	−0.6 (−0.9; −0.3)***	−0.5 (−0.8; −0.2)**
Model 4			−0.8 (−1.0; −0.6)****	−0.7 (−0.9; −0.4)****	−0.6 (−0.9; −0.3)****
Intention to treat‡					
Model 1	0.1 (−0.3; 0.5)	0.1 (−0.2; 0.5)	−0.7 (−1.0; −0.4)****	−0.6 (−0.9; −0.2)**	−0.6 (−1.0; −0.3)***
Model 2	0.1 (−0.3; 0.5)	0.2 (−0.2; 0.5)	−0.7 (−1.0; −0.4)****	−0.5 (−0.9; −0.2)**	−0.6 (−1.0; −0.3)**
Model 3		0.1 (−0.1; 0.4)	−0.7 (−1.0; −0.4)****	−0.6 (−0.9; −0.2)**	−0.6 (−1.0; −0.3)***
Model 4			−0.7 (−1.0; −0.5)****	−0.6 (−0.9; −0.3)***	−0.7 (−1.0; −0.3)****
Intention to treat§					
Model 1	0.1 (−0.3; 0.5)	0.1 (−0.2; 0.5)	−0.7 (−1.0; −0.4)****	−0.3 (−0.7; 0.1)	−0.3 (−0.7; 0.1)
Model 2	0.1 (−0.3; 0.5)	0.2 (−0.2; 0.5)	−0.7 (−1.0; −0.3)****	−0.3 (−0.7; 0.1)	−0.3 (−0.6; 0.1)
Model 3		0.1 (−0.1; 0.4)	−0.7 (−1.0; −0.4)****	−0.3 (−0.7; 0.0)	−0.3 (−0.7; 0.0)
Model 4			−0.7 (−1.0; −0.5)****	−0.4 (−0.7; −0.0)*	−0.3 (−0.7; 0.0)

Shown are model-based estimators and 95% CIs of the estimated treatment difference (TeLiPro vs. control) in HbA_{1c} reduction. Analyses were performed using several adjustment models: model 1 = mixed model adjusted for repeated measurements, model 2 = model 1 + adjustment for potential confounders (i.e., sex, age, diabetes duration, and baseline values of excess weight, BMI, fasting blood glucose, systolic and diastolic blood pressure), model 3 = model 2 + adjustment for HbA_{1c} at time point −12, model 4 = model 2 + adjustment for HbA_{1c} at time point 0 (= baseline). In the analyses, all available values per patient (n = 202) were used and for the intention-to-treat analyses missing values owing to dropout or loss to follow-up were imputed using the following methods: †LOCF principle; ‡missing values simulated based on the mean of each group at each time point; §the lower limit of the 95% CI for the control group vs. the upper limit for the TeLiPro group. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.

supervision could show whether improved clinical outcomes could be maintained and whether the development of diabetes complications could be inhibited.

Conclusion

The current study shows that TeLiPro can significantly improve HbA_{1c} levels in patients with advanced stage type 2 diabetes and poor glycemic control. Significant improvements in body weight, blood pressure, quality of life, eating behavior, and medication suggest that TeLiPro might be a new promising tool for lifestyle intervention in type 2 diabetes.

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