D8 Final report on evaluation of the changing health app in the context of a 12-week low-calorie diet

Vitality

EIT Health

Düsseldorf | 14 December 2018

Contents

1 Introduction

Type 2 diabetes affects almost one in ten adults in Germany and is a very common, chronic metabolic disease that is partly influenced by hereditary factors and environmental influences (such as obesity, lack of exercise, stress, lack of sleep, unhealthy eating habits and smoking). The development of the disease is strongly related to weight gain and obesity in adult life [1]. Ectopic fat accumulation within the liver and muscle disrupts the ability of these organs to maintain and adjust blood glucose in a physiological rage and promote disease progression [2]. The course of the disease is usually progressive, i.e. increasingly difficult to control therapeutically. Although the focus lies on multiple drug treatments to reduce blood glucose and the associated elevated risks of cardiovascular disease, weight loss is an effective measure to improve metabolic health in this cohort [3]. Moderate weight reduction by a moderately hypocaloric very-low-fat diet resulted in normalization of fasting hyperglycemia and reversal of hepatic insulin resistance in patients with poorly controlled type 2 diabetes [4]. The Diabetes Remission Clinical Trial (DiRECT) revealed that utilizing a total diet replacement by a low-energy formula diet for 3 months led to a 15 kg or more weight loss in 24% participants and diabetes remission 46% of the participants [5]. To date it remains unknown whether similar results can be achieved with a natural, non-formula based diet in connection with an educative smartphone application and telephone coaching.

1.1 Overall aim

The overall aim of the project is to assess whether induction of a negative energy balance by intensive weight management utilizing a very low calorie diet in connection with a smartphone app especially for patients with diabetes would result in remission of type 2 diabetes in patients with recently-diagnosed diabetes.

Specifically, we set out to:

- Study the usability of the Changing health platform among patients with type 2 diabetes
- Study feasibility and adherence to a smartphone-based application
- Explore potential impact of the dietary intervention on body weight and metabolism

2 Methods

2.1 Participants

In our study we included patients with type 2 diabetes, fulfilling the following inclusion criteria: Volunteers of 18 years and older with an existing type 2 diabetes diagnosis but without insulin therapy, who have a smartphone or PC for app installation and can use it and are able to communicate in German, will be recruited. Individuals will not be included in our study, when they have on or more of the following:

physical disability which leads to a considerable lack of mobility (wheelchair, walking aid, walking stick, walking stick or crutches).

2.2 Ethical approval

The study protocol with the study number 4508, Amendment 20, „Deutsche Diabetes-Studie (DDS): Phänotypisierung und Verlaufsbeobachtung von Patienten mit neu diagnostiziertem Diabetes“, substudy „Changing Health“ was approved by the ethics committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf on 17th of July 2018.

2.3 Coaching

After inclusion into the study, individuals received weekly telephone coaching calls to assist with nutrition-related questions and motivate participants to maintain their adherence. Participants uploaded their readings of their body weight on a weekly basis and further take pictures of every item they ate during the day with the camera of their smartphone. This information and the pictures of the food they consumed was uploaded to a coaching portal that the coaches used to further tailor their coaching.

2.4 Analyses

The following analyses were carried out at the point 0 weeks (before using the app) and at the end of the 12-week period of using the app:

A) Clinical chemistry analyses:

1. Basic laboratory analysis:

    a. Serum clinical chemistry: triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, creatinine, cystatin C, GOT/AST, GPT/ALT, gGT, AP, cholinesterase, CK, LDH, hsCRP, TSH, fT4, bilirubin total, urea, uric acid, amylase (total and pancreatic), lipase, ferritin, iron (Fe), total protein, electrolytes (Na, K, Ca, Cl, Mg), ethanol
    b. Coagulation status: Quick, INR, PTT;

2. Diabetes-specific hormones, glucose

a. Fasting glucose (hexokinase method), insulin total (Axsym), C-peptide, HbA1c;
b. Mixed-Meal-Tolerance-Test (MMTT) to measure meal-induced insulin secretion and incretin response. A mixed meal tolerance test (MMT) with liquid nutrient mixture Resource Protein was performed to assess ß-cell function. The test was performed by drinking 378 ml Resource Protein within 5 minutes. Blood samples are taken to determine glucose, insulin, C-peptide, glucagon, incretins, triglycerides and free fatty acids (FFA).

B) Fibroscan: a non-invasive ultrasound-based method for the evaluation of liver fibrosis

C) ^{1}H-magnetic resonance spectroscopy (MRS): an MR-based method for the non-invasive assessment of fatty liver.

2.5 Statistical analysis

All data are presented as mean with standard deviation (SD), or indicated if otherwise. All statistical analyses are performed and graphs are drawn using GraphPad Prism version 8 (GraphPad, San Diego, CA). Two-sided p-values below 0.05 were considered statistically significant.

3 Results

3.1 Participants characteristics

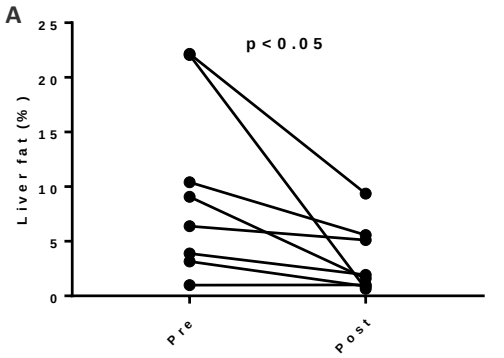
Preliminary (status 13th December 2018) baseline and follow-up characteristics of 8 participants are shown in the table below. The intervention resulted in a significant reduction in body-mass index (BMI), fasting plasma glucose and insulin sensitivity derived from oral glucose insulin sensitivity index (OGIS) with a strong trend for a reduction of glycated hemoglobin A1c (HbA1c; p=0.05).

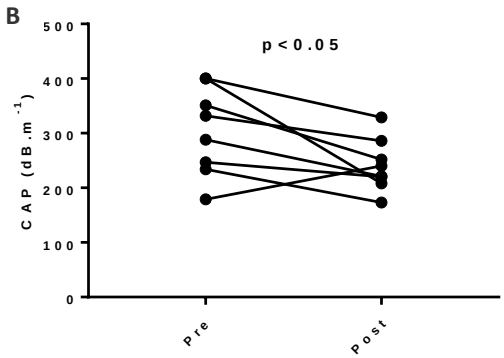
Parameter	Pre n=8	Post n=8
Age (years)	51 ± 12	52 ± 9
Sex (% female)	50	50
BMI (kg.m^{-2})	32.0 ± 4.4	29.0 ± 3.6**
Fasting plasma glucose (mg.dl^{-1})	119.7 ± 26.2	99.9 ± 16.8*
HbA1c (%; [mmol.mol^{-1}])	6.7 ± 1.3; [50 ± 14.2]	6.0 ± 0.6; [42 ± 6.6]
OGIS (ml.min^{-1}.m^{-2})	319 ± 60	355 ± 49*
Total cholesterol (mg.dl^{-1})	185 ± 52	172 ± 45
Fasting triglycerides (mg.dl^{-1})	197 ± 190	124 ± 69
Free fatty acids (µmol.l^{-1})	685 ± 352	620 ± 176

T-test for dependent samples, n=6, *p<0.05, **p<0.01 (difference pre-post); HbA1c-glycated hemoglobin A1c, OGIS-oral glucose insulin sensitivity index

3.2 Effects on liver fat content

The very-low calorie diet in connection with the smartphone application and regular telephone coaching lead to a significant reduction in liver fat as assessed by the gold standard method ^{1}H-MRS (Fig. 1A). The CAP-value as a proxy for liver steatosis derived from Fibroscan was significantly reduced after the intervention (Fig. 1B) while the E-value as a marker for liver fibrosis showed a strong trend for reduction (Fig. 1C).





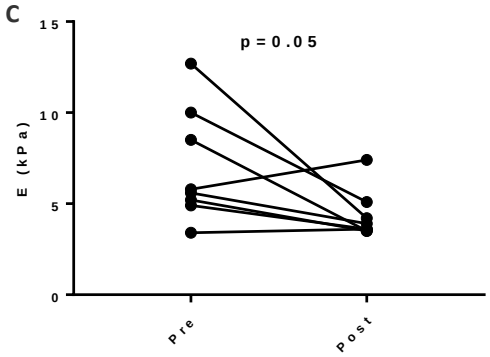
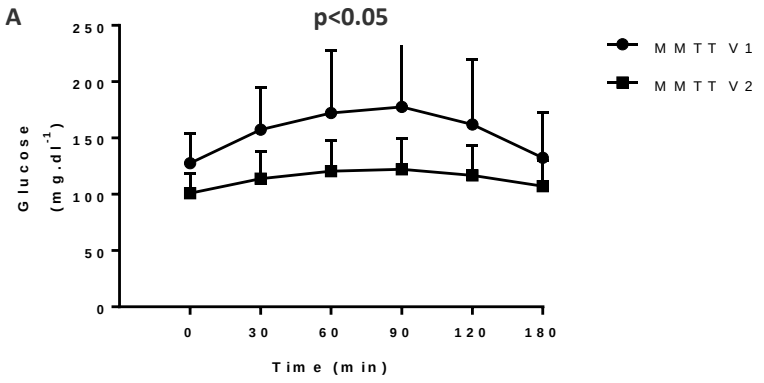


Figure 1 Liver fat from ^{1}H-MRS (A) is significantly reduced after 12 weeks of a very-low calorie diet in connection with the use of a smartphone app and telephone coaching. There is a significant reduction of the degree of steatosis indicated by the CAP value (B) from Fibroscan with a strong trend for a reduced E value (C); t-test for paired samples, n=8.

3.3 Results from the mixed-meal tolerance test

In order to assess the insulin secretory capacity and glucose metabolism, we determined areas under the curve (AUC) for glucose, C-peptide and insulin after a mixed-meal tolerance test. We find a decreased AUC for glucose and C-peptide in response to the intervention (Fig. 2A and 2B) with no differences in insulin AUC (Fig. 2C).



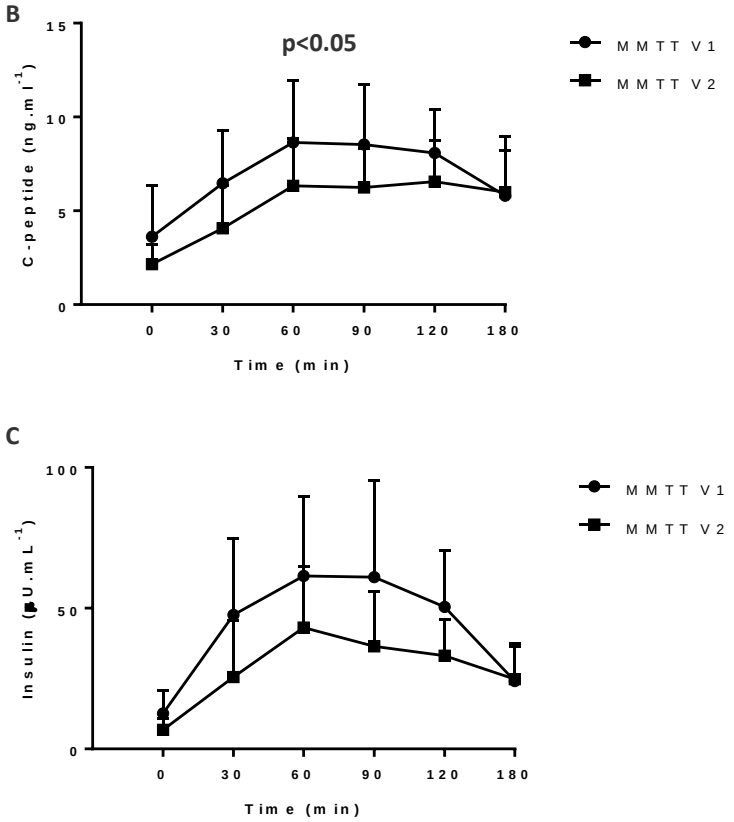


Figure 2: Mean glucose (A), C-peptide (B) and insulin (C) values over the time course of the mixed-meal tolerance test (MMTT). Area under the curve (AUC) is significantly reduced after the intervention for glucose and C-peptide but not for insulin; t-test for paired samples, n=8, V1-visit 1, V2-visit 2.

4 Discussion

Our study shows that intensive weight management utilizing a very low calorie diet in connection with a smartphone app for patients with diabetes results in marked reduction of BMI, fasting glucose, liver fat content and improvements of degree of steatosis as well as glycemic control and beta-cell function during a mixed-meal tolerance test. The results of our study show that patients with type 2 diabetes benefit from smartphone-based e-learning and telephone coaching by reducing their BMI and improvement of metabolic health. We show that smartphone application may provide a useful extension to standard care for individuals with type 2 diabetes for diabetes management.

Health interventions based on smartphone applications are promising tools to support the improvement of weight loss, diabetes care and self-management [6, 7]. Nonetheless, more evidence on the efficacy of healthcare-related applications in diabetes care is needed [7]. Our study indicates, that a combined approach of e-learning based smartphone application with remote self-monitoring for weight loss and dietary habits in combination with regular telephone coaching has the potential to induce clinically meaningful improvements of metabolic health in a cohort of patients with type 2 diabetes. Participants included in this study were obese at the time of inclusion, middle-aged and not using insulin therapy for their type 2 diabetes, which makes them a good target population for this intervention. Following the 12 week intervention, patients achieved significant weight loss, enabling them to transition from being obese to overweight (mean BMI 32 to 29 $kg.m^{-2}$). Induction of a significant negative energy balance contributed to significant loss of liver fat, likely linked to improved glucose metabolism, insulin sensitivity and beta-cell function.

Previous studies have shown that dietary and lifestyle interventions are able to achieve type 2 diabetes remission [5]. Our population was not yet on insulin therapy, which made it safe and feasible to implement a low-calorie diet without changing the baseline medication throughout the study period and minimizing the risk hypoglycemia [8].

In our study, it remains to be elucidated whether this approach could be used to maintain weight loss long term. It will most likely not be able to adhere to this approach of a very-low-calorie diet long-term, as applied during our 12-week intervention [9]. Nevertheless, after the follow-up meeting patients were informed on their basal metabolic rate and were instructed to maintain their caloric intake based on these readings in form of an adjusted, balanced low-calorie diet.

The strengths of our study relies on the well characterized metabolism of patients with type 2 diabetes [10]. Patients included in our study underwent gold-standard methods following standardized operating procedures to evaluate liver fat content, glucose metabolism and beta-cell function. A further strength of our study lies in the diagnosis of diabetes according to the American Diabetes Association Standards of Care as compared to self-reported diagnosis of diabetes used by others in a previous intervention within this project [11].

The specific metabolic features of patients with type 2 diabetes who participate in a 12-week lifestyle intervention using app-based education, dietary restriction and human coaching should raise clinical awareness as these patients will benefit from said intervention by improving key metabolic features contributing to development and progression of type 2 diabetes. We could show that metabolic parameters improved even in well-controlled patients with diabetes (mean HbA1c <7%) [11, 12].

Taken together, our study shows that intensive weight management employing a very low calorie diet together with a smartphone app for patients with diabetes results in marked reduction of BMI, fasting glucose, liver fat content and improvements of degree of steatosis as well as glycemic control and beta-cell function during a mixed-meal tolerance test. Our study indicates that smartphone-based e-learning and telephone coaching can be an additional promising approach for patients with type 2 diabetes besides the standard care.

5 References

1. Wilding, J.P.H., *The importance of weight management in type 2 diabetes mellitus.* International journal of clinical practice, 2014. **68**(6): p. 682-691.
2. Szendroedi, J., et al., *Role of diacylglycerol activation of PKCtheta in lipid-induced muscle insulin resistance in humans.* Proc Natl Acad Sci U S A, 2014. **111**(26): p. 9597-602.
3. Van Gaal, L. and A. Scheen, *Weight management in type 2 diabetes: current and emerging approaches to treatment.* Diabetes Care, 2015. **38**(6): p. 1161-72.
4. Petersen, K.F., et al., *Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes.* Diabetes, 2005. **54**(3): p. 603-8.
5. Lean, M.E., et al., *Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial.* Lancet, 2018. **391**(10120): p. 541-551.
6. Boyle, L., et al., *Use of and Beliefs About Mobile Phone Apps for Diabetes Self-Management: Surveys of People in a Hospital Diabetes Clinic and Diabetes Health Professionals in New Zealand.* JMIR mHealth and uHealth, 2017. **5**(6): p. e85-e85.
7. Chavez, S., et al., *Mobile Apps for the Management of Diabetes.* Diabetes Care, 2017. **40**(10): p. e145-e146.
8. Henry, R.R. and B. Gumbiner, *Benefits and limitations of very-low-calorie diet therapy in obese NIDDM.* Diabetes Care, 1991. **14**(9): p. 802-23.
9. Soleymani, T., S. Daniel, and W.T. Garvey, *Weight maintenance: challenges, tools and strategies for primary care physicians.* Obesity reviews : an official journal of the International Association for the Study of Obesity, 2016. **17**(1): p. 81-93.
10. Szendroedi, J., et al., *Cohort profile: the German Diabetes Study (GDS).* Cardiovasc Diabetol, 2016. **15**: p. 59.
11. American Diabetes, A., *2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018.* Diabetes Care, 2018. **41**(Suppl 1): p. S13-S27.
12. American Diabetes, A., *6. Glycemic Targets: Standards of Medical Care in Diabetes-2018.* Diabetes Care, 2018. **41**(Suppl 1): p. S55-S64.

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EIT Health is supported by the EIT