Seven-day Fasting as a multimodal complex interventionfor Adults with Type 1 Diabetes – Feasibility, Benefit and Safety in a Controlled Pilot StudyFeasibility of Fasting for Adults with Type 1 Diabetes

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Abstract

Aims/Hypothesis: Intermittent as well as prolonged fasting are receiving considerable attention and appear favorable in conditions like the metabolic syndrome, type 2 diabetes, rheumatic diseases and others. Fasting for people with type 1 diabetes is generally considered too risky. However, the ability and possibility to change from carbohydrate to ketone-based fuel supply might also be relevant for people with type 1 diabetes. The aim of this patient-led research was to investigate the feasibility, benefit and safety of a seven-day multimodal fasting intervention in people with type 1 diabetes.

Methods: A non-randomized controlled pilot study, with 20 participants with and 10 without type 1 diabetes. Data acquisition took place prior, post and four months after the intervention and daily during intervention.

Results: 29 of 30 participants finished the intervention. Mean ß-hydroxybutyrate as representative ketone body increased to 2.8 ± 1.9 mmol/L on day 7 while average glucose remained between 4.9 ± 1.5 to 7.5 ± 2.3 mmol/L [89 ± 27 and 136 ± 40 mg/dL]. Fasting-related side effects were all temporary, and slightly more prevalent in those with type 1 diabetes. Mean daily insulin dose was adjusted from 24.4 (3-50) IU on the day before fasting to 7.6 (0-26.7) IU on day 7. Quality of life (WHO-5) normalized from 54.0 ± 4.4 to 68.8 ± 15.0 ($p = 0.01$) after fasting. There was a decrease from before until the follow-up four month later of weight from 77.6 ± 20.4 kg to 76.6 ± 20.9 kg ($p = 0.023$) and for the BMI from (27.68 ± 7.04) to (26.74 ± 7.15) kg/m^2 ($p = 0.008$). Diastolic blood pressure increased from 69.75 ± 11.41 mmHg to 75.74 ± 8.42 mmHg ($p = 0.028$) and stayed in a healthy range on average.

Conclusions/Interpretation: This study demonstrates the feasibility, benefits and safety aspects of a 7-day fast in adults with type 1 diabetes.

Research In Context

What is already known about this subject?

- People with type 1 diabetes have a high risk of developing diabetes-related complications including metabolic syndrome and type 2 diabetes
- Multimodal 7 day fasting can improve metabolic parameters in people with metabolic syndrome and type 2 diabetes
- Only recently has the role of ketones in metabolic signaling and downregulation of inflammation become a topic of research, including the prospective roles for ketones in obesity-related and cardiovascular diseases

What is the key question?

- Can multimodal 7 day fasting, including a desired augmentation of ketone bodies, be used as safe intervention to support people with type 1 diabetes

What are the new findings?

- No ketoacidosis occurred during 7 day fasting in a group of 20 type 1 diabetics
- Change from carbohydrate- to ketone-based fuel is possible for people with type 1 diabetes under stable blood sugar values
- By fasting, BMI and other symptoms and risk factors may show long-term improvements in adults with type 1 diabetes

How might these results change the focus of research or clinical practice?

- Multimodal 7 day fasting in type 1 diabetes, as a method preferred by many patients, could serve as a possible additional treatment option, when efficacy could be proved within a randomized controlled trial

Introduction

Type 1 diabetes appears to be on the rise in Europe, and with it the burden across a number of outcomes including health status, productivity, activity, and use of healthcare resources [1]. The complex nature of diabetes itself, fluctuations in blood glucose and the fear of long-term complications contribute to a high level of diabetes-specific distress [2]. People with type 1 diabetes are inherently exposed to an elevated risk of developing psychological and neurological long-term consequences such as depression and cognitive decline [3], [4]. Taken together, this suggests that treatment strategies should address clinical, humanistic, and economic burden [1]. A multimodal, medical supervised fasting regimen called “Buchinger Fasting”, has a long tradition in Europe and is a defined therapeutic approach in specialized fasting hospitals [5].This multimodal type of fasting intervention has shown to be effective in a number of conditions that could potentially be relevant to people with type 1 diabetes, such as depressive disorders, exhaustion / fatigue, the metabolic syndrome including type 2 diabetes and autoimmune diseases such as rheumatoid arthritis [6],[7],[8]. A guideline on the method has been published [5]. The evaluation of 1422 subjects following a Buchinger fasting lasting 21 days showed that this intervention is safe and well tolerated in people without type 1 diabetes. An increase in physical and emotional well-being was observed during prolonged fasting [9].

Currently, type 1 diabetes is seen as a relative contraindication for prolonged fasting due to the supposed risk of ketoacidosis, which is not seen during Ramadan fasting, because of its intermittent character [10]. Diabetic ketoacidosis (DKA) is related to an absolute or relative lack of insulin. Its definition includes prolonged 250 mg/dL hyperglycaemia (blood glucose above >13.9 mmol/L) plus pH levels dropping below 7.3, and/or bicarbonate levels below 18 mmol/L, according to the consensus statement of the American Diabetes Association (ADA) [11], or below 15 mmol/L according to the German and British guidelines [12, 13]. In fasting, increase of ketone bodies (β-hydroxybutyrate (BHB)) is warranted, as they serve as essential fuel source during lack of carbohydrates [14]. Their normal concentration is typically < 0.3 mmol/L, with a range of nutritional ketosis defined as 0.5–3 mmol/L. During prolonged fasting, the BHB level for adults typically ranges between 5–7 mmol/L [14]. The perception of ketones in type 1 diabetes is extending from an alarming hallmark of DKA to an indicator of an alternative fuel source [15, 16]. Only recently has the role of ketones in metabolic signaling and downregulation of inflammation become a topic of research, including the prospective roles for ketones in obesity-related and cardiovascular diseases [17],[18].

Anyway, most fasting clinics and diabetologists advise against fasting as a health intervention for people with type 1 diabetes. Nevertheless, people with type 1 diabetes are expressing the desire to fast, as a reprieve from the constant efforts of managing food-related blood glucose levels, and as a means of improving quality of life, reducing body weight and improving their long-term prognosis [22].

Hence, there is a demand for research to prove the principal feasibility, possible harms and benefits of fasting for those with type 1 diabetes. Due to lack of research, a patient-led research project was initiated. Patient involvement in designing studies is increasingly welcomed, as it can bring research nearer to patient's needs [23].

Research Design And Methods

A non-randomized controlled pilot study was performed with 20 participants with and 10 without type 1 diabetes. Data acquisition took place prior, post and four months after the intervention and daily during intervention. This publication follows the checklist in reporting a pilot or feasibility trial (Consort 2010 checklist supplement) as far as applicable [24] enriched by aspects of process (acquisition of participants), and management (realization in a non-medical center) [25]. The description of the intervention follows the TIDieR Checklist [26].

Participants

This controlled feasibility study was performed with 20 participants with and 10 participants without type 1 diabetes as reference. The number of participants was limited by staff-related and setting-related resources. For Germany-wide recruitment we established three sites with diabetologist/fasting doctors for inclusion and follow-up visits in East (Berlin); West (Witten) and South Germany (Überlingen). The trial site (Rosenwaldhof, Großkreutz) was different from these inclusion sites (Fig. 1).

Inclusion criteria: Adults were invited to apply for participation if they had had type 1 diabetes for at least two years, including LADA, were using Blood-Glucose-Self-Management (BGSM), showed interest in participating in a 9 day intervention with 7 fasting days, were ready to travel to the study doctor before and four months after the intervention. Exclusion criteria: Acute psychiatric disease, severe internal diseases, febrile diseases, kidney diseases, dialysis, pregnancy, lactation, addictions, malignancies, BMI <21 kg/m², diabetes insipidus, ongoing application procedures for occupational disability, participation in other clinical studies within the preceding four weeks.

Description of the intervention using the TIDieR guidelines

The intervention was composed following the guidelines for fasting according to Buchinger, defined as a medically supervised, inpatient multimodal fasting regimen with 3 dimensions (medical, psychosocial, spiritual) [5]. The 9-day inpatient stay including one day preparing (reducing caloric intake to 1500 kcal), seven days fasting and one day reintroducing solid foods (Tab 1: Timetable for the duration of the stay). Fasting started with oral ingestion of a laxative salt (30-40 g sodium sulfate, according to body weight). The daily intake included vegetable broth (0.25 to 0.5 L), and vegetable juices (0.25 to 0.5 L), limited to max. 400 kcal. Participants were strongly advised to drink 2 to 3 L of fluids daily. Enema for bowel movement were introduced and advised for every second day. A warm liver wrap was advised daily during a rest for at least half an hour. The "Zurich Resource Model" (ZRM), an evaluated self-management tool, was offered for 1 hour daily to increase awareness of and activate somatic, emotional, social and mental resources [27]. Since the timetable for both interventions (Eurythmy and Mindfulness Training) was too tight, we decided to offer both as facultative of which one should be selected. The ZRM intervention was shortened from 1.5 hours to 1 hour per day. Two hours per day were scheduled for individualized exercise (jogging, hiking, swimming, Nordic walking, cycling). The main format was group based; massage and diabetes counseling were provided individually. As the team stayed in the same location as the participants, individual face-to-face counseling, also by medical doctors, was possible at any time, if needed.

The team consisted of nine members: Medical doctors (endocrinology, internal medicine, one of them with many years of experience with therapeutically fasting, and psychotherapy), diabetes and/or nutrition counselor, fasting guides, mindfulness trainer, eurythmist, ZRM coach, massage therapist and study nurse (some members fulfilled several roles). Participants received a booklet including the fasting guidelines and descriptions for fasting related self-management treatments in German language (available on demand).

The location at the seminar centre close to the Berlin Immanuel Hospital (specialized in fasting), enabled daily visits from experienced fasting doctors and offered accommodation for participants and team-members during the intervention time, plus two large group meeting halls and a fasting kitchen. Necessary laboratory equipment was installed in the center. The participants could give feedback daily and at the end of the intervention, both orally and in written form. Attendance to ZRM, Eurythmy/Mindfulness and exercise were documented daily. Qualitative interviews were conducted on day 7 and during the follow up meetings four months later.

Adverse Events

The program was continuously monitored for safety and supervised by the medical staff. Symptoms that could be classified as adverse events were reported daily by participants, approved by signature of attending medical doctors and discussed daily in the team meetings. For evaluation and reporting, the adverse events during the intervention and during the three first set-up days were grouped according to the tables of Wilhelmi et al. [9], adding further symptoms not presented by Wilhelmi (Table 2). This publication uses two manners of reporting adverse events: a) only events occurring three or more times per participant, as did Wilhelmi et al. [9], and b) each mild symptom and each abnormal value. We defined ketoacidosis as an additional serious adverse events (SAE), following the German and British guidelines [12],[13].

Ketoacidosis was defined as: bicarbonates < 15 mmol/L, blood glucose > 13.9 mmol/L [> 250 mg/dL] and blood pH < 7.3, measured by blood gas analysis and blood ketone values > 3 mmol/L only if combined with subjectively feeling unwell, combined with clinical symptoms (gastrointestinal symptoms, signs of dehydration and respiratory symptoms) and changes in consciousness. While the state of consciousness is not restricted in mild ketoacidosis, moderate ketoacidosis is associated with impaired consciousness (sleepiness) [11],[12], [13]. The severity of diabetic ketoacidosis (DKA) can be classified as mild, moderate or severe based on the severity of metabolic acidosis and the presence of altered mental status [11], [12]. Severe hypoglycemia is defined as need for external support or loss of consciousness.

Risk management

During fasting, participants were advised to omit meal-related insulin doses, to maintain basal insulin substitution, and to check blood glucose at least four times per day. Each participant was given glucose- and ketometers (GlucoMen Areo® 2K) and trained to use them correctly four times per day. To control the risk of DKA, blood pH; glucose and standard bicarbonate (SBC) were measured every morning and as needed by blood gas analysis (BGA, using an ABL90 FLEX PLUS™). To prevent diabetes related Ketoacidosis, 2-4 IU insulin together with two carbohydrate units (e.g. apple juice) were advised and documented in case of a feeling unwell and/or ketone values > 6 mmol/L together with bicarbonate BGA values < 15 mmol/L, or blood glucose > 13.9 mmol/L [> 250 mg/dL], or a blood pH < 7.3. Measurements of blood glucose and ketones and, if necessary, the administration of 2 carbohydrate units and 2-4 IU insulin were to be repeated every two hours until normalization. Criteria to prematurely discontinue the fast on the part of the study management were pre-defined in the study protocol [28].

Outcome parameters

Data acquisition took place prior, post, four months after the intervention, and daily during intervention. We expected improvement of quality of life and physiological parameters and a decrease of diabetes related problems – all of which were assessed before and after intervention, as well as four months later at follow-up. We chose a generic quality of life instrument (WHO-5 [29]) as well as a diabetes-related psychometric instrument (Problem Areas in Diabetes (PAID)) [30], as a one-item screening tool (Question 12: Worrying about the future and the possibility of serious complications) with a sensitivity and specificity for the recognition of diabetes-related emotional distress of approximately 80% [31]. Physiological parameters were weight, body mass index (BMI), total cholesterol, HDL, LDL; systolic (SBP) and diastolic (DBP) blood pressure and HBA_{1c}.

Informed consent and ethics committee approval

Written informed consent was obtained from all patients included. The reported investigations have been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2008. Ethic approval was obtained by the Ethic Committee of the University Witten/Herdecke (No. 239/2017). The study protocol has been published in German [28]. The study was registered in the German Clinical Trial register under the number DRKS00017504. Intervention took place in a stationary, but not a clinical setting, therefore insurance was provided for participants to guaranty hospitalization in case of emergency.

Results

Of the 39 people with type 1 diabetes who applied for participation, nobody was excluded. 20 agreed to be included, the others refused participation due to time conflicts. Demographic data is shown in Table 2.

Table 2: Demographics of participants at baseline

	With type 1 diabetes (n=20)	Without type 1 diabetes (n=10)
Baseline demography		
Age in years, mean ± SD	56.4 ± 6.2	45.7 ± 13.8
Sex femal/male	19/1	7/3
Weight in kg, mean ± SD	77.60 ± 20.47	75.94 ± 15.00
BMI, mean ± SD	27.68 ± 7.04	26.20 ± 4.74
Experience level of fasting		
Never	8	4
Occasionally	10	3
Yearly	2	3
Nutrition		
Normal	7	6
Low carb	7	0
Vegan	0	1
Vegetarian	6	2
Other diet	0	1
Diabetes type		
Type 1 diabetes	15	
LADA (latent autoimmune diabetes in adults)	5	
Duration of diabetes disease in years	34.3 ± 3.54	
Insulin therapy		
Pump/ICT	15/5	
Blood glucose self-management		
Individual measurement, bloody	2	
Continuous glucose monitoring	4	
Free Style Libre™	14	
Pre-existing conditions		
Retinopathy	6	0
Nephropathy	2	0
Coronary artery disease	2	0
Hypertension	7	4
Polyneuropathy	3	0
Parodontitis	1	0
Skin diseases	2	0
Problems with skin in area of injections		
Hyper-/hypodystrophy	3	
Inflammation	3	
Autoimmun-diseases		
Rheumatoid arthritis	1	0
Hashimoto thyreoditis	11	1

Other autoimmun-disease	6	0
Psychotherapeutic treatments in the past		
Total	14 (70%)	2 (20%)
Biographic burdens	1 (5%)	2 (20%)
Depression, burnout	7 (35%)	0
PTBS, abuse	2 (10%)	0
Type 1 diabetes	2 (10%)	0
Eating disorder	2 (10%)	0

Ten people without type 1 diabetes served as a reference group for adverse events and ketosis. Participants adapted insulin doses autonomously, with support of a diabetes counselor. In the course of the fast, daily Insulin dosage was reduced from an average of 24.0 (3-50) IU to 7.6 (0-26.7) IU (Table 3). The need for additional carbohydrates to prevent or treat hypoglycemia during exercise started with 48.5 (5 - 60) g/person on the first fasting day and decreased to 24.8 (2 - 40) g/person on the last fasting day (Table 2). The use of a non-medical environment for a fasting intervention was feasible and was considered helpful and positive by the participants.

Table 3: Insulin doses and additional carbohydrate units

	preparation day	fasting day* 1	fasting day* 2	fasting day* 3	fasting day* 4	fasting day* 5	fasting day* 6	fasting day* 7	set up day$ 8
Total daily insulin doses (IU)									
Total IU per day	448.2	311.1	235.3	212.1	191.3	181.5	163.1	152.8	131.9
per person (n=20)§	22.4	15.6	11.8	10.6	9.6	9.1	8.2	7.6	6.6
Median	28.1	16.0	11.0	9.6	8.9	9.5	8.9	7.2	9.3
IQR#	16.0	7.4	5.5	7.3	7.3	6.0	7.2	6.1	3.0
Maximum	50.0	32.5	29.7	26.2	30.2	28.6	27.2	26.7	20.7
Minimum	3	3	2	1	0	0	0	0	0
Additional carbohydrate units (one unit = 10 g)									
Total per day	131.0	97.2	89.8	64.5	63.2	67.1	59.5	50.0	122.4
per person (n=20)	6.6	4.9	4.5	3.2	3.2	3.4	3.0	2.5	6.1
Median	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
IQR	1.5	1.0	0.8	0.5	1.0	1.0	0.8	1.0	1.0
Maximum	6.0	4.0	4.5	2.5	2.0	3.0	3.0	4.0	56.0
Minimum	0.5	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.3
**fasting day. ranging from 6am to 6am the day after*									
$ set up day 8 = day of breaking fast									
§per person = total per day / 20									
# IQR = 3rd quartile to 1st quartile									

Feasibility in relation to adverse events (AE)

The intervention was successfully completed by 29 of 30 participants. One participant with type 1 diabetes interrupted the intervention prematurely due to anxiety about missing important events at work and a rebound of her chronic back pain. No serious adverse event occurred. All adverse events were investigated in detail to exclude ketoacidosis. No DKA occurred. There were no severe hypo-/hyperglycemia with e.g. loss of consciousness or need for external support. Single hypo- or hyperglycemic values were all easily managed by the affected participants using apple juice or insulin. All adverse events are listed in Table 4.

Table 4: Reported adverse events and ketoacidosis relevant blood measurements

	Participants with =/> 3 adverse events					Total number of adverse events		
	During fasting days	During 7 fasting days & fast break		During set-up days (day 8-9)		During 7 fasting days & fast break		During set-up days (day 8-9)
	Reference study in subjects without T1DM	Presented feasibility study in subjects with and without T1DM fasting for 7 days						
Adverse Events (self reported)	Toledo et al. 2019 (N = 1422)	With T1DM (N = 20)	Without T1DM (N = 10)	With T1DM (N = 20)	Without T1DM (N = 10)	With T1DM (N = 19)	Without T1DM (N = 10)	With T1DM (N = 19)
Sleep disturbance	169 (14.94%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3	0	0
Fatigue	155 (13.7%)	2 (10%)	0 (0%)	3 (15%)	0 (0%)	19	5	8
Dry Mouth	100 (8.84%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0	0
Back pain	84 (7.43%)	2 (10%)	0 (0%)	2 (10%)	0 (0%)	13	1	8
Hunger	77 (6.81%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0	0
Halitosis	61 (5.39%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0	0
Headache	61 (5.39%)	3 (15%)	0 (0%)	0 (0%)	0 (0%)	16	0	1
Muscle pain	49 (4.33%)	4 (20%)	1 (10%)	0 (0%)	0 (0%)	25	6	23
Abdominal bloating	47 (4.16%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0	1
Diarrhea	38 (3.36%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	6	1	2
Sensitivity to cold	33 (2.92%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	15	2	0
Cravings	29 (2.65%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0	0
Vertigo	28 (2.48%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	6	2	0
Blurred vision	23 (2.03%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	2	0
Restless legs	23 (2.03%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2	0	0
Skin rash	19 (1.68%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	5	0	3
Nausea	13 (1.15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7	2	0
Palpitation	13 (1.15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5	0	1
Dyspepsia	12 (1.06%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1	0	0
Muscular cramping	4 (0.35%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4	4	0
Vomiting	1 (0.07%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4	0	0
Mood swings, feelings of sadness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4	0	0
Cold symptoms	0 (0%)	2 (10%)	0 (0%)	2 (10%)	0 (0%)	20	0	11
Stress	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	5	0	0
Inflamed oral flora	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	4	0	0
Cystitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1	0	0

	T1DM	Without T1DM
Ketoacidosis-relevant blood value categories (measured)		
pH 7.2 to <7.3	2	0
pH <7.2	0	0
SBC (mmol/L) 15 to 18*	3	1
SBC (mmol/L) < 15#	0	0
Glucose (mg/dl) <60	52	3
Glucose (mg/dl) >250	5	0

pH and standard bicarbonate (SBC) were measured once a day capillary,

blood glucose was measured capillary at four defined times and whenever required.

*mild ketoacidosis according to Kitabchi et al. (2009) who defined SBC <18 to 15 already as a mild

ketoacidosis according to guidelines

Table 5: Detailed analyses of four participants with type 1 diabetes with vomiting as an adverse event

Internal code	Fasting day	Grade of adverse event*	Repor-ted In-tensity of com-plains	probable origin	Ketone bodies (mmol/L)	Glucose (mg/dL) [mmol/L]	Potas-sium (mmol/L)	pH-value	standard bicarbonate (mmol/L)	Interpreta-tion of acidity
23_01_13_MD	4	II – III†	low	Psycho-genic	3.8	144 [8.0]	4.3	7.467	26.9	Basic
23_02_05_MD	4	II	low	due to fasting	0.8	74 [4.1]	4.9	7.288	17.8	Acidic
23_02_09_MD	5	II	moderate	due to fasting	5.5	94 [5.2]	4.8	7.384	23.1	Basic
23_02_25_MD	7	II	low	unclear	2.4	139 [7.7]	4.7	7.400	23.6	Basic

* Common Terminology Criteria for Adverse Events (CTCAE) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health, National Cancer Institute. Published November 27, 2017, Version 5.0: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf † hospitalization was not acquired, but limit self-care for half a day

Feasibility in relation to Benefits

Participants with type 1 diabetes developed fasting-induced blood ketone values < 3.0 ± 1.49 mmol/L, but no acidosis and maintained target levels of glucose control on average between 5.0 to 10.0 mmol/L [90 to 180 mg/dL] (Fig. 2). Mean daily insulin dosage decreased from 24.4 (3-

50) IU on the last day before fasting to 7.6 (0-26.7) IU on day 7. One participant with LADA could do without insulin for around six weeks before she returned to her former doses, but her C-Peptide values indicate enough own insulin production (28.09.2018: 2,05 ng/ml; 21.02.2019: 1,77 ng /ml). Participants with LADA diabetes should therefore be analyses as separate subgroup.

In participants without type 1 diabetes, ketone values rose to 3.9 ± 2.88 mmol/L (Fig. 3). In both groups, those already experienced in fasting intervention developed faster and higher ketosis than those without fasting experience, and had less malaise in doing so. One participant with type 1 diabetes, experienced in fasting, had ketone values up to 7.4 mml/L on day 6 without symptoms and feeling perfectly well.

Quality of life (WHO-5) improved during the intervention from 54.0 ± 4.44 to 68.84 ± 15.00, resulting in a significant improvement by 13.68 ± 20.76 ($p = 0.010$) for the type 1 diabetes group immediately after the intervention. PAID-1 improved not-significantly.

Focusing on the results of the type 1 diabetes group (Table 6), weight decreased from 77.6 ± 20.4 kg before to 76.6 ± 20.9 kg four month after intervention ($p = 0.023$), and BMI from (27.68 ± 7.04) to (26.74 ± 7.15) kg/m^2 ($p = 0.008$). The increase in HDL cholesterol and therefore LDL/HDL ratio remained significant even after four months. Diastolic blood pressure increased from 69.75 ± 11.41 mmHg to 75.74 ± 8.42 mmHg ($p = 0.028$) and stayed in a healthy range on average. Single values temporarily left the normal range, but without the need for medical support or intervention. HBA_{1c} values remained between (53.33 ± 14.10 mmol/mol [7.03 ± 0.86%]) before the fasting and (53.77 ± 14.10 mmol/mol [7.07 ± 0.86%]) four months after the intervention. (Table 6)

Table 6: Biological and psychological changes in type 1 diabetes during intervention and 4 months follow-up

N=20	Before Intervention mean ± SD	Day 8 of intervention* mean ± SD	Change during intervention mean (95% CI)	p-Value†,	4 months Follow-up mean ± SD	Change 4 months from baseline mean (95% CI)	p-Value†
Weight in kg	77.60 ± 20.47	75.94 ± 15.00	- 3.11 (-1.7; -3.5)	< 0.001	76.61‡ ± 20.96	-1.27‡ (-2.36; - 0.20)	0.023‡
BMI (kg/m^2)	27.68 ± 7.04	26.20 ± 4.74	-1.19 (-1.64; -0.75)	<0.001	26.74‡ ± 7.15	-0.91‡ (-1.55; - 0.27)	0.008‡
Total Chol. (mmol/L)	5.49 ± 1.20	4.90 ± 1.22	-0.67 (-0.93; -0.4)	<0.001	5.30* ± 0.91	-0.19* (-0.65; -0.27)	0.387*
HDL	1.75 ± 0.34	1.44 ± 0.31	-0.31 (-0.45; -0.18)	<0.001	2.04 ± (0.49)	0.29 (0.17; 0.42)	< 0.001
LDL	3.27 ± 0.91	3.13 ± 1.05	-0.21 (-0.43; -0.01)	0.066	3.31 ± 0.94	0.04 (-0.19; 0.27)	0.735
LDL/HDL ratio	1.96 (0.66)	2.32 ± 1.02	0.33 (0.00; 0.65)	0.048	1.75 ± 0.71	- 0.21 (-0.36; -0.05)	0.012
Systolic blood pressue (mmHg)	128.25 ± 16.00	126.11 ± 20.48	-2.50 (-13.30; 8.30)	0.631	125.61 ± 11.85	- 2.45 (-10.2; 5.31)	0.518
Diastolic blood pressue (mmHg)	69.75 ± 11.41	69.17 ± 9.12	- 0.28 (-7.74; 7.18)	0.938	75.74 ± 8.42	5.83 (0.63; 11.04)	0.028
WHO-5	54.00 ± 17.77	68.84 ± 15.00	13.68 (3.68; 23.69)	0.010	59.80 ± 13.64	5.80 (-2.45; 14.05)	0.158
PAID-1	1.10 ± 1.02	0.89 ± 0.81	-.26 (-0.74 -0.21)	0.262	1.00 ± 0.80	-0.10 (-0.47; 0.27)	0.577
HbA1c % (Mmol/mol)	7.03 ± 0.86 (53.33 ± 14.10)		7.07 ± 0.86 (53.77 ± 14.10)		0.00 (-0.22; 0.22)		1.000

* only N = 19 values; † One Sample T-Test on difference; ‡ only N = 17 values.

Discussion

Principal findings: This study shows that a 7-day fast is feasible for people with type 1 diabetes and that their risk of DKA is easily controlled by adapting insulin dosage to blood glucose levels. Insulin substitution and occasional intake of carbohydrates in case of hypoglycemia are the most probable reasons for the lower ketone bodies in participants with type 1 diabetes compared to participants without type 1 diabetes. Lower metabolic flexibility may be a further factor. The three people with type 1 diabetes already experienced in fasting interventions developed faster and higher ketosis than participants without fasting experience, suggesting a training effect in metabolic flexibility [32]. Various parameters

related to the risk of metabolic syndrome or type 2 diabetes, such as weight, BMI blood pressure and the LDL/HDL ratio improved significantly and remained so at follow-up. This is an important result considering the long-term metabolic risks of people with type 1 diabetes [33].

Recruitment and contraindications

Acquisition was feasible. However, the intervention length of 9 days without the opportunity for sick leave from work was the primary reason to decline participation. We did not exclude people with a history of eating disorders. These should be warned that fasting can trigger relapses. Poorly controlled glycemia may also be a relative contraindication, especially in people with no previous fasting experience. Use of SGLT2 inhibitors may present a further contraindication (see below).

Insulin dosage and DKA

Participants were able to manage their insulin dosing with some support. Even basal insulin could be reduced during the fast, which, alongside the replacement of energy intake by ketones, may also reflect the stress-reducing effect of the whole intervention and its context. Stress has been shown to affect glucose levels following food intake, but not in fasting conditions [34]. Hence, stress might be better tolerated while fasting, especially in relation to blood glucose levels. Based on our data we recommend a reduction of basal insulin by 10% at the start of fasting to avoid hypoglycemia. To prevent ketoacidosis, we strongly advise fasting people with type 1 diabetes to maintain a minimal basal insulin rate, even if they think they can do without it. Only one woman with LADA completely stopped insulin for 6 weeks under close blood glucose supervision. The management of adverse events appears feasible but should be accompanied by daily observation of values outside of the norm. DKA, a potentially lethal event [35], can occur in all circumstances, theoretically also during fasting. This study provides initial data for safety rules that can be further evaluated in larger controlled trials [36]. There are differing definitions of DKA. The American guidelines already define SBC values of 15 to 18 mmol/L as mild DKA. We elected to rely on the German and British guidelines which use SBC < 15 mmol/L, but we additionally report the values of SBC between 15 and 18 mmol/L (Table 4). Values remained outside the norm for less than 24-36 hours. Hence, no professional medical intervention was required. Adverse events were compared with those registered in a larger clinical investigation [9], demonstrating that fasting related adverse events were temporary but slightly higher in the group with than without type 1 diabetes. Vomiting was interpreted as a psychological reaction in one case (when rethinking about her child-abuse in a ZRM session), considering the absence of any acidosis, and related to an alkaline overload in two other cases. The fourth case is interpreted as reaction to an acid overload but does not fulfill the criteria of mild ketoacidosis following the American guidelines, because of missing altered mental status. In all cases, the values normalized within 24 hours without medical intervention (Table 4). Even though no DKA occurred, the risk of euglycemic ketoacidosis must be discussed. Hyperglycaemia is usually the hallmark for the diagnosis of diabetes related ketoacidosis. However, there is a subset of patients in whom the serum glucose levels are within the normal limits. This condition is termed as euglycemic DKA (EDKA) [37]. The conditions for EDKA to occur appear to be dehydration, lack of insulin, or both [38]. Both were monitored intensively during the intervention. In 2015, regulatory agencies warned that sodium-glucose co-transporter-2 inhibitors (SGLT2i) may facilitate DKA [39]. Therefore, people using SGLT2i should only fast under very controlled conditions, if at all.

Benefits

The psychometric measures improved during the fast. The WHO-5 questionnaire improved to values comparable with the reference group at the end of the intervention, but decreased again four months later. The results of the WHO-5 questionnaire indicate that many of the participants with type 1 diabetes can be classified as being on the verge of depression, as has been determined from large cohort studies of adults with type 1 diabetes [3]. The PAID-1 showed no significant change, indicating that intervention was not perceived as a further burden.

Limits in relation to feasibility:

The intervention was organized and realized through an affected person supported from an engaged team. Participants were highly motivated to prove the concept of fasting for people with type 1 diabetes. Realization of such a complex intervention in a non-clinical setting was demanding and repetition might be limited. This is a first feasibility study without the aim of gaining information about efficacy, due to a missing randomized control group. We included everybody meeting the inclusion criteria, but anyway, all participants were highly motivated. The intervention included few participants and concentrated on feasibility. An interventional study including a calculated case number to show efficacy is necessary. Further possible parameters for fasting interventions might be discussed. In animal research, diet restriction inhibits up-regulation of inflammatory cytokines (IL-1β, IL-4, and IL-6) and TNF-α, activates IL-10 and haptoglobin in the plasma of streptozotocin-induced diabetic rats [40]. The interventional trial should investigate efficacy in relation to diabetes relevant outcome parameters like the risk of the development of metabolic syndrome and type 2 diabetes, the improvement of metabolic flexibility and quality of life. Based on the reports of participants, time in range (TIR) was improved during intervention. Therefore, TIR should be included as patient relevant outcome in the interventional study.

Meaning of the study: possible explanations and implications for clinicians and policymakers

This study shows that a 7-day fast in type 1 diabetes is possible. It also contributes eligibility criteria and cut-off values to ensure safety of future participants. Fasting interventions should be further investigated in relation to their benefits and limitations in controlled interventional designs

including long-term follow-up. Promising primary outcome parameters for a subsequent randomized controlled efficacy trials might be benefits in quality of life (WHO-5), BMI, blood fat levels, as well as changes in life-style and diet and, ultimately, long-term metabolic benefits and longevity in regular fasters.

Possibilities to reduce body weight in people with type 1 diabetes become more and more important. Reduction of body weight recently turned out as one of the most important patient preferences [41]. Most recent studies show, that diabetes has rapidly emerged as a major comorbidity for COVID-19 severity. As an independent prognostic factor for COVID-19 severity, BMI, but not diabetes appears to be relevant in the population with diabetes requiring hospital admission [42]. In fact, fasting could be considered as a therapeutic strategy to lower (the risk of) the severity of COVID -19 to some extent before or even during the infection.

Conclusions

A seven-day liquid-based fast as a multimodal, medical supervised intervention is principally feasible and has potential short-term and long-term benefits for people with type 1 diabetes. Ketosis as physiological fasting reaction does not equate (euglycemic) diabetic ketoacidosis as long as insulin substitution is ensured. Nevertheless, the risk of fasting-related acidosis should be taken seriously and people with type 1 diabetes should fast under medical supervision. In case of nausea, carbohydrates or lemon juice are recommended. This study might open a new avenue of research for the possibility of improvement in quality of life and long-term complications in adults with type 1 diabetes.

Declarations

Acknowledgement

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Conflict of interest

BB has type 1 diabetes herself. Her interest is to find evidence-based, helpful solutions for affected people. DK has a passion for fasting. RS and AM are responsible speakers of the society of Physicians for Nutrition and Fasting. AB, DM, JS, EJ have no conflict of interest to declare.

Contributions

BB was the main initiator and developer of the trial and its realization; EJ realized the statistics and worked on the manuscript, JS developed and realized tables, DM, RS and AM supervised the study and the manuscript, DM and KS revised the study protocol and publication as diabetologists, AB, RS and DK supported the publication with their expertise in fasting and basic research. DM is sponsor and diabetologist of this trial and personally accompanied all stages. All authors read and approved the manuscript.

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References

[1] Rydén A, Sörstadius E, Bergenheim K, et al. (2016) The Humanistic Burden of Type 1 Diabetes Mellitus in Europe: Examining Health Outcomes and the Role of Complications. PloS one 11(11): e0164977. 10.1371/journal.pone.0164977

[2] Bollepalli S, Smith LB, Vasquez A, Rodriguez H, Vehik K (2012) Addressing the burdens of Type 1 diabetes in youth. Clin Pract 9(4): 409–424

[3] Hochberg G, Pucheu S, Kleinebreil L, Halimi S, Fructuoso-Voisin C (2012) WHO-5, a tool focusing on psychological needs in patients with diabetes: the French contribution to the DAWN study. Diabetes & metabolism 38(6): 515-522. 10.1016/j.diabet.2012.06.002

[4] Buchberger B, Huppertz H, Krabbe L, Lux B, Mattivi JT, Siafarikas A (2016) Symptoms of depression and anxiety in youth with type 1 diabetes: A systematic review and meta-analysis. Psychoneuroendocrinology 70: 70-84. 10.1016/j.psyneuen.2016.04.019

[5] Wilhelmi de Toledo F, Buchinger A, Burggrabe H, et al. (2013) Fasting therapy - an expert panel update of the 2002 consensus guidelines. Forsch Komplementmed 20(6): 434-443. 10.1159/000357602

[6] Fond G, Macgregor A, Leboyer M, Michalsen A (2013) Fasting in mood disorders: neurobiology and effectiveness. A review of the literature. Psychiatry research 209(3): 253-258. 10.1016/j.psychres.2012.12.018

[7] Li C, Ostermann T, Hardt M, et al. (2013) Metabolic and psychological response to 7-day fasting in obese patients with and without metabolic syndrome. Forsch Komplementmed 20(6): 413-420. 10.1159/000353672

[8] Kjeldsen-Kragh J, Haugen M, Borchgrevink CF, et al. (1991) Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. Lancet 338(8772): 899-902. 10.1016/0140-6736(91)91770-u

[9] Wilhelmi de Toledo F, Grundler F, Bergouignan A, Drinda S, Michalsen A (2019) Safety, health improvement and well-being during a 4 to 21-day fasting period in an observational study including 1422 subjects. PloS one 14(1): e0209353. 10.1371/journal.pone.0209353

[10] Salti I, Bénard E, Detournay B, et al. (2004) A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes Care 27(10): 2306-2311. 10.2337/diacare.27.10.2306

[11] Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN (2009) Hyperglycemic crises in adult patients with diabetes. Diabetes Care 32(7): 1335-1343. 10.2337/dc09-9032

[12] Deutsche Diabetesgesellschaft (DDG) (2018) S3-Leitlinie Therapie des Typ-1-Diabetes. 2. Auflage. AWMF-Registernummer: 057-013. In, p 105

[13] Joint British Diabetes Societies Inpatient Care Group (2013) The management of diabetic ketoacidosis in adults, Second edition, update: September 2013. In, p 43

[14] Cahill GF, Jr. (2006) Fuel metabolism in starvation. Annu Rev Nutr 26: 1-22. 10.1146/annurev.nutr.26.061505.111258

[15] Owen OE (2005) Ketone bodies as a fuel for the brain during starvation. Biochemistry and Molecular Biology Education 33(4): 246-251. 10.1002/bmb.2005.49403304246

[16] Bolla AM CA, Laurenzi A, Scavini M, Piemonti L. (2019) Low-Carb and Ketogenic Diets in Type 1 and Type 2 Diabetes. . Nutrients 11(5)((5)): 962. 10.3390/nu11050962

[17] Newman JC, Verdin E (2017) β-Hydroxybutyrate: A Signaling Metabolite. Annu Rev Nutr 37: 51-76. 10.1146/annurev-nutr-071816-064916

[18] Puchalska P, Crawford PA (2017) Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. Cell Metab 25(2): 262-284. 10.1016/j.cmet.2016.12.022

[19] Balasse EO, Féry F (1989) Ketone body production and disposal: Effects of fasting, diabetes, and exercise. Diabetes/Metabolism Reviews 5(3): 247-270. 10.1002/dmr.5610050304

[20] Féry F, Balasse EO (1985) Ketone Body Production and Disposal in Diabetic Ketosis: A Comparison with Fasting Ketosis. Diabetes 34(4): 326-332. 10.2337/diab.34.4.326

[21] Musil F, Smahelova A, Blaha V, et al. (2013) Effect of low calorie diet and controlled fasting on insulin sensitivity and glucose metabolism in obese patients with type 1 diabetes mellitus. Physiol Res 62(3): 267-276

[22] Berger B, Stange R, Michalsen A, Martin DD (2017) Prolonged Fasting in T1DM – case study from patient perspective In: European conference of Integrativ medicine Berlin

[23] Sacristán JA, Aguarón A, Avendaño-Solá C, et al. (2016) Patient involvement in clinical research: why, when, and how. Patient Prefer Adherence 10: 631-640. 10.2147/ppa.S104259

[24] Eldridge SM, Chan CL, Campbell MJ, et al. (2016) CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot Feasibility Stud 2: 64. 10.1186/s40814-016-0105-8

[25] Thabane L, Ma J, Chu R, et al. (2010) A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol 10: 1. 10.1186/1471-2288-10-1

[26] Hoffmann TC, Glasziou PP, Boutron I, et al. (2014) Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 348: 175-188. 10.1136/bmj.g1687

[27] Storch M (2004) Resource-activating Selfmanagement with the Zurich Resource Model (ZRM). European Psychotherapy 5(1): 27-64

[28] Berger B, Stange R, Baumann A, et al. (2019) Fasten für Menschen mit Typ-1-Diabetes (FaMeD1): Pilotstudie in Hinblick auf Machbarkeit und diabetesbezogene Lebensqualität. Ernährung und Medizin 34(02): 74-81

[29] Topp CW, Østergaard SD, Søndergaard S, Bech P (2015) The WHO-5 Well-Being Index: a systematic review of the literature. Psychother Psychosom 84(3): 167-176. 10.1159/000376585

[30] Snoek FJ, Pouwer F, Welch GW, Polonsky WH (2000) Diabetes-related emotional distress in Dutch and U.S. diabetic patients: cross-cultural validity of the problem areas in diabetes scale. Diabetes Care 23(9): 1305-1309. 10.2337/diacare.23.9.1305

[31] McGuire BE, Morrison TG, Hermanns N, et al. (2010) Short-form measures of diabetes-related emotional distress: the Problem Areas in Diabetes Scale (PAID)-5 and PAID-1. Diabetologia 53(1): 66-69. 10.1007/s00125-009-1559-5

[32] Corpeleijn E, Saris WH, Blaak EE (2009) Metabolic flexibility in the development of insulin resistance and type 2 diabetes: effects of lifestyle. Obes Rev 10(2): 178-193. 10.1111/j.1467-789X.2008.00544.x

[33] Merger SR, Kerner W, Stadler M, et al. (2016) Prevalence and comorbidities of double diabetes. Diabetes research and clinical practice 119: 48-56. 10.1016/j.diabres.2016.06.003

[34] Wiesli P, Schmid C, Kerwer O, et al. (2005) Acute psychological stress affects glucose concentrations in patients with type 1 diabetes following food intake but not in the fasting state. Diabetes Care 28(8): 1910-1915

[35] Fazeli Farsani S, Brodovicz K, Soleymanlou N, Marquard J, Wissinger E, Maiese BA (2017) Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review. BMJ open 7(7): e016587. 10.1136/bmjopen-2017-016587

[36] Leon AC, Davis LL, Kraemer HC (2011) The role and interpretation of pilot studies in clinical research. J Psychiatr Res 45(5): 626-629. 10.1016/j.jpsychires.2010.10.008

[37] Rawla P, Vellipuram AR, Bandaru SS, Pradeep Raj J (2017) Euglycemic diabetic ketoacidosis: a diagnostic and therapeutic dilemma. Endocrinol Diabetes Metab Case Rep 2017. 10.1530/edm-17-0081

[38] Hine J, Paterson H, Abrol E, Russell-Jones D, Herring R (2015) SGLT inhibition and euglycaemic diabetic ketoacidosis. Lancet Diabetes Endocrinol 3(7): 503-504. 10.1016/s2213-8587(15)00204-1

[39] Fadini GP, Bonora BM, Avogaro A (2017) SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA Adverse Event Reporting System. Diabetologia 60(8): 1385-1389. 10.1007/s00125-017-4301-8

[40] Ugochukwu NH, CL. F (2007) Caloric restriction inhibits up-regulation of inflammatory cytokines and TNF-alpha, and activates IL-10 and haptoglobin in the plasma of streptozotocin-induced diabetic rats. 120-126. . J Nutr Biochem 18: 120-126. doi:10.1016/j.jnutbio.2006.03.008

[41] Pettus JH, Kushner JA, Valentine V, et al. (2019) Adjunct Therapy in Type 1 Diabetes: A Survey to Uncover Unmet Needs and Patient Preferences Beyond HbA1c Measures. Diabetes Technol Ther 21(6): 336-343. 10.1089/dia.2019.0027

[42] Cariou B, Hadjadj S, Wargny M, et al. (2020) Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia. 10.1007/s00125-020-05180-x

Figures

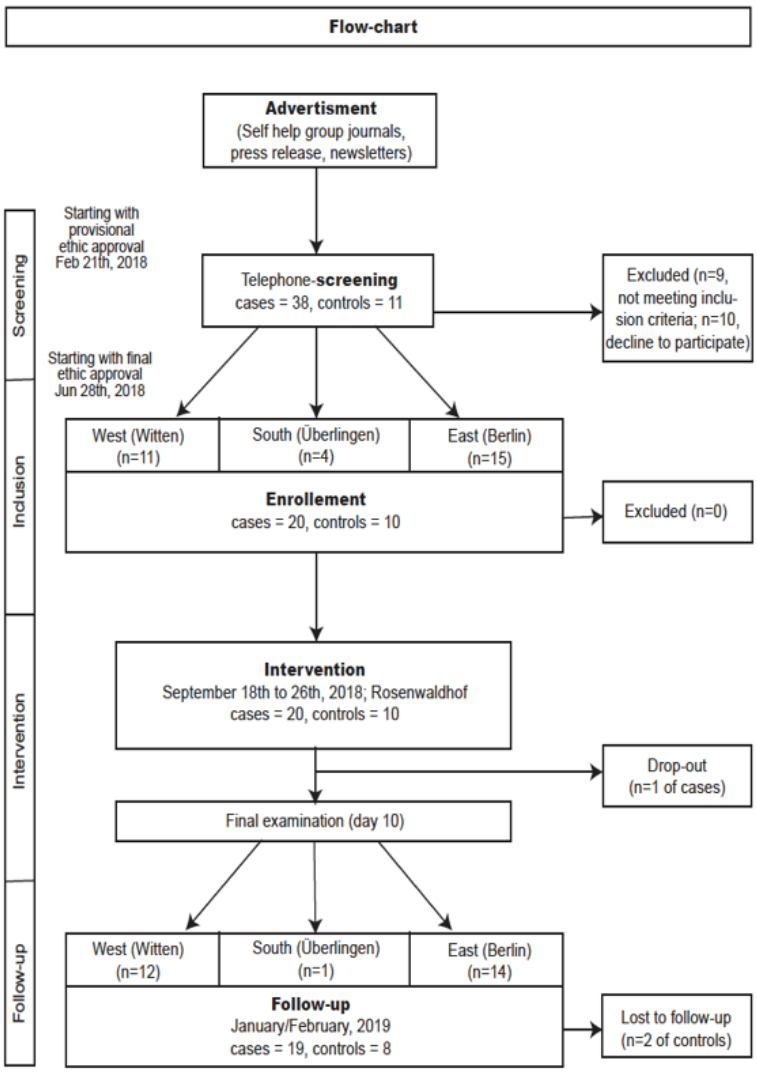

Figure 1

Flow chart of intervention

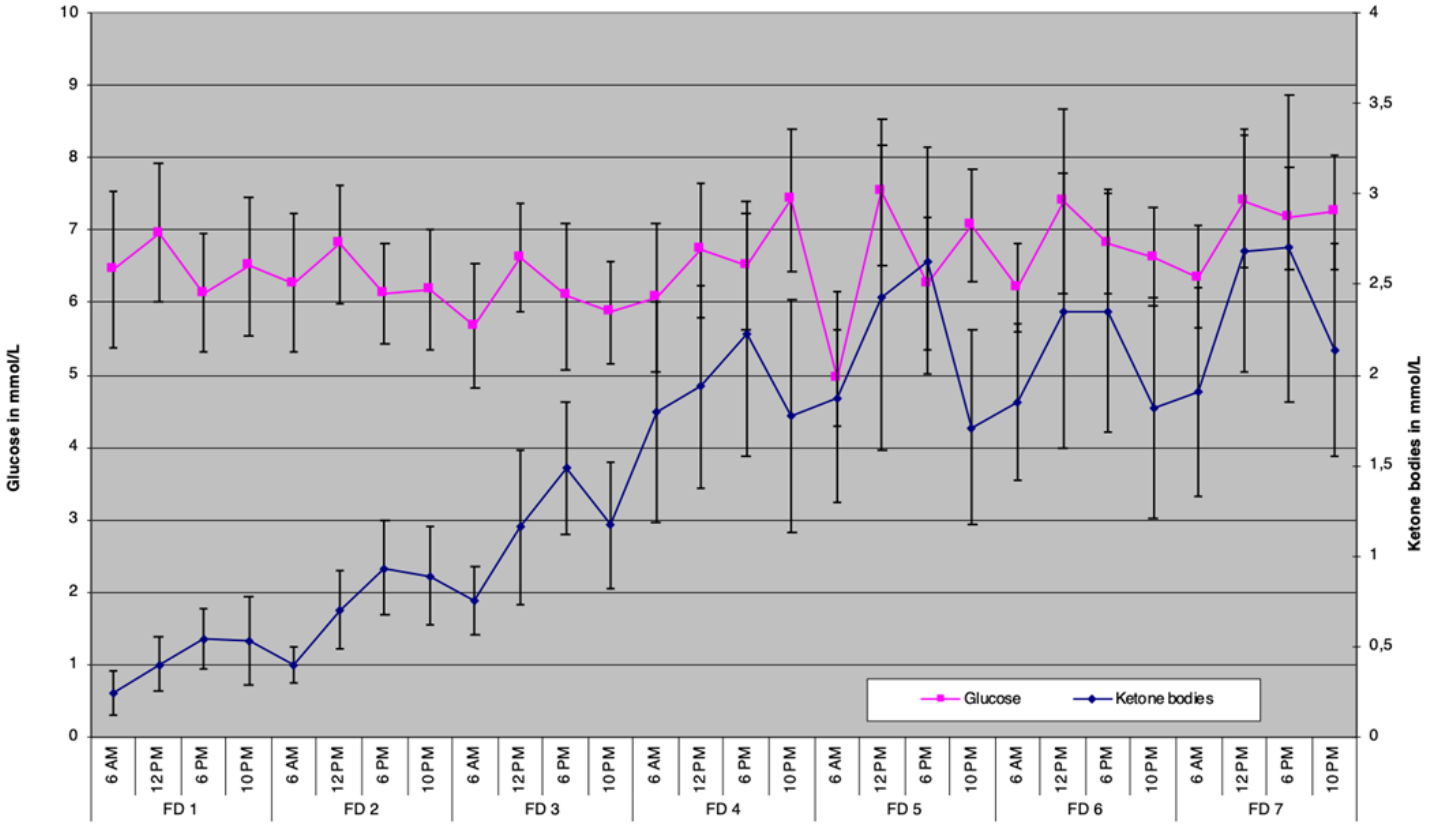

Figure 2

Timetable for fasting interventionKetone body development under fasting conditions in participants with and without type 1 diabetes

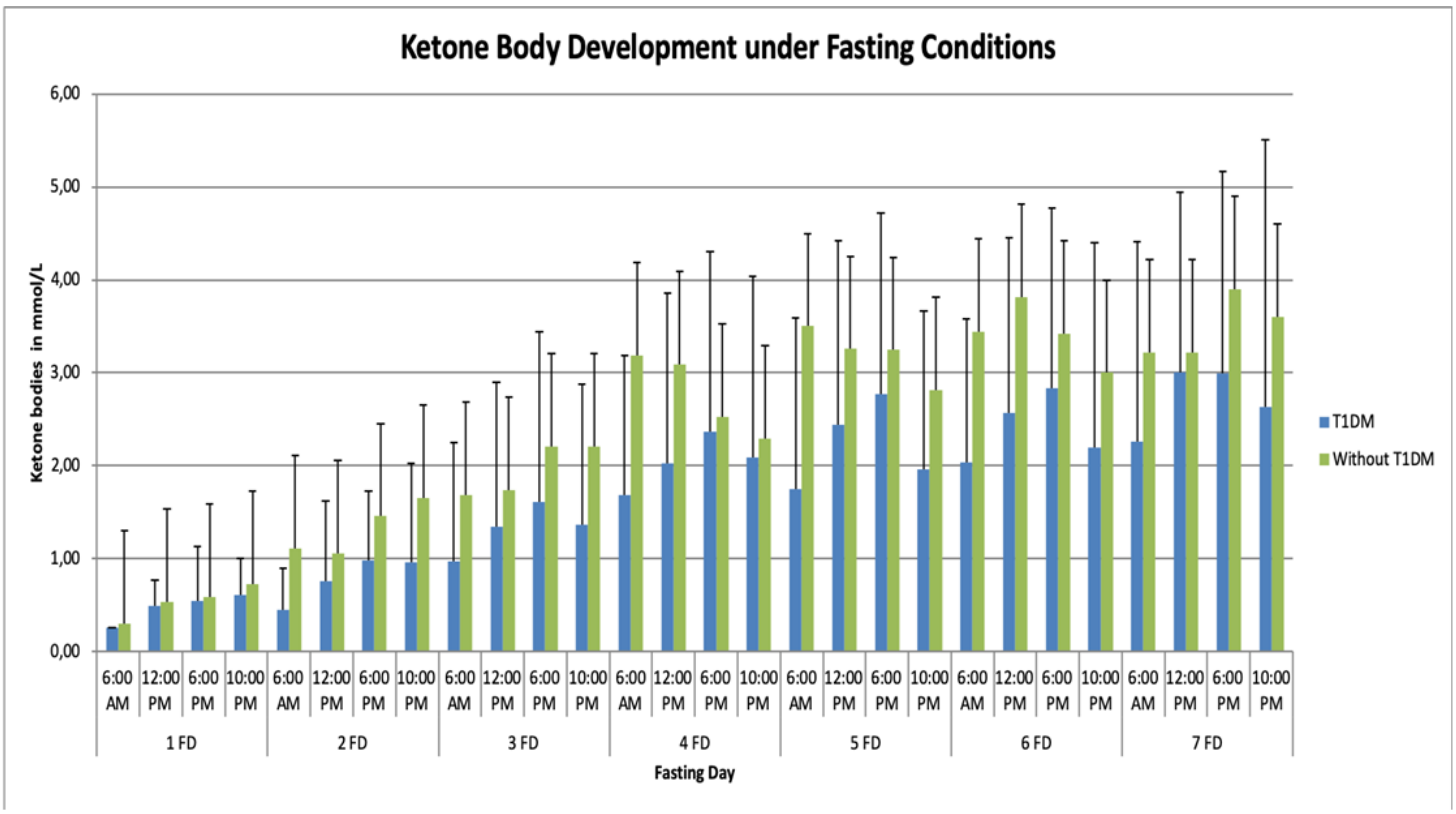

Figure 3

Ketone bodies and glucose under fasting in participants with type 1 diabetes

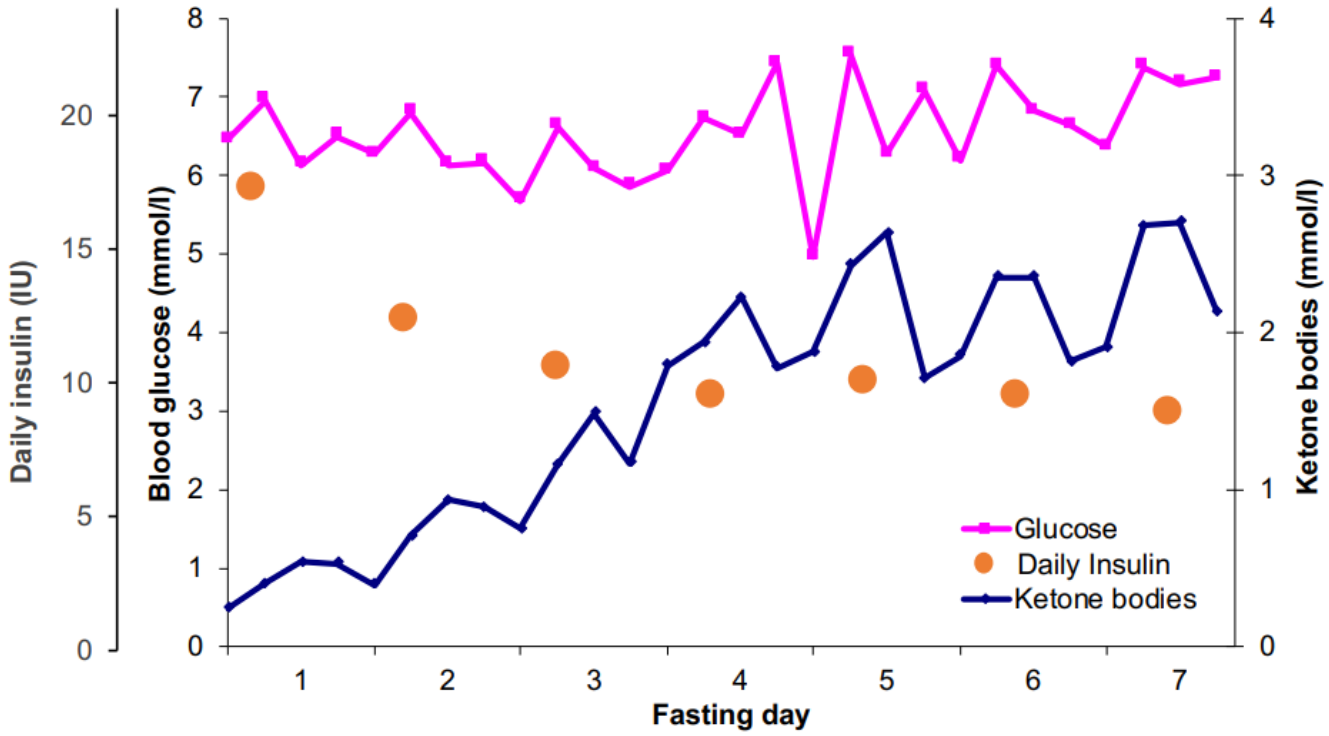

Figure 4

Ketone body development under fasting conditions in participants with and without type 1 diabetes