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# Seven-day fasting as a multimodal complex intervention for adults with type 1 diabetes: Feasibility, benefit and safety in a controlled pilot study

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ABSTRACT

*Objectives:* Intermittent as well as prolonged fasting are receiving considerable attention and appear favorable in conditions such as metabolic syndrome, type 2 diabetes, and rheumatic diseases. Fasting for individuals with type 1 diabetes (T1D) is generally considered too risky. However, the ability and possibility to change from carbohydrate- to ketone-based fuel supply might be relevant for individuals with T1D. The aim of this patient-led research was to investigate the feasibility, benefit, and safety of a 7-d multimodal fasting intervention in individuals with T1D.

*Methods:* This was a non-randomized controlled pilot study, with 20 participants with T1D and 10 without the disease. Data acquisition took place before, after, and 4 mo after the intervention and daily during intervention.

*Results:* Of the individuals with T1D, 19 finished fasting. A mean β-hydroxybutyrate as representative ketone body increased to 2.8 ± 1.9 mmol/L on day 7; whereas average glucose remained between 4.9 (±1.5) and 7.5 (±2.3) mmol/L (89 ± 27 and 136 ± 40 mg/dL). 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 (±4.4) to 68.8 (±15; $P = 0.01$) after fasting. There was a decrease from before until the follow-up 4 mo later of weight from 77.6 (±20.4) to 76.6 (±20.9) kg ($P = 0.023$) and for body mass index 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) to 75.74 (±8.42) mm Hg ($P = 0.028$) and stayed in a healthy range on average. Fasting-related side effects were all temporary, and slightly more prevalent in those with type 1 diabetes compared with the reference group.

*Conclusions:* This study demonstrated the feasibility, benefits, and safety aspects of a 7-d fast in adults with T1D.

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## Introduction

Type 1 diabetes (T1D) 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 health care 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]. Individuals with T1D are inherently exposed to an elevated risk for developing psychological and neurologic long-term consequences such as depression and cognitive decline [3,4]. Taken together, this suggests that treatment strategies should address clinical, humanistic, and economic burdens [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 been shown to be effective in a number of conditions that could potentially be relevant to individuals with T1D, such as depressive disorders, exhaustion/fatigue, metabolic syndrome including type 2 diabetes, and autoimmune diseases such as rheumatoid arthritis [6–8]. A guideline on the method was previously published [5]. The evaluation of 1422 individuals after a Buchinger fast lasting 21 d showed that this intervention is safe and well tolerated in people without T1D. An increase in physical and emotional well-being was observed during prolonged fasting [9].

Currently, T1D is seen as a relative contraindication for prolonged fasting due to the supposed risk for 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 hyperglycemia (blood glucose >13.9 mmol/L) plus pH levels dropping below 7.3, and/or bicarbonate levels <18 mmol/L, according to the consensus statement of the American Diabetes Association [11], or <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 to 3 mmol/L. During prolonged fasting, the BHB levels for adults typically range between 5 and 7 mmol/L [14]. The perception of ketones in T1D 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].

Research on ketones under fasting conditions in individuals with T1D with sufficient insulin supply is scarce. Studies of Balasse showed no difference of ketone body removal capacity between individuals with or without T1D [19]. Féry identified 10 to 12 mmol/L as the highest ketone body levels during prolonged fasting, and found similar levels in healthy individuals and in insulin-deprived patients with diabetes [20]. It is obvious, that as long as ketogenesis is controlled by sufficient insulin supply, fasting should be possible in patients with T1D.

There are very few studies on fasting in patients with T1D. Musil et al. investigated a 7-d fasting period in obese individuals with T1D compared with normal weight individuals with T1D, resulting in a relevant decrease of weight and low-density lipoprotein cholesterol (LDL-C). The intervention was combined with a very low-carbohydrate diet (LCD) after the 7 d of fasting and demonstrated relevant improvements. Obese individuals with T1D lost 6.1 (±1.1) kg after fasting and maintained the reduction in body weight after 21 d of LCD. Ketone and blood glucose values were not monitored [21].

Most fasting clinics and diabetologists advise against fasting as a health intervention for individuals with T1D. Nevertheless, individuals with T1D 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 (QoL), reducing body weight, and improving their long-term prognosis [22].

### *Buchinger fasting as complex intervention*

Hence, there is a demand for research to prove the principal feasibility, possible harms, and benefits of fasting for those with T1D. Due to lack of research, a patient-led research project was initiated. Pilot or feasibility studies are important aspects of the evaluation of complex intervention as what Buchinger fasting might be regarded, using different stages of evaluation following the Medical Research Council framework for design and evaluation of complex interventions (phase 0: preclinical or theoretical; phase 1: modeling; phase 2: exploratory or pilot trial; phase 3; definitive randomized controlled trial; and phase 4: implementation) [23]. Complex interventions are built from a number of components, which may act both independently and interdependently. Many health service activities can be considered complex. Unless the trials illuminate processes and mechanisms, they often fail to provide useful information [24].

The complexity of the fasting intervention and the management of T1D might have led to the lack of research in this field until now. But patients themselves are able to manage the complexity of fasting as individuals, so, medical supervised fasting should be possible as well. There are several examples of patient led research [25]. Meanwhile, patient involvement in designing studies is increasingly welcomed, as it might be able to bring research closer to their needs [26].

## Research design and methods

A non-randomized controlled pilot study was performed with 20 participants with T1D and 10 without the disease. Data acquisition took place before, after, and 4 mo 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 [27] enriched by aspects of process (acquisition of participants), and management (realization in a non-medical center) [28]. The description of the intervention follows the Template for Intervention Description and Replication (TIDieR) Checklist [29].

### *Participants*

This controlled feasibility study was performed with 20 participants with T1D and 10 participants without the disease 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 T1D for ≥2 y, including latent autoimmune diabetes in adults (LADA), were using self-monitoring of blood glucose, showed interest in participating in a 9-d intervention with 7-d of fasting, and were ready to travel to the study doctor before and 4 mo after the intervention.

#### *Exclusion criteria*

Exclusion criteria included presence of acute psychiatric disease, severe internal diseases, febrile diseases, kidney diseases, dialysis, pregnancy, lactation, addictions, malignancies, body mass index (BMI) <21 kg/m$^2$, and diabetes insipidus; ongoing application procedures for occupational disability; and participation in other clinical studies within the preceding 4 wk.

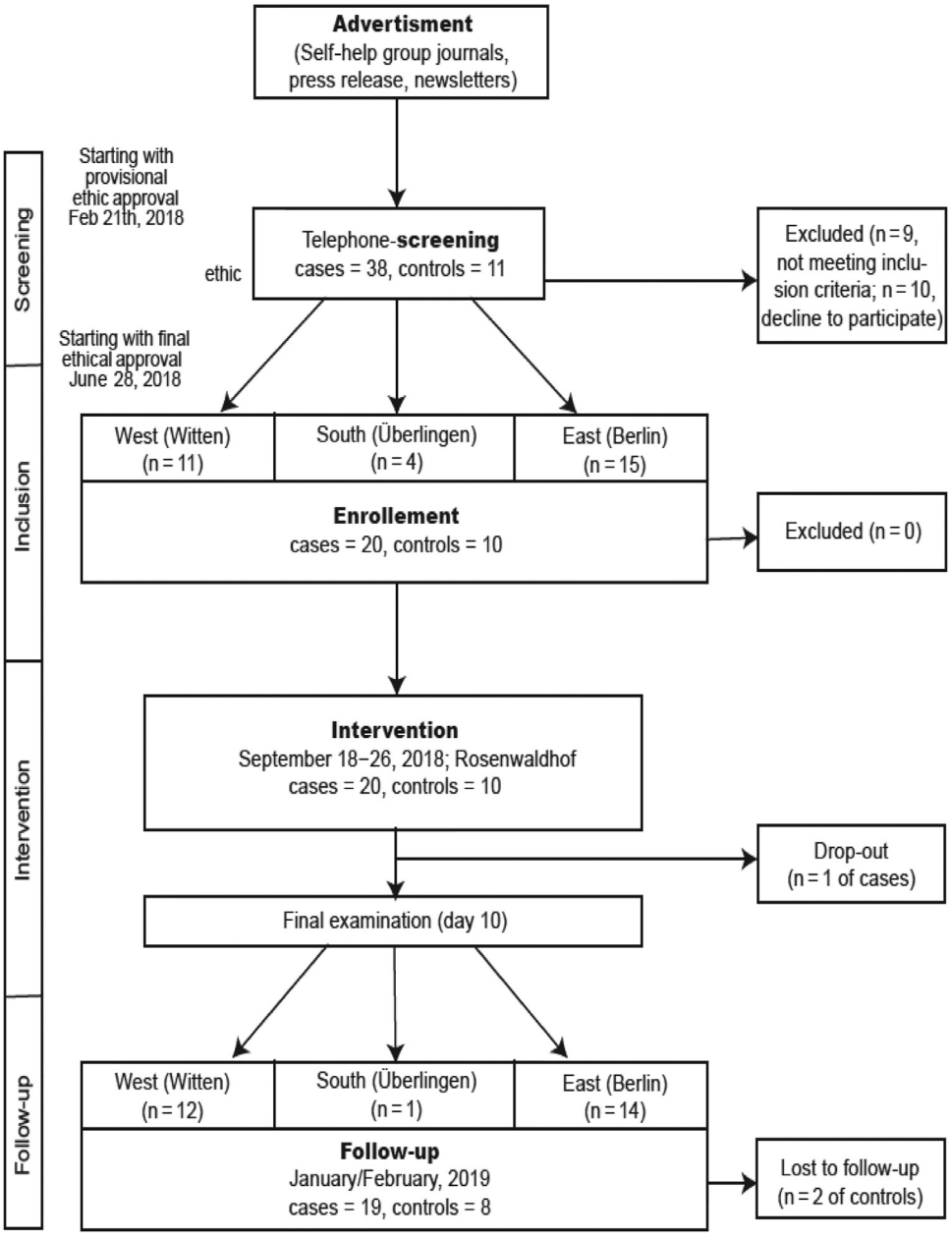


**Fig. 1.** Flowchart of intervention.

*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 three dimensions (medical, psychosocial, spiritual) [5]. The 9-d inpatient stay including 1 d preparing (reducing caloric intake to 1500 kcal), 7 d fasting and 1 d reintroducing solid foods (Figure 2) shows the 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 (0.25−0.5 L), and vegetable juices (0.25−0.5 L), limited to maximum 400 kcal. Participants were strongly advised to drink 2 to 3 L/d of fluids. Enema for bowel movement were introduced and advised for every second day. A warm liver wrap was advised daily during a rest for ≥30 min. The Zurich Resource Model (ZRM), an evaluated self-management tool, was offered for 1 h/d to increase awareness of and activate somatic, emotional, social, and mental resources [30]. Because 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 to 1 h/d. Individualized exercise (jogging, hiking, swimming, Nordic walking, cycling) was scheduled for 2 h/d. 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 center 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

**Table 1**
Demographic characteristics of participants at baseline

| | With T1D (n = 20) | Without T1D (n = 10) |
|---|---|---|
| Baseline demography | | |
| Age (y), mean ± SD | 56.4 ± 6.2 | 45.7 ± 13.8 |
| Women/Men | 19/1 | 7/3 |
| Weight (kg), mean ± SD | 77.60 ± 20.47 | 75.94 ± 15 |
| BMI (kg/m$^2$), 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 carbohydrate | 7 | 0 |
| Vegan | 0 | 1 |
| Vegetarian | 6 | 2 |
| Other diet | 0 | 1 |
| Diabetes type | | |
| T1D | 15 | |
| LADA | 5 | |
| Duration of diabetes disease (y) | 34.3 ± 3.54 | |
| Insulin therapy | | |
| Pump/ICT | 15/5 | |
| Blood glucose self-management | | |
| Individual measurement, bloody | 2 | |
| Continuous glucose monitoring | 4 | |
| FreeStyle Libre | 14 | |
| Preexisting 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 | |
| Autoimmune diseases | | |
| Rheumatoid arthritis | 1 | 0 |
| Hashimoto's thyroiditis | 11 | 1 |
| Other autoimmune diseases | 6 | 0 |
| Previous psychotherapeutic treatments | | |
| Total, n (%) | 14 (70) | 2 (20) |
| Biographic burdens | 1 (5) | 2 (20) |
| Depression, burnout | 7 (35) | 0 |
| PTBS, abuse | 2 (10) | 0 |
| T1D | 2 (10) | 0 |
| Eating disorder | 2 (10) | 0 |

BMI, body mass index; ICT, intensified conventional therapy; LADA, latent autoimmune diabetes in adults; PTSD, posttraumatic stress disorder; T1D, type 1 diabetes.

feedback daily and at the end of the intervention, both orally and in written form. Attendance in ZRM, eurythmy/mindfulness, and exercise were documented daily. Qualitative interviews were conducted on day 7 and during the follow-up meetings 4 mo later.

*Adverse events*

The program was continuously monitored for safety and supervised by the medical staff. Symptoms that could be classified as adverse events (AEs) were reported daily by participants, approved by signature of attending medical doctors, and discussed daily in the team meetings. For evaluation and reporting, the AEs 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 3. This publication uses two manners of reporting AEs: only events occurring three or more times per participant, as did Wilhelmi et al. [9], and 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 >3.9 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. Although the state of consciousness is not restricted in mild ketoacidosis, moderate ketoacidosis is associated with impaired consciousness (sleepiness) [11–13]. The severity of 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 daily. Each participant was given glucose and ketometers (GlucoMen Areo 2 K) and trained to use them correctly four times daily. To control the risk for 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 to 4 IU insulin together with two carbohydrate units (e.g., apple juice) were advised and documented in case of 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 two carbohydrate units and 2 to 4 IU insulin were to be repeated every 2 h until normalization. Criteria to prematurely discontinue the fast on the part of the study management were predefined in the study protocol [31].

*Outcome parameters*

Data acquisition took place before, immediately after, 4 mo after the intervention, and daily during intervention. We expected improvement in QoL and physiologic parameters and a decrease of diabetes-related problems—all of which were assessed before and after intervention, as well as 4 mo later at follow-up. We chose a generic QoL instrument (WHO-5 [32]) as well as a diabetes-related psychometric instrument (Problem Areas in Diabetes [PAID]) [33], 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 ~80% [34]. Physiologic parameters were weight, BMI, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL); systolic and diastolic (DBP) blood pressure; and glycated hemoglobin ($HBA_{1c}$).

*Biometrics and sample size calculation*

Our main question was the risk of getting a major acute metabolic complication of T1D, DKA, during the investigated fasting intervention. There is a lack of knowledge about the true incidence of the serious event of DKA in T1D. Even the definition of DKA varies. According to a review by Farsani et al., eight studies reported incidence of DKA with a range of 0 to 56/1000 person-years (PYs), with one outlying study reporting an incidence of 263/1000 PYs. Eleven studies reported prevalence with a range of 0 to 128/1000 PYs [35]. Expressed in other terms, in most studies the incidence probably will be <5.6% during 1 y.

Due to the new character of the investigated intervention, we decided not to observe a larger number of individuals with T1D at risk and limit this pilot trial to 20 participants with T1D. In future efficacy trials more individuals with T1D who were diagnosed for a longer time will be investigated for DKA and related safety issues to specify whether the DKA incidence would differ from the basic DKA incidence up to 5.6%.

*Informed consent and ethics committee approval*

Written informed consent was obtained from all included patients. The reported investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2008. Ethical approval was obtained by the Ethic Committee of the University Witten/Herdecke. The study protocol was published in German [31]. The study was registered in the German Clinical Trial register. 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 individuals with T1D who applied for participation, none were excluded. Twenty agreed to be participate, whereas the remaining 19 refused participation due to time conflicts. Demographic data is shown in Table 1.

**Table 2**
Insulin doses and additional carbohydrate units

| | | Fasting day* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Preparation day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Set-up day† 8 |
| Total daily insulin doses (IU) | | | | | | | | | |
| Total IU/d | 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 | 11 | 9.6 | 8.9 | 9.5 | 8.9 | 7.2 | 9.3 |
| IQR§ | 16 | 7.4 | 5.5 | 7.3 | 7.3 | 6 | 7.2 | 6.1 | 3 |
| Maximum | 50 | 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 (1 unit = 10 g) | | | | | | | | | |
| Total/d | 131 | 97.2 | 89.8 | 64.5 | 63.2 | 67.1 | 59.5 | 50 | 122.4 |
| Per person (n = 20) | 6.6 | 4.9 | 4.5 | 3.2 | 3.2 | 3.4 | 3 | 2.5 | 6.1 |
| Median | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| IQR | 1.5 | 1 | 0.8 | 0.5 | 1 | 1 | 0.8 | 1 | 1 |
| Maximum | 6 | 4 | 4.5 | 2.5 | 2 | 3 | 3 | 4 | 56 |
| Minimum | 0.5 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.2 | 0.3 |

IQR, interquartile range.
*Ranging from 6 AM to 6 AM the day after.
†Set-up day 8 is the day of breaking fast.
‡Per person = total/d of 20.
§Third to first quartile.

Ten people without T1D served as a reference group for AEs 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 (3–50) to 7.6 (0–26.7) IU (Table 2). The need for additional carbohydrates to prevent or treat hypoglycemia during exercise started with 48.5 (5–60) g per person on the first fasting day and decreased to 24.8 (2–40) g per 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.

*Feasibility in relation to AEs*

The intervention was successfully completed by 29 of 30 participants. One participant with T1D interrupted the intervention prematurely due to anxiety about missing important events at work and a rebound of chronic back pain. No SAE occurred. All AEs were investigated in detail to exclude ketoacidosis. No DKA occurred. There were no severe hypo-/hyperglycemia with 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 AEs are listed in Table 3.

Four participants vomited once each. Because vomiting is usually regarded as a symptom of ketoacidosis, we analyzed these events separately (Table 4). One of the four individuals felt weak thereafter and laid in her bed for half a day. She received antiemetic support. There was no further need for medical intervention. None of the four cases fulfilled the definition of ketoacidosis.

In the follow-up period, one participant with a past history of anorexia reported a mild transitory recurrence of the eating disorder, which may have been triggered by fasting. Two participants reported temporarily higher insulin needs after the fasting.

*Feasibility in relation to benefits*

Participants with T1D developed fasting-induced blood ketone values <3 (±1.49) mmol/L, but no acidosis and maintained target levels of glucose control on average between 5 and 10 mmol/L (90–180 mg/dL;) Figure 3. 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 6 wk before she returned to her former doses, but her C-peptide values indicated enough insulin production (September 28, 2018: 2.05 ng/mL; February 21, 2019: 1.77 ng/mL). Participants with LADA should therefore be analyzed as a separate subgroup.

In participants without T1D, ketone values rose to 3.9 (±2.88) mmol/L (Figure 4). 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 T1D and experienced in fasting, had ketone values ≤7.4 mml/L on day 6 without symptoms and was feeling perfectly well.

QoL (WHO-5) improved during the intervention from 54 (±4.44) to 68.84 (±15), resulting in a significant improvement of 13.68 (20.76; $P = 0.010$) for the group with T1D immediately after the intervention. PAID-1 improved non-significantly.

Focusing on the results of the group with T1D (Table 5), weight decreased from 77.6 (±20.4) kg before to 76.6 (±20.9) kg 4 mo after the 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-C and therefore the LDL-to-HDL ratio remained significant even after 4 mo. DBP increased from 69.75 (±11.41) to 75.74 (±8.42) mm Hg ($P = 0.028$) 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%]) 4 mo after the intervention (Table 5).

## Discussion

*Principal findings*

The present study demonstrated that a 7-d fast is feasible for individuals with T1D and that their risk for DKA is easily controlled by adapting insulin dosage to blood glucose levels. Insulin substitution and occasional intake of carbohydrates in cases of hypoglycemia are the most probable reasons for the lower ketone bodies in participants with T1D compared with participants without the condition. Lower metabolic flexibility may be a further factor. The three people with T1D already experienced in fasting interventions developed faster and higher ketosis than participants without fasting experience, suggesting a training effect in metabolic flexibility [36]. Various parameters related to the risk for Metabolic Syndrom

**Table 3**
Reported adverse events and ketoacidosis-relevant blood measurements

| | Participants with ≥3 AEs | | | | | Total number of AEs | | |
|---|---|---|---|---|---|---|---|---|
| | During FDs | During 7 FDs and fast break | | During set-up days (days 8–9) | | During 7 FDs and fast break | | During set-up days (days 8–9) |
| | Reference study in participants without T1D | Presented feasibility study in participants with and without T1D fasting for 7 d | | | | | | |
| AEs (self-reported) | Toledo et al. 2019 [9] (n = 1422), n (%) | With T1D (n = 20), n (%) | Without T1 D (n = 10), n (%) | With T1D (n = 20), n (%) | Without T1D (n = 10), n (%) | With T1D (n = 19) | Without T1D (n = 10) | With T1D (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 |
| Muscle 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 |
| Ketoacidosis-relevant blood value categories (measured) | | | | | | T1D | Without T1D | |
| pH 7.2 to <7.3 | | | | | | 2 | 0 | |
| pH <7.2 | | | | | | 0 | 0 | |
| SBC (mmol/L) 15–18* | | | | | | 3 | 1 | |
| SBC (mmol/L) <15† | | | | | | 0 | 0 | |
| Glucose (mg/dL) <60 | | | | | | 52 | 3 | |
| Glucose (mg/dL) >250 | | | | | | 5 | 0 | |

AE, adverse event; FD, fasting day; SBC, standard bicarbonate; T1D, type 1 diabetes.
pH and SBC were measured once daily capillary, blood glucose was measured capillary at four defined times and whenever required.
*Mild ketoacidosis according to Kitabchi et al. [11], who defined SBC <18 to 15 already as mild.
†Ketoacidosis according to guidelines.

**Table 4**
Detailed analyses of four participants with T1D with vomiting as an AE

| Internal code | FD | Grade of AE* | Reported intensity of complaints | Probable origin | Ketone bodies (mmol/L) | Glucose (mg/dL) [mmol/L] | Potassium (mmol/L) | pH value | SBC (mmol/L) | Interpretation of acidity |
|---|---|---|---|---|---|---|---|---|---|---|
| 23_01_13_MD | 4 | II–III† | Low | Psychogenic | 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 |

AE, adverse event; FD, fasting day; SBC, standard bicarbonate; T1D, type 1 diabetes.
*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: Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5×11.pdf.
†Hospitalization was not required, but limited self-care for half a day.

| | Sept 17 | Sept 18 | Sept 19 | Sept 20 | Sept 21 | Sept 22 | Sept 23 | Sept 24 | Sept 25 | Sept 26 | Sept 27 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Preparation day | Fasting day 1 | Fasting day 2 | Fasting day 3 | Fasting day 4 | Fasting day 5 | Fasting day 6 | Fasting day 7 | Breaking the fast | Closing day |
| 7 to 7:45 am | | Tea and measurements | | | | | | | | | Closing visits with medical doctors |
| 8 to 9 am | | Talking circle: How it is and how I do! Physical, emotional and mental state | | | | | | | | | |
| 9:15 to 10:15 am | | Eurythmy/mindfulness practice | | | | | | | | | |
| 11 am to 12:30 pm | | Introduction to fasting | ZRM*: Where I am and where I want to go | How do I nourish my body? | Somatic marker and embodyment | How do I nourish my soul? | How do I nourish my relationships? | How do I nourish my mind? | Working with metaphors | Closing circle | |
| 12:30 to 1 pm | | Fasting lunch | | | | | | | | | Departure |
| 1 to 2:30 pm | | Break and external applications (liver wrap) | | | | | | | | | |
| 2:30 to 5 pm | Arrival of participants | Free time for exercise (cycling, walking, hiking, jogging) or lessons about diet after fasting | | | | | | | | | |
| 5 to 6:30 pm | | Fasting visit with medical doctors | | | | | | | | | |
| 6:30 to 7:30 pm | | Fasting dinner | | | | | | | | | |
| 7:30 to 8:30 pm | Talks | Effects of fasting on health | Keton bodies - friends or foes? | T1D and your Biography | Anthroposphy and T1D | Half-time party, singing, dancing | Consciousness and diabetes | Free evening | Singing and dancing | Relaxation | |
| 8:30 to 9 pm | | Poems, songs or dancing | | | | | | | | | |

*ZRM = Zurich Resource Model

**Fig. 2.** Timetable for fasting intervention. T1D, type 1 diabetes; ZRM, Zurich Resource Model.

or type 2 diabetes, such as weight, BMI, blood pressure and the LDL-to-HDL ratio improved significantly and remained so at follow-up. This is an important result considering the long-term metabolic risks for people with T1D [37].

### *Recruitment and contraindications*

Acquisition was feasible. However, the intervention length of 9 d without the opportunity for sick leave from work was the primary reason that individuals declined participation. We did not exclude people with a history of eating disorders. These individuals should be warned that fasting can trigger relapses. Poorly controlled glycemia also might be a relative contraindication, especially in those with no previous fasting experience. Use of sodium-glucose co-transporter-2 (SGLT2) inhibitors may present a further contraindication.

### *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 after food intake, but not in fasting conditions [38]. 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 individuals with T1D who are fasting 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 wk under close blood glucose supervision. The management of AEs appears feasible but should be accompanied by daily observation of values outside of

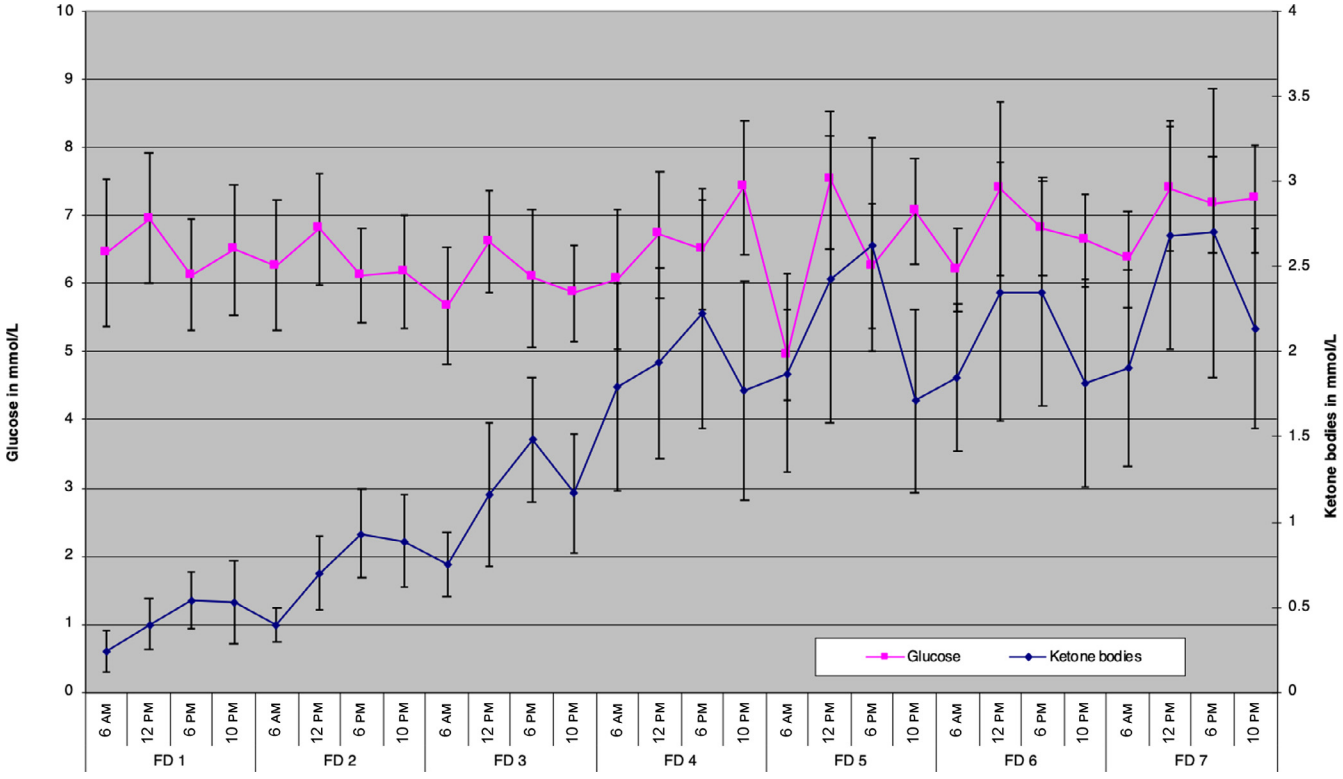


**Fig. 3.** Ketone bodies and glucose under fasting in participants with type 1 diabetes. FD, fasting day.

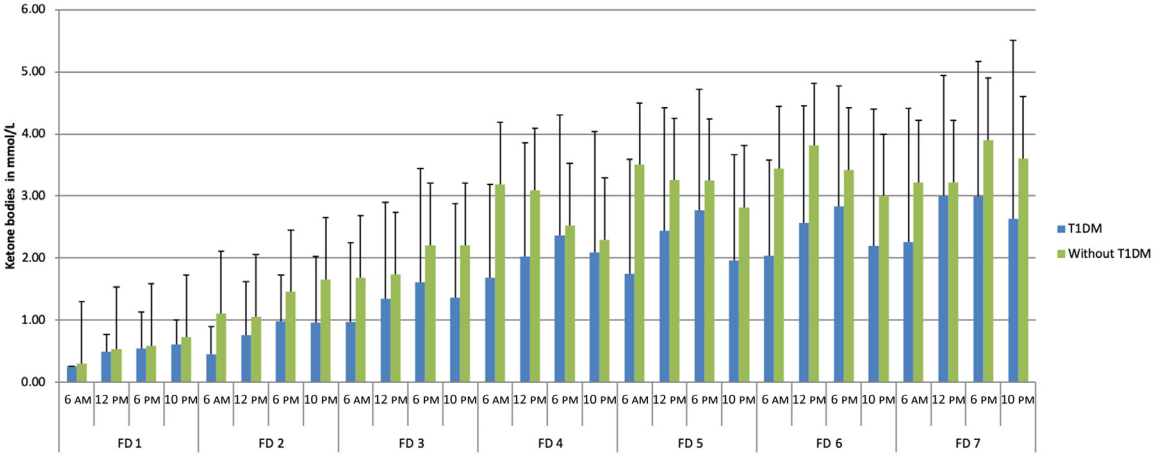


**Fig. 4.** Ketone body development under fasting conditions in participants with and without type 1 diabetes. FD, fasting day; T1DM, type 1 diabetes mellitus.

the norm. DKA, a potentially lethal event [35], can occur in all circumstances, theoretically also during fasting.

*Biometric analysis*

We treated 20 patients with T1D with an observation period of 4 mo. However, there have not been any cases of DKA in these individuals, corresponding to a 95% binominal confidence interval between 0 and 16.8%. If instead we would have had 60 instead of 20 patients, we could lower the upper limit of the 95% confidence interval to at least normal DKA incidence rate. However, it has to be considered that this study was not a confirmatory one but one of safety and proof of principle trial for an intervention that previously has been considered as impossible for T1D. One DKA in 20 people with T1D would refer to a normal incidence rate of about 5%.

This study provides initial data for safety rules that can be further evaluated in larger controlled trials [39]. There are differing definitions of DKA. The U.S. 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 reported the values of SBC between 15 and 18 mmol/L (Table 3). Values remained outside the norm for <24 to 36 h. Hence, no professional medical intervention was required. AEs were compared with those registered in a larger clinical investigation [9], demonstrating that

**Table 5**
Biological and psychological changes in T1D during intervention and at 4 mo follow-up

| n = 20 | Before intervention mean ± SD | Day 8 of intervention* mean ± SD | Change during intervention mean (95% CI) | *P*-value† | 4-mo follow-up mean ± SD | Change at 4 mo from baseline mean (95% CI) | *P*-value† |
|---|---|---|---|---|---|---|---|
| Weight (kg) | 77.60 ± 20.47 | 75.94 ± 15 | −3.11 (−1.7 to −3.5) | <0.001 | 76.61‡ ± 20.96 | −1.27‡ (−2.36 to − 0.20) | 0.023‡ |
| BMI (kg/m$^2$) | 27.68 ± 7.04 | 26.20 ± 4.74 | −1.19 (−1.64 to −0.75) | <0.001 | 26.74‡ ± 7.15 | −0.91‡ (−1.55 to −0.27) | 0.008‡ |
| TC (mmol/L) | 5.49 ± 1.20 | 4.90 ± 1.22 | −0.67 (−0.93 to; −0.4) | <0.001 | 5.30* ± 0.91 | −0.19* (−0.65 to −0.27) | 0.387* |
| HDL | 1.75 ± 0.34 | 1.44 ± 0.31 | −0.31 (−0.45 to −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 to −0.01) | 0.066 | 3.31 ± 0.94 | 0.04 (−0.19 to 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 to −0.05) | 0.012 |
| SBP (mm Hg) | 128.25 ± 16.00 | 126.11 ± 20.48 | −2.50 (−13.30 to 8.30) | 0.631 | 125.61 ± 11.85 | −2.45 (−10.2 to 5.31) | 0.518 |
| DBP (mm Hg) | 69.75 ± 11.41 | 69.17 ± 9.12 | −0.28 (−7.74 to 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 to 14.05) | 0.158 |
| PAID-1 | 1.10 ± 1.02 | 0.89 ± 0.81 | −0.26 (−0.74 to 0.21) | 0.262 | 1.00 ± 0.80 | −0.10 (−0.47 to 0.27) | 0.577 |
| $HbA_{1c}$ % (mmol/mol) | 7.03 ± 0.86 (53.33 ± 14.10) | | | | 7.07 ± 0.86 (53.77 ± 14.10) | 0.00 (−0.22 to 0.22) | 1.000 |

BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAID, Problem Areas in Diabetes Scale; SBP, systolic blood pressure; TC, total cholesterol; T1D, type 1 diabetes; WHO, World Health Organization.
*Only n = 19 values.
†One sample *t* test on difference.
‡Only n = 17 values.

fasting-related AEs were temporary but slightly higher in the group with T1D. 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 was interpreted as reaction to an acid overload but did not fulfill the criteria of mild ketoacidosis following the U.S. guidelines, because of missing altered mental status. In all cases, the values normalized within 24 h without medical intervention (Table 4). Although no DKA occurred, the risk for euglycemic ketoacidosis must be discussed. Hyperglycemia 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) [40]. The conditions for EDKA to occur appear to be dehydration, lack of insulin, or both [41]. Both were monitored intensively during the intervention. In 2015, regulatory agencies warned that SGLT2 inhibitors may facilitate DKA [42]. Therefore, people using SGLT2 inhibitors 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 4 mo later. The results of the WHO-5 questionnaire indicate that many of the participants with T1D can be classified as being on the verge of depression, as has been determined from large cohort studies of adults with T1D [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 individuals with T1D. Realization of such a complex intervention in a nonclinical setting was demanding and repetition might be limited. This was 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, and 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 upregulation of inflammatory cytokines (interleukin (IL)-1 β, IL-4, and IL-6) and tumor necrosis factor-α, activates IL-10, and haptoglobin in the plasma of streptozotocin-induced diabetic rats [43]. The interventional trial should investigate efficacy in relation to diabetes-relevant outcome parameters like the risk for developing Metabolic Syndrom and type 2 diabetes, the improvement of metabolic flexibility and QoL. Based on the reports of participants, time in range (TIR) was improved during intervention. Therefore, TIR should be included as a patient-relevant outcome in the interventional study.

*Meaning of the study: Possible explanations and implications for clinicians and policymakers*

This study showed that a 7-d fast in T1D is possible. It also contributes eligibility criteria and cutoff 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 subsequent randomized controlled efficacy trials might benefits QoL (WHO-5), BMI, blood fat levels, as well as changes in lifestyle and diet and, ultimately, long-term metabolic benefits and longevity in regular fasters.

Possibilities of reducing body weight in individuals with T1D become increasingly important. Reduction of body weight recently turned out to be one of the most important patient preferences [44]. 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 [45]. In fact, fasting could be considered a therapeutic strategy to lower (the risk for) the severity of COVID-19 to some extent before or even during the infection.

## Conclusions

A 7-d liquid-based fast as a multimodal, medically supervised intervention is principally feasible and has potential short- and

long-term benefits for individuals with T1D. Ketosis as physiologic fasting reaction does not equate (euglycemic) DKA as long as insulin substitution is ensured. Nevertheless, the risk for fasting-related acidosis should be taken seriously and individuals with T1D 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 QoL and long-term complications in adults with T1D.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2021.111169. Documentary video: https://www.uni-wh.de/gkls/forschung/projekte/integrative-typ-1-diabetologie/

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