Aus dem Institut für Sozialmedizin, Epidemiologie und Gesundheitsökonomie der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Clinical Effects of Fasting Therapy for Treating Type-2 Diabetes Mellitus and Fibromyalgia

zur Erlangung des akademischen Grades

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1. Summary

1.1 Abstract (German)

Daten aus Beobachtungsstudien und langjährige Erfahrung von Anwendern legen nahe, daß medizinisch überwachtes therapeutisches Fasten (periodisches Fasten, „Heilfasten, very low calorie diet“) bei der Behandlung von Metabolischem Syndrom sowie chronischen Schmerzsyndromen des Bewegungsapparates eine wirksame Maßnahme darstellt. Zugeschrieben werden dem Fasten eine antiinflammatorische Wirkung, die Verlangsamung von chronisch degenerativen Prozessen sowie die Induzierung von gesundheitsfördernder Lebensstiländerung und stimmungsaufhellende Effekte. Inzwischen wird Fasten international zunehmend eingesetzt, u.a. Auch im Rahmender der Integrativen Medizin in den USA und China. Ziel der kontrollierten Pilotstudien dieser Dissertation ist es, die klinischen Effekte einer Fastenbehandlung zu evaluieren und damit zur Einschätzung des Fastens als gesundheitsfördernder komplementärmedizinischer Behandlung beizutragen.

In der ersten Studie untersuchten wir die kombinierte Wirkung einer additiven Phytotherapie nach Empfehlungen der Traditionellen Chinesischen Medizin (TCM) im Zusammenhang mit einem kurzzeitigen, 5-tägigen Fasten mit Energieaufnahme <550 kcal / Tag bei Patienten mit Typ-2-Diabetes mellitus (T2DM). Es zeigte sich in beiden Gruppen eine Verbesserung metabolischer und glukoregulatorischer Parameter, in der Kombinationstherapie aber mit stärkerer Ausprägung einschließlich eines reduzierter Bedarfs an Antidiabetika nach drei Monaten. Ein integrativer Behandlungsansatz, der die Standard-T2DM Behandlung, VLCD und ein TCM-Dekokt umfasst, könnte somit vorteilhafte Wirkungen haben. In einer weiteren randomisiert-kontrollierten Studie untersuchten wir die mittelfristige (vier Monate) metabolische Reaktion auf ein ambulantes periodisches Fasten über 7 Tage nach der Buchinger Technik (Energieaufnahme ca. 300 kcal/Tag durch Säfte) bei Patienten mit T2DM. Das Fasten führte im Vergleich zur Kontrollgruppe mit konventioneller Ernährungsberatung zu Gewichtsabnahme, Verringerung des abdominalen Umfangs, signifikanter Senkung des Blutdrucks und erhöhter Lebensqualität. Es wurden jedoch nur nicht signifikante Verbesserungen für HbA1c, Insulin und HOMA-Index beobachtet. Diese Ergebnisse legen nahe, dass verlängertes Fasten positive klinische Auswirkungen auf T2DM haben könnte und somit als gut durchführbare Therapieergänzung in größeren konfirmatorischen Studien weiter evaluiert werden sollte. In einer dritten Untersuchung verglichen wir in einer kontrollierten Pilotstudie die therapeutischen Effekte der rheumatologisch-stationären Komplex Therapie (RT) mit denen der integrativen Medizin (IM), einschließlich des Schwerpunktes einer stationären Fastentherapie mit begleitender Mind Body Medizin bei Patienten mit Fibromyalgie Syndrom. Die Ergebnisse deuten darauf hin, dass eine multimodale IM-Behandlung mit Fasten-Therapie und Mind Body Medizin der CM kurzfristig überlegen und mittelfristig nicht unterlegen sein könnte. Darüber hinaus veröffentlichten wir einen narrativen Review Artikel, zur aktuellen Studienlage bezüglich der Wirksamkeit von Fastenbehandlungen zur Behandlung und Vorbeugung von Erkrankungen.

1.2 Abstract (English)

There is large empirical and observational evidence that medically supervised modified fasting is efficacious in the treatment of metabolic syndrome and chronic pain syndromes. Beneficial effects of fasting are attributed to distinct anti-inflammatory effects and the deceleration of chronic degenerative pathways, accompanied by enhancement of health-related lifestyle modification and mood enhancement. Recently, there is increasing international use and demand of fasting therapy within the concept of integrative medicine, e.g. in the U.S. and China. The goal of the studies that make up this dissertation is to evaluate the clinical effects of fasting therapy with controlled pilot trials, hence, contribute to the evaluation of fasting therapy as a health-promoting complementary treatment.

In the first study, we evaluated the effects of a Traditional Chinese Medicine (TCM) herbal decoction combined with short-term fasting over 5 days (energy intake < 550 kcal/day) on the therapeutic response in type 2 diabetes mellitus (T2DM) patients. Both groups showed improvement of glycemic control, but with combination therapy a more pronounced glucoregulatory and metabolic effect including the reduced use of anti-diabetic medication could be found after three months. These results point to a putative beneficial effect of a combination approach of fasting and traditional herbal Chinese Medicine in T2DM treatment. To further explore the clinical effect of fasting therapy on T2DM, in the second study, we investigated the mid-term (four months) metabolic response of prolonged fasting (7 days, energy intake < 300 kcal/day) in patients with T2DM within a randomized controlled outpatient study. Fasting led to greater weight decrease, reduction of abdominal circumference, significant decrease of blood pressure and increased quality-of-life. However, only non-significant improvements were observed for HbA1c, insulin and HOMA-index. These results suggest that prolonged fasting is feasible and might have beneficial clinical effects on T2DM. The effectiveness should be proven in larger confirmatory trials. In the third study, we conducted a controlled pilot study to compare the therapeutic effects on fibromyalgia treated with conventional rheumatological inpatient care (RT) versus integrative medicine (IM) including fasting therapy. Findings indicate that a multimodal IM treatment with fasting therapy might be superior to CM in the short term and not inferior in the mid-term. Beyond, we published a narrative review summarizing the current state of fasting therapy for treating and preventing diseases.

1.3 Introduction

Fasting as a medical treatment has been claimed to be a valuable therapeutic method for chronic and acute diseases in a multitude of traditional and ethnomedical systems worldwide (*Buchinger 1932; Fahrner 1991*). In the last two decades, modified fasting attracted a growing popularity in the German public, i.e. as a self-care method for prevention and health promotion and particularly to initiate lifestyle modification (*Lützner 2002; Hartel and Volger 2004*). Moreover, fasting cures have been developed and successfully established in a couple of specialized fasting sanatoriums, thereby embedding defined periods of modified or subtotal fasting within holistic lifestyle modification programmes and a focus on Mind-Body Medicine and aspects of spirituality.

Physiologically, nutritional energy supply below a threshold of about 500 kcal/day leads to strong neuroendocrine responses accompanied by rapid mobilization of glycogen stores (phase I), followed by metabolism of fat mass via lipolysis after a fasting duration longer than 24 hours (phase II) before the phase of late starvation with accelerated protein loss (phase III). A maintained daily intake of some calories reduces protein catabolism by a significant amount (*Owen 1998*). Therefore, the daily intake between 200 and 500 kcal is established in clinical fasting and defines the currently most frequently used form of therapeutic fasting, the "fasting cure" or "Buchinger fasting" (*Buchinger 2000; Wilhelmi de Toledo et al. 2002; Wilhelmi de Toledo et al. 2013*). Very-low-calorie-diets (VLCD) allow a higher nutritional intake up to 800 kcal/day (*Wilhelmi de Toledo et al. 2013*). Yet, while VLCD also leads to substantial weight loss, the adaptive physiological and psychological responses are reduced and the mind-body medicine approach is not included. Finally, continuous caloric restriction is defined as a long term reduction in energy intake without malnutrition, mostly consisting of a 30-40% reduction of daily nutritional energy intake (*Varady and Hellerstein 2007*). Caloric restriction is commonly used in experimental animal research. As an alternative to traditional caloric restriction, intermittent fasting has also been established. One of the intermittent regimens involves a "feast day" on which food is consumed ad libitum that alternates with a "fast day" on which food is withheld (*Varady and Hellerstein 2007; Varady 2009*), which is the so-called alternate-day fasting. The feast and the fast periods are typically 24h and commonly weight is not changed by alternating diets. Another category of the intermittent fasting is the 5–2-days eating/fasting method. For this fasting method, five days of one week have normal caloric energy intake, while the other two days include a maximum calorie intake of 500 per day for women and 600 for men. All the fasting methods above are characterized by a reduction of calorie intake. Instead, as a particular form, intermittent fasting and time-restricted eating allow to consume an unchanged energy intake, but modulate the meal frequency (*Rothschild 2014*). A popular form of time-restricted eating involves fasting for 16

hours per day and eating during the consecutive 8 hours, typically on the same schedule each day.

Fasting now is an upcoming issue in China with its developing economy and an increasing number of population suffering from metabolic syndrome due to excessive nutritional intake. In this context, fasting therapy has been introduced in the first hospitals in China. As one of the pioneers the Department of Traditional Chinese Medicine in the First affiliated Hospital of the Sun-Yat Sen University (Guangzhou, *http://www.gzsums.net/zhuanke_614.aspx*) already established the fasting therapy as a standard in-patient and out-patient treatment for patients with metabolic syndrome. Moreover, they combine the fasting therapy with other therapeutic tools of TCM to improve the treatment effects and relieve the adverse effects of fasting. I worked on TCM in the First Affiliated Hospital of the Sun-Yat Sen University before my scientific work at Charité Berlin. There is an ongoing cooperation for research in fasting therapy between Sun-Yat Sen University and Charité Berlin.

Very-low-calorie-diets had come to clinical researcher's attention since the 1990s due to its effects on weight loss, lifestyle modification and improvement of cardiovascular risk factors in the obese patients with T2DM (*Henry and Gumbiner 1991; Kelley et al. 1993; Capstick et al. 1997; Lara-Castro et al. 2008; Lin et al. 2009; Krebs et al. 2008; Baker et al. 2009; Jazet et al. 2007*). Recently, a study on a rat model of type 2 diabetes in molecular level demonstrated that fasting/VLCD improves glucose metabolism before weight loss through beneficial metabolic effects on liver function (*Perry et al. 2018*). There are multiple mechanisms related to the putative beneficial effects of fasting therapy in T2DM and the metabolic syndrome, including reduced DAG-PKCε-induced hepatic insulin resistance, reduced hepatic glycogenolysis, and reduced hepatic acetyl-CoA content and gluconeogenesis (*Perry et al. 2018*).

On the other hand, there are characteristic descriptions on the physical signs and the constitution of T2DM patients in TCM indicating a specific treatment according to the concept of TCM with a focus on herbal treatments. These treatments are typically combined with diet. In T2DM the characterisitc pattern is described as so-called "turbid mucus distressing the spleen" according to the principles of TCM. Hence, at the Chinese centre we developed a new treatment, combining short-term modified fasting/VLCD with a TCM herbal treatment, i.e. modified *Ling-Gui-Zhu-Gan* decoction, which is postulated to warm and resolve mucus (*wen-hua-tan-yin*) as well as to strengthen the spleen and to remove turbidity (*jian-pi-xie-zhuo*). Preliminary clinical observations suggested that this treatment approach may promote the acceptance of caloric restriction and, moreover, may improve glycemic control. We evaluated the clinical effects of this integrative treatment with a 5-day peridoic

fasting period and additive herbal therapy for the first time by means of a randomized controlled pilot study (D. Chen and C. Li et al. 2012).

Prolonged periodic fasting is a strong physiological stimulus equivalent to a mild-to-moderate biological stress and activates numerous endocrine and neurobiological responses from systemic levels up to molecular signal pathways (*Varady et al. 2007; Gredilla et al. 2001; Hall et al. 2013; Choi et al. 2013; Bierhaus et al. 2005; Brecchia et al. 2006*). Two prospective but uncontrolled studies found beneficial effects of a 7-day modified subtotal fasting period (200-300 kcal/day) on insulin sensitivity, blood pressure and regulation of adipokines (*Li et al. 2013; Stange et al. 2013*). Furthermore, a recent small randomized trial evaluating a fasting-mimicking diet with periodic restricted nutritional energy intake (up to 600 kcal/day) found beneficial effects on cardiovascular risk factors and blood lipids in healthy subjects after 3 months (*Brandhorst et al. 2015*). However, so far there are no data from randomized trials in humans evaluating the clinical effects of prolonged periodic fasting (≥ 5days) in patients with T2DM. Therefore, we aimed to investigate the mid-term metabolic and clinical effects of a one-week outpatient fasting program in persons with T2DM by means of an explorative randomized pilot study (C. Li et al. 2017).

The general pain-relieving effect of fasting is a frequent empirical observation made by fasting therapists. Clinical experience and preliminary evidence from uncontrolled prospective studies suggest that an integrative approach including nutritional and fasting therapies may help to decrease symptoms and increase the quality-of-life in patients with fibromyalgia that is a complex clinical pain syndrome (*Michalsen and Hoffmann et al. 2005; Michalsen and Riegert et al. 2005*). Prolonged fasting has been found effective in several randomized trials on rheumatoid arthritis (*Kjeldsen-Kragh et al. 1991; Müller et al. 2000*). The anti-inflammatory, pain relieving, anti-nociceptive, and mood-enhancing effects of fasting and caloric restriction have been well described in experimental and clinical studies (*Johnstone 2007; Michalsen 2010; Molina et al. 1995; Nenonen 1998*). Patients with rheumatoid arthritis and fibromyalgia frequently report that elimination diets and meal skipping alleviate their symptoms (*Michalsen and Riegert et al. 2005; Haugen et al. 1991; Kjeldsen-Kragh et al. 1992*). In a trial with a heterogeneous sample of chronic pain patients fasting led to enhancement of mood and well-being (*Michalsen and Schneider et al. 2003*). Fasting in its typical in-patient treatment approach is delivered as a multimodal complex treatment. It is critical to assess better the effectiveness of this complex treatment approach including fasting therapy within the concept of Integrative Medicine (IM) and to compare it to the rheumatological conventional multimodal treatment approach. Therefore, we conducted a first controlled nonrandomized pilot study to compare an integrative treatment strategy

including fasting cure with a conventional rheumatologic (RT) treatment strategy (A. Michalsen and C. Li et al. 2013).

1.4 Methods

Methods are discussed separately for the therapeutic response of short-term fasting/ VLCD combined with TCM decoction on T2DM (D. Chen and C. Li et al. 2012), the clinical effects of prolonged fasting therapy on T2DM (C. Li et al. 2017) and the comparison of RT versus IM for treating fibromyalgia (A. Michalsen and C. Li et al. 2013).

In the first study (D. Chen and C. Li et al. 2012), all patients were admitted to the First affiliated Hospital of the Sun-Yat Sen University (Guangzhou, China) for in-patient treatment of T2DM. A total of 60 eligible patients (34 male and 26 female) participated in the trial. The study was designed as a clinical randomized pilot study. All patients were allocated randomly to either the intervention group or to the control group. Each group consisted of 30 patients.

Patients in the intervention group were treated internally with a modified *Ling-Gui-Zhu-Gan* decoction combination with a 5-day modified fasting/VLCD. The modified *Ling-Gui-Zhu-Gan* decoction contained Sclerotium Poriae Cocos (*fu ling*) 20 g, Ramulus Cinnamoni Cassiae (*gui zhi*) 12 g, Rhizoma Atractylodis Macrocephalae (*bai zhu*) 15 g, Radix Glycyrrhizae Preparata (*zhi gan cao*) 9 g, Radix Codonopsis Pilosulae (*dang shen*) 30g, and Radix et Rhizoma Rhei (*da huang*) 9 g.

As previously described (*Chen et al. 2010*), the dietary fasting/VLCD treatment consists of three phases: (1) the pre-fasting phase, (2) the 5-day strict modified fasting/VLCD phase and (3) the food reintroduction phase. The pre-fasting phase consists of 1-2 dietary “relief” days with an intake of fruits and vegetables only, aiming to prepare patients for the fasting phase, to adapt digestion and to stepwise control subjective perception of hunger. The fasting/VLCD phase followed throughout the subsequent 5 days started with the intake of 10-20 g thenardite powder for bowel-cleaning purposes. During fasting patients were advised to sip hot millet soup, prepared with ≤ 150 g millet and 1000 ml water, along with drinking 3 Lof mineral water per day. Patients could also choose to drink moderate quantities of sugar-free sports beverages every day to maintain electrolyte balance. Solid food was refrained throughout the modified fasting phase. Nutritional energy intake was limited to < 550 kcal/day. After the fasting phase patients reintroduced solid food items stepwise, increasing food intake gradually to an amount still smaller than standard diabetic diets. During the fasting phase the modified *Ling-Gui-Zhu-Gan* decoction was administered twice a day. Prescription of the decoction was continued for maximum one month, according to the condition of the patients.

The in-patient treatment period comprised 7 days in both groups: in the fasting/VLCD group 5 modified fasting days and one day for relief and food reintroduction respectively; in the

control group 7 days for continuous nutritional therapy and diet control, physical therapy and educational programs.

After fasting, patients of both groups received dietary counseling and were asked to follow the suggested nutrition program. All patients were suggested to engage in moderate physical activity (walking) twice a day for 60 min. Anti-diabetic drugs were not changed during the study, but physicians could adapt the dosage of the drugs according to patients' plasma glucose. No other drugs were added during the therapy. Within the following 3 months, all participants were required to re-visit the outpatient clinic once in two weeks in order to assess diabetic control and to supervise the implementation of recommended physical activities and diets as well as to adapt the oral dosage of anti-diabetic drugs.

Fasting plasma glucose (FG), 2-h plasma glucose after oral glucose tolerance-test (2hG), and glycated hemoglobin A_{1c} (HbA_{1C}) were measured by standard methods. FG was measured by the glucose oxidase technique and HbA_{1C} level was measured by Bio-Rad HPLC. Serum total cholesterol (TC) and triglycerides (TG) were measured by Olympus 2700 automatic biochemical standard analysis. Documentation of oral dosage of anti-diabetic drugs and records of hypoglycemic events and symptoms of strong hunger, palpitations, cold sweats, tremor, pale face were based on interviews and semi-standardized inventories. FG levels of ≤3.9 mmol/L during monitoring were defined as hypoglycemic. All measurements were performed at baseline and at the 3-months study follow-up visit.

All normally distributed variables were expressed as mean ± standard deviation (m ± SD) and data were compared using a t-test. Group comparisons for discrete variables were performed using a chi-square-test. Differences were considered statistically significant at a $p < 0.05$ level. All data were analyzed with the Statistical Package for the Social Sciences (SPSS for Windows version 17.0). As this was an explorative pilot-study no adjustments for multiple testing were performed.

The second study (C. Li et al. 2017) was designed as a randomized controlled clinical pilot outpatient study. 46 persons with T2DM met the inclusion criteria and gave their written informed consent. They were randomly assigned to either the fasting group or control group. Study procedures and data collection were carried out at the outpatient department of the Immanuel Hospital Berlin, Department of Internal and Complementary Medicine and at a specialized diabetes outpatient clinic.

The fasting group received an initial fasting program followed by recommendations for a Mediterranean diet. The fasting program consisted of 2 pre-fasting days with moderate caloric restriction followed by 7 modified fasting days according to the method of Buchinger (*Wilhelmi de Toledo et al. 2013*) and subsequent stepwise re-introduction of ordinary food items over 3 days. Fasting took place only once in the 4 months period. During the initial 2

pre-fasting days subjects received a low-calorie (approx. 1200 kcal) and low-salt diet with intake of pure cooked rice and vegetables only. The fasting period started on the evening of study day 3 and lasted to the evening of study day 11. During the fasting period, participants received unrestricted amounts of water, herbal tea (no black or green tea), 200 ml fruit juice and small standardized quantities of light vegetable soup with a maximum total daily energy intake of 300 kcal. Participants were advised to drink at least 2.5 L of fluids daily. The fasting period was followed by three low-calorie diet days with stepwise reintroduction of solid food. A normocaloric diet was reached again thereafter and participants were then advised to follow the recommendations of a Mediterranean diet.

Participants allocated to the control group were advised to follow the principles of a Mediterranean diet and were offered participation in the fasting program after termination of the study (waiting list design).

During the study, participants continued their usual daily and professional activities. No other therapies were delivered. Compliance with the fasting procedure was recorded using personal interviews by study physicians. All participants received standard medical care as determined by their individual requirements.

All measurements were performed at baseline and at a follow-up visit after 16 ± 2 weeks on an outpatient basis. Subjects' height and body weight were measured following a standardized protocol while patients wore light clothing and no shoes after an overnight fast. Body mass index (BMI) was calculated as weight [kg]/height^2 [m^2].

Blood pressure and heart rate were measured using an automatic sphygmomanometer (Dynamap, Criticon, Norderstedt, Germany) after participants had rested in a seated position for 5 min. A blood sample was drawn at baseline and after 16 weeks. Insulin sensitivity was estimated with the homeostasis model assessment (HOMA) and calculated as fasting plasma glucose (mmol/L) x serum insulin (µU/mL)/25. Blood count and assays for blood lipids, haemoglobin A_{1c} (HbA_{1c}) and C-peptide were performed with standard methods. Serum concentrations of insulin were measured by immunonephelometric methods. Adverse events were monitored by standardized questionnaires.

As a pilot study it aimed to enhance the probability of success in the larger subsequent pivotal trial that is anticipated. It was not used primarily for hypothesis testing, but in explorative context. We hypothesized a significant beneficial effect of fasting versus diet on HbA_{1C}. Further endpoints included serum glucose, blood lipids, blood pressure and quality of life and safety outcomes. The sample size was based on the pragmatics of recruitment, the necessities for examining feasibility and on the basis of the results of the previous uncontrolled studies (*Li et al. 2013; Stange et al. 2013*). We defined a minimum sample size of n = 30 participants. All statistical analyses were carried out on the basis of the intention-to-

treat population after excluding the early drop-outs (participants that withdrew informed consent before beginning of the interventions). Missing data were not replaced. As this was not a confirmatory clinical trial we did not adjust for multiple testing.

If not indicated otherwise, results were expressed as means ± standard deviation. Change of values before and after fasting was calculated by Wilcoxon signed rank test. Group differences were calculated on mean change from baseline using Wilcoxon rank sum test. ANCOVA assumptions were checked in order to introduce some adjustment for the baseline differences between groups but found non normality of distribution using the Shapiro-Wilk test. Therefore and because of small samples size we used non parametric tests in the final analyses. When performing ANCOVA the overall results did not change relevantly. A *p*-value <0.05 was considered as statistically significant. All statistical computations were performed using the computing environment R (version 3.2.1). Additional software packages (xlsx, psych, ggplot2, tidyr, coin, car, ez, (all updated)) were used.

The third study (A. Michalsen and C. Li et al. 2013) was conducted as a prospective, controlled nonrandomized study. All participants were inpatients from two departments of the Immanuel Hospital Berlin specialized in the treatment of rheumatic and chronic pain diseases, (1) patients of the Department of Integrative and Complementary Medicine and, (2) patients of the Department of Internal Medicine and Rheumatology. The primary diagnosis and reason for hospital admission of all participants was primary fibromyalgia. The study sample consisted of consecutively admitted inpatients during a 9-month period, who regularly stayed 14 ± 2 days in hospital for multidisciplinary treatment.

The conventional rheumatologic (RT) treatment consisted of a complex multidisciplinary treatment schedule with group physiotherapy, hydrotherapy, thermal therapy, psychosomatic therapy, aerobic exercise, pool exercise, cognitive behavioral therapy, and education. The Integrative and Complementary Medicine (IM) approach used the same treatment elements. In addition, fasting therapy and nutritional therapy supported by a group-based Mind-Body-Medicine concept was applied. The patients of both departments received a similar global amount of treatments with a total of 1600 to 2200 treatment minutes within the 2-week hospital period.

The fasting method was adapted from the Buchinger fasting approach (*Wilhelmi de Toledo et al. 2013*). A fasting period with 7 to 8 days of subtotal caloric restriction (daily energy intake < 500 kcal) was predefined. Fasting was preceded by one or two prefasting days, using an 800 kcal/day monodiet of fruit, rice, or potatoes according to patients' choice. Fasting then began the following day with ingestion of an oral laxative, Natrium sulfuricum ("Glauber's salt", 20–40 g). During fasting an enema or, if not wished by the patient, a mild laxative was applied every other day. The patients were recommended to drink 2-3 L of fluids each day

(mineral water, small quantities of juice, and herbal teas). Vegetable broth was taken at lunch. The daily energy intake during the fast amounted to 350 kcal/day. For breaking the fast an apple was eaten. The breakfast was followed by stepwise reintroduction of food with the aim of normocaloric intake by vegetarian meals on the third postfasting day.

Inpatient treatments for fibromyalgia syndrome are recommended by German S-3 guidelines (*Häuser et al. 2009*) and by health insurance companies for patients which do not respond adequately to outpatient care, including multimodal outpatient treatment. Patients are referred to both departments by internists, family practitioners and rheumatologists comparably with patients' preference for Integrative Medicine and fasting treatment being the main criteria for choice of hospital department.

All measures were assessed by trained study nurses at baseline, after 2 weeks (at dismissal from hospital) and at study week 12 (10 weeks after dismissal). The primary outcome measure was the change in the Fibromyalgia Impact Questionnaire (FIQ) score from baseline to the end of the in-hospital intervention. The FIQ is a validated, multidimensional measure to assess the severity of fibromyalgia as rated by patients. The total score ranges from 0 to 100, with higher scores indicating more severe symptoms (*Burckhardt et al. 1991*). Global pain status was assessed additionally by asking the patients for the global severity of the disease-related pain by means of a self-rating 100 mm Visual Analogue Scale (VAS) with a value of 100 indicating maximum pain and 0 indicating no pain.

Pre-specified other secondary outcomes included (1) a 100 mm visual analogue scale for self-rated global quality of sleep; (2) the German version of the Spielberger State-Trait Anxiety Inventory (STAI), which consists of 20 items relating to state anxiety and 20 items relating to trait anxiety (*Spielberger 1986*); (3) the Bf-S Zerssen well-being scale, which measures momentary emotional well-being and consist of three answer categories with higher scores indicating lower well-being (*Von Zerssen and Koeller 1976*); (4) the German version of the Hospital Anxiety and Depression Scale (HADS) (*Barth and Martin 2005*), a validated standard measure for anxiety and depression which uses a 14-item scale with seven of the items related to anxiety and seven related to depression (*Snaith 2003*); (5) the German version of the Pain Perception Scale for Adolescents (SES), which assesses sensory pain perception in chronic pain patients (*Nagel et al. 2002*). Subjects height and body weight were measured following a standardized protocol. BMI was calculated as weight (kg)/height^2 (m). Seated blood pressure was measured after 5 min rest with a calibrated sphygmomanometer at the nondominant arm by trained nurses.

As the study was designed as a nonrandomized pilot study no sample size calculation was conducted. However, we planned to include 60 patients giving a study sample of about 50 patients if assumed a drop-out rate of 15%. Baseline differences were calculated by Kruskal-

Wallis test. All outcome criteria were analyzed by intention-to-treat. For each outcome we fitted a generalized estimation equation (GEE), analysis of covariance (ANCOVA) which included treatment group (binary covariate), and the respective baseline value (linear covariable) as independent variables. Treatment effects were estimated within these models, and reported as adjusted group differences including their respective 95% confidence intervals (CI) and *p* values. All *p* values were based on two-sided tests, and $p < 0.05$ was considered significant. All statistical computations were performed with SAS/STAT statistical software version 9.1 (SAS institute, Cary, North Carolina, USA).

1.5 Results

Results will be discussed separately for the three studies.

In the first study (D. Chen and C. Li et al. 2012), a total of 60 persons were enrolled in the study, 30 in each group. There were no significant differences between the two groups at baseline. All patients in the intervention group completed the trial. 4 patients in the control group stopped the trial because of repeated hypoglycemic events. A similar decrease of weight was observed in the intervention group and the control group after 3 months.

Importantly, the VLCD combined with TCM decoction significantly improved the glycemic control and lipid levels, whereas the only VLCD induced slight improvement. Patients in the intervention group showed pronounced and clinically relevant decreases in the levels of FG, 2hG, HbA_{1C}, TC and TG, while patients in the control group only showed mild decreases of these parameters, resulting in significant group differences (Table 1). Moreover, occurrence of hypoglycemic events was also improved (Table 2). Throughout the study 4 patients in the control group dropped out because of repeated hypoglycemic events, while patients in the intervention group tended to be more capable of controlling appetite and no hypoglycemia occurred. Furthermore reduced acute hunger, and fewer symptoms of palpitations or tremors were observed. In addition, with the 3-month study period, much more patients in the intervention group had stopped their oral antidiabetics or decreased the dosage than the patients in the control group (Table 3). This indicates a superior clinical effect of the VLCD combined with TCM decoction for treating T2DM.

For the second study (C. Li et al. 2017), a total of 46 persons were enrolled in the study, with 23 in each group. 17 persons in the fasting group completed the entire fasting period. 2 participants dropped out due to headache and gastric pain, respectively. And 4 more lost motivation to fast in the course of the program. Despite randomization there were some relevant baseline differences between groups for insulin sensitivity ($p = 0.07$), glucose ($p = 0.001$) and diastolic blood pressure ($p = 0.048$). Baselines values for HbA_{1c}, C-peptide, blood lipids, renal function and quality of life were balanced between groups.

After 4 months, mean weight decreased by 3.5 ± 4.5 kg in the fasting group and by 2.0 ± 4.8 kg in the control group. Fasting was accompanied by a significant decrease in abdominal circumference, systolic and diastolic blood pressure, and an increase in quality of life as assessed by the WHO-5. For all other metabolic outcomes, including HbA_{1c}, insulin, HOMA-index and blood lipids, the fasting group showed non-significant improvements than the control group with exception of mean total cholesterol which decreased non-significantly more in the control group (table 4).

48 participants were enrolled in the third study (A. Michalsen and C. Li et al. 2013): 20 in the department of Rheumatology and 28 in the department of Integrative and Complementary Medicine. Data assessments were complete for study visits 1 (baseline) and 2 (week 2). After 12 weeks, data from 25 patients of the department of Integrative and Complementary Medicine and 17 of the department of Rheumatology were available. Patients of the Department of Rheumatology showed more serious symptoms compared to ones of the Department for Integrative and Complementary Medicine at the baseline level (Table 5).

The FIQ score decreased substantially in the Integrative Medicine Group and to a significantly greater extent compared to the Rheumatologic group after 2 weeks (Table 5). At 12 weeks, the FIQ score increased again in both groups showing improvements of only 12% for the integrative and fasting approach and 6% for the control group, resulting in a nonsignificant difference between the groups. At 2 weeks, the Integrative Medicine group had greater mean improvements in all secondary outcomes and most pronounced in the scores of quality of sleep, pain, pain perception, and anxiety. At 12 weeks, the pain score and pain perception score only showed a trend towards a beneficial outcome for the Integrative Medicine group compared to the Rheumatology group. All psychological outcomes were better in the Integrative Medicine group compared to the Rheumatologic group, however group differences were reduced and no longer statistically significant with the exception of anxiety. All of the outcomes deteriorated again compared to the 2-weeks data resulting in mild mid-term treatment effects compared to baseline levels.

1.6 Discussion

In the following section results from the three studies are discussed.

In D. Chen and C. Li et al. 2012, we evaluated the clinical effects of short-term modified fasting/VLCD combined with modified *Ling-Gui-Zhu-Gan* decoction on T2DM for the first time by means of a randomized controlled pilot study. The results demonstrate a clear and clinically relevant effect of this combined integrative treatment on improving glycemic control, need of anti-diabetic medication and reduction of hypoglycemic events.

Table 1

Levels of fasting glucose, post prandial glucose, HBA_{1C}, total cholesterol and triglyceride before intervention and after three months in both groups.

Groups	Baseline					3-Months follow-up				
	FG (mmol/L)	2hG (mmol/L)	HbA_{1C} (%)	TC (mmol/L)	TG (mmol/L)	FG (mmol/L)	2hG (mmol/L)	HbA_{1C} (%)	TC (mmol/L)	TG (mmol/L)
Control (26 patients)	6.6 ± 0.8	11.2 ± 4.0	7.51 ± 1.27	6.67 ± 0.99	5.01 ± 1.95	6.3 ± 1.0	10.1 ± 4.5	7.21 ± 1.33	6.18 ± 1.3	3.1 ± 1.85
Intervention (30 patients)	6.8 ± 1.2	10.9 ± 4.3	7.53 ± 1.19	6.98 ± 1.05	5.83 ± 2.06	5.5 ± 0.9*	8.1 ± 2.7**	6.23 ± 0.9***	5.12 ± 0.96#	1.74 ± 1.03##

FG, fasting plasma glucose; 2hG, 2-h plasma glucose after OGTT; HbA_{1C}, glycated hemoglobin A_{1C}; TC, total cholesterol; TG, triglyceride. Between-group differences after 3-months.

* p-Value = 0.027.

** p-Value = 0.043.

*** p-Value = 0.024.

Comparison to the baseline after the treatment.

\# p-Value = 0.041.

\#\# p-Value = 0.008.

Table 2

Frequency of hypoglycemic events during study phase in both groups.

	Control group	Intervention group
Patients with hypoglycemic events (n)	13	5
Absolute number of hypoglycemic events	33	5

Table 3

Course of antidiabetic medication within the 3-months study period.

Groups	Decreased dosage	Discontinued	Maintained dosage	Total
Control	7	1	18	26
Intervention	19	9	2	30

Table 4 Study outcomes at baseline, at 4-month follow-up; mean within-group difference of change and p-value and median between group difference of change with 95%CI and p-value.

	Fasting group				Control group				Between-Group difference of change	
	Baseline	Follow-up	Mean Change	P-Value *	Baseline	Follow-up	Mean Change	P-Value *	Median of Difference (95 % CI)	P-Value * *
HbA_{1c}, mmol/mol (%)	60.0±7.7	57.0±13.1	−2.2±12.0	0.3	62.0±8.7	61.0±9.8	−2.2±8.7	0.28	−0.1(−0.7, 0.7)	0.70
	7.6±0.7	7.4±1.2	−0.2±1.1		7.8±0.8	7.7±0.9	−0.2±0.8			
Weight, kg	89.3±12.6	85.8±13.4	−3.5±4.5	0.01	95.3±17.9	93.3±15.6	−2.0±4.8	0.83	−3 (−6.0, −0.4)	0.03
BMI, kg/m²	30.7±2.9	29.5±3.5	−1.2±1.7	0.16	34.0±6.7	33.3±6.6	−0.6±2.6	0.08	−1 (−2.0, −0.1)	0.03
Waist, cm	110.1±9.0	105.6±9.6	−4.4±4.3	0.001	114.1±14.3	113.8±14.4	−0.3±2.0	0.72	−4 (−6.0, −2.0)	0.001
RRsys, mmHg	141.9±16.0	128.0±17.0	−13.9±15.3	0.04	136.3±16.9	136.7±19.5	0.4±15.8	0.25	−15 (−25.0, −2.0)	0.01
RRdia, mmHg	85.0±10.8	76.0±10.5	−9.0±12.3	0.02	76.3±13.1	79.5±9.4	3.2±11.9	0.17	−11.5 (−20.0, −5.0)	0.003
Trigly, mg/dl	192.5±121.4	165.9±110.3	−26.6±88.5	0.2	248.7±192.6	246.1±187.6	−2.5±81.9	0.9	−21.3 (−75.0, 40.0)	0.50
HDL/LDL	2.4±1.1	2.4±1.2	0.0±1.0	0.6	2.4±0.8	2.4±0.9	0.0±0.7	0.7	0 (−0.5, 0.5)	0.90
Glucose, mg/dl	152.8±18.5	142.1±28.4	−10.6±30.4	0.15	189.6±44.0	151.1±28.7	−38.4±46.0	0.02	20.5 (−9.0, 51.0)	0.13
Insulin, µU/ml	14.8±11.1	11.4±7.6	−3.5±9.3	0.42	15.9±10.6	15.7±11.9	−0.2±5.4	0.05	−2 (−6.0, 0.7)	0.09
HDL-C, mg/dl	51.4±18.0	58.0±21.0	6.5±23.3	0.2	53.6±18.6	51.4±18.8	−2.3±6.9	0.2	6 (−2.0, 11.0)	0.14
LDL-C, mg/dl	112.5±44.8	109.9±37.1	−2.6±26.9	0.9	116.9±37.3	109.1±35.3	−7.8±17.3	0.41	7.6 (−10.0, 20.0)	0.20
Total-C, mg/dl	197.8±45.4	197.3±29.4	−0.5±27.1	0.5	217.5±37.7	202.0±38.7	−15.5±27.4	0.84	14 (−6.0, 34.0)	0.14
HOMA-IR	5.8±5.2	4.3±3.7	−1.5±4.6	0.08	7.6±6.1	6.2±6.2	−1.5±2.1	0.06	0 (−1.5, 2.4)	1.0
WHO-5	16.4±4.1	18.2±4.0	1.8±2.2	0.003	14.8±6.5	15.7±5.1	0.9±2.7	0.61	1(0.0, 2.0)	0.04

* Wilcoxon signed rank test; * * Exact Wilcoxon Mann-Whitney Rank Sum Test; C = cholesterol

* Wilcoxon signed rank test; * * Exact Wilcoxon Mann-Whitney Rank Sum Test; C = cholesterol

Table 5 Outcomes in both groups at baseline, week 2 and 12 with group difference as indicators of change.

	Integrative medicine group			Rheumatology group			Mean diff		Mean diff (95% CI)	
	Baseline	Visit 2	Visit 3	Baseline	Visit 2	Visit 3	∇ 1-2 (95% CI)	*P* value	∇ 1–3 (95% CI)	*P* Value
FIQ score	54.3 ± 15.0	38.0 ± 17.3	47.7 ± 19.3	68.0 ± 8.9	59.1 ± 15.3	63.9 ± 20.7	−11.2 (−20.1, −2.3)	0.014	−6.7 (−17.5, 4.1)	0.223
Pain score	58.2 ± 19.6	37.4 ± 19.9	48.8 ± 26.1	66.5 ± 19.5	58.3 ± 22.8	64.4 ± 25.7	−17.5 (−28.8, −6.1)	0.003	−13.0 (−28.0, 2.1)	0.091
Quality of sleep	60.5 ± 26.7	43.6 ± 27.8	48.3 ± 26.4	68.3 ± 27.6	61.1 ± 29.0	67.4 ± 20.4	−15.5 (−30.6, −0.4)	0.044	16.5 (−30.0, −3.1)	0.016
HADS Anxiety	10.4 ± 3.8	6.9 ± 3.2	8.9 ± 3.9	11.3 ± 5.1	10.3 ± 5.0	11.6 ± 4.2	−2.9 (−4.6, −1.3)	<.001	−2.3 (−3.8, −0.9)	0.002
HADS Depression	8.3 ± 4.8	6.1 ± 4.2	7.8 ± 4.1	11.1 ± 5.2	9.3 ± 5.1	11.6 ± 4.2	−1.5 (−3.3, 0.3)	0.097	−2.0 (−4.0, −0.0)	0.046
SES Pain Perception	30.7 ± 9.1	22.1 ± 6.6	29.8 ± 10.2	36.4 ± 8.6	34.2 ± 9.1	37.0 ± 10.5	−10.1 (−14.7, −5.5)	<.001	−5.2 (−11.0, 0.5)	0.075
STAI State Score	50.4 ± 11.2	39.7 ± 10.2	48.2 ± 11.5	58.4 ± 13.0	51.4 ± 12.6	57.6 ± 11.5	−8.2 (−13.9, −2.4)	0.005	−6.1 (−11.8, −0.4)	0.036
STAI Trait Score	51.1 ± 11.2	43.9 ± 9.7	48.6 ± 9.3	54.3 ± 12.0	53.5 ± 10.0	55.5 ± 9.6	−8.3 (−12.3, −4.2)	<.001	−4.8 (−8.9, −0.7)	0.022
BfS Well-being	21.3 ± 11.6	17.5 ± 14.1	23.4 ± 11.8	27.2 ± 9.0	27.8 ± 8.2	26.0 ± 10.4	−6.8 (−12.5, −1.2)	0.018	−1.4 (−8.0, 5.2)	0.675

Values are mean ± SD if not indicated otherwise. SBP: systolic blood pressure; DBP: diastolic blood pressure.
STAI: State and Trait Anxiety questionnaire, FIQ: Fibromyalgia impact questionnaire; HADS: Hospital Anxiety and Depression scale;
∇ 1-2 = difference between groups from baseline to visit 2 at 2 weeks, ∇ 1–3 = difference between groups from baseline to visit 3 at 12 weeks,
*P values for between group difference of change, adjusted.

In China, the prevalence of diabetes mellitus is increasing rapidly. However, because of the large variety of ethnic groups and related lower energy dietary in China, heavy obesity is rare compared to Western countries. Modified fasting/VLCD is established as intensified dietary approaches to initiate weight loss processes and to improve weight control. Preliminary data also suggest that periods of fasting might be useful in improving insulin sensitivity and diabetic control (*Henry and Gumbiner 1991*).

Since Mc Garry (*Mc Garry 2001*) named T2DM as a "glycolipid disease" in 2001, the treatment of T2DM has shifted from a mere control of glucose levels to a control of glucose and lipids at the same time. Concomitantly, with improved glycemic control we found beneficial reductions in blood lipids in the patients of the intervention group. According to the knowledge of modern Chinese medicine, the pathogenesis of T2DM and hyperlipidemia is related to dysfunction of transportation and transformation of the spleen, resulting in insufficient metabolism of nutrients which then are thought to lead to an accumulation of mucus, fat and to dampness and turbidity. The *Ling-Gui-Zhu-Gan* decoction aims to warm and resolve mucus (*wen-hua-tan-yin*), to strengthen the spleen and to remove turbidity (*jian-pi-xie-zhuo*). Hence, a combination of the modified *Ling-Gui-Zhu-Gan* decoction with fasting/VLCD may foster the renewing of the so called "spleen function of transformation and transportation" (*Chen and Qin 2010*).

In TCM it is believed that the spleen also governs processes of pharmacokinetics in human bodies based on the notion of homology of Chinese Medicine and food. So if the spleen shows dysfunction, this will have detrimental effects on metabolism and pharmacokinetics will also show pathological characteristics. Thus it might be the case that the TCM treatment also restores patients' therapeutic responses to drugs and increase insulin sensitivity by recovering spleen function (*Chen and Qin 2010*).

The mean BMI of patients in this study was only slightly over 25 kg/m^2. However, all patients adhered to and well-tolerated the modified fasting treatment. Therefore, we regard the combined treatment approach as suitable for nonobese T2DM patients. Yet, this integrative therapeutic concept should be further evaluated by differentiate the anti-diabetic effects of each single treatment module, and explore to what extend the results of this trial can be transferred to Western populations.

In the second study (C. Li et al. 2017), by randomized controlled pilot method we investigated for the first time the mid-term (4 months) clinical and metabolic effects of a prolonged (7 days) fasting therapy in patients with T2DM. The most pronounced effect was seen for the weight loss, blood pressure reduction and improvement of quality of life. An overall non-significant improvement on glucoregulation was found as well.

Recent studies reported the beneficial effects of fasting and caloric restriction on blood lipids and glucose control, insulin sensitivity, receptor sensitivity of atrial natriuretic peptides and blood pressure in T2DM patients (*Brandhorst et al. 2015; Malandrucco et al. 2012; Dessì-Fulgheri et al. 1999; Li et al. 2013; Stange et al. 2013*). Several possible mechanisms may explain the beneficial effects of prolonged fasting. Long periods of fasting represent a strong physiological stimulus and induce pronounced hormonal changes, e.g. stimulation of the HPA-axis that may be interpreted as a hermetic stress reaction (*Longo and Mattson 2014*)

In our study the one-week fasting period was a stand-alone intervention and the follow-up of 4 months aimed to reveal any lasting effects of such an intervention. However, compared to a small study that assessed the effects of an 8-week continuous VLCD (max. 700kcal/day) (*Steven and Taylor 2015*) the weight loss and metabolic effect of the one-week fasting therapy were rather modest. All retrievable literature does not investigate clearly the role of length of fasting and its potential for lasting effects by periodic repeating of fasting or combining prolonged and intermittent fasting to assure optimal effects. However, we believe that for achieving more pronounced and stable effects in T2DM the prolonged initial fasting period should to be followed by an intermittent fasting scheme (for example: 2:5 per week; 4 days per months).

Beside the metabolic effects of the one-week fasting therapy, we found an increase in quality of life through the intervention. The mood and quality of life-enhancing effects of fasting and of calorie restriction have been described in earlier studies and several mechanisms have been suggested (*Michalsen 2010*), among them increased central serotonin availability, endorphin release and a modified sleep architecture. In an evolutionary context, mood-enhancement after several days of food deprivation seems to be an important beneficial psychological adaptation in the search for food and the chance for survival. In addition, the greater weight loss by fasting may have contributed to better quality of life.

Some baseline differences between groups despite the randomized group allocation may introduce bias in the group comparisons. We therefore performed ancillary statistical analyses with adjustments for the major baseline differences, which did not change the overall results and statistical significances. Nevertheless the interpretation of our data has to be done cautiously.

In conclusion, our findings indicate that a periodic fasting treatment might be useful in the management of diabetes type 2 and that further larger randomized trials are warranted.

In the third study (A. Michalsen and C. Li et al. 2013), with controlled nonrandomized trial we compared the effectiveness of two time- and attention-balanced inpatient multimodal treatment strategies: an Integrative Medicine approach that included fasting therapy versus the conventional Rheumatologic therapy. While patients in the Rheumatologic group were more

diseased at baseline, adjusted data analysis showed a more beneficial effect of the Integrative Medicine approach after 2 weeks for all of the clinical outcomes. At week 12, effects in both groups were reduced but still favored the Integrative Medicine approach. Thus, our results point to a relevant immediate effect of the Integrative Medicine approach while the long term effects appear to be only mild.

A recent study has evaluated the effects of a conventional multimodal inpatient treatment of 3 weeks within the setting of a specialized Rheumatologic rehabilitation hospital (*Michalsen and Kuhlmann 2006*). For the outcomes that were used (Pain, HADS) the results of the Integrative Medicine approach used in this study were also favorable, thus confirming our results. However, only a few studies have investigated multimodal treatment programs for fibromyalgia that focus on Integrative and Complementary Medicine. A small uncontrolled study in 28 patients found an Ayurvedic program, also focusing on nutrition and mind-boy techniques, to be effective with a lasting effect up to 24 months (*Rasmussen 2009*). Yet, the treatment was not compared to another intervention, thus selection bias and unspecific effects were most likely contributing factors to the effect.

In this study, we found a partially persisting mood-enhancing effect in the integrative medicine group which may be related to fasting therapy. Previous research has documented mood-enhancing effects of caloric restriction and fasting. Several mechanisms including increased central serotonin availability have been described experimentally (*Michalsen et al. 2010*).

In view of our documented effects and safety of the Integrative Medicine approach further research on the effectiveness of complex multimodal Integrative treatments and comparisons with standard care in fibromyalgia is warranted. Such a study should have a larger sample size, allocate patients randomly, and include an attention control for the fasting intervention. Here the conventional group could be deprived of some specific food ingredient without inducing fasting metabolism. As it is difficult to randomize patients into complete treatment settings due to patient preferences and obligations of cost coverage, also outcome research might be useful in benchmarking the best strategy in intensified treatment strategies of fibromyalgia.

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2. Own work declaration and detailed statement of originality

I, Chenying Li, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic [Clinical Effects of Fasting Therapy for Treating Type-2 Diabetes Mellitus and Fibromyalgia] I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My contributions in the selected publications for this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author of correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date Signature

Declaration of any eventual publications

Chenying Li had the following share in the following publications:

Publication 1:

Chenying Li, Badri Sadraie, Nico Steckhan, Christian Kessler, Rainer Stange, Michael Jeitler, Andreas Michalsen

Effects of A One-week Fasting Therapy in Patients with Type-2 Diabetes Mellitus and Metabolic Syndrome – A Randomized Controlled Explorative Study

Experimental and Clinical Endocrinology & Diabetes, 2017

Contribution in detail:
The first author
Idea and concepts come from Chenying Li. Chenying Li carried out the data interpretation and contributed to the manuscript writing. Chenying Li also submitted the manuscript to the journal.

Publication 2:

Andreas Michalsen, **Chenying Li**, Katharina Kaiser, Rainer Lüdtke, Larissa Meier, Rainer Stange and Christian Kessler

In-Patient Treatment of Fibromyalgia: A Controlled Nonrandomized Comparison of Conventional Medicine versus Integrative Medicine including Fasting Therapy

Evidence-Based Complementary and Alternative Medicine, 2013

Contribution in detail:
The second author
-Involved in the experiment design
-Contribution to the data interpretation
-Contribution to the manuscript writing

Publication 3:

Andreas Michalsen, **Chenying Li**

Fasting Therapy for Treating and Preventing Disease – Current State of Evidence

Forsch Komplementmed, 2013

Contribution in detail:
Co-author of this review paper
-Reading and summarizing some of the reference papers

-Contribution to the manuscript writing

Publication 4:

Dingsheng Chen*, **Chenying Li***, Andreas Michalsen, Christian Kessler, Yingjuan Huang, Jun Meng, Bin Ke, Yuanyuan Wang, Junjie Zhang, Jian Qin (*These authors contributed equally to this work.)

Modified Ling-Gui-Zhu-Gan decoction combined with short-term fasting improves therapeutic response in type 2 diabetic patients

European Journal of Integrative Medicine, 2012

Contribution in detail:

The common first author

Chenying Li is involved in the experiment design. Chenying Li contributed to the manuscript writing. Chenying Li also submitted the manuscript to the journal.

Signature, date and stamp of the supervising University teacher

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Signature of the doctoral candidate

_____

3. List and print copies of the selected publications

Impact Factor (IF) according to Thompson Reuters, Journal Citations Report, ISI Web of Knowledge, 2016

Publication 1:

"Effects of A One-week Fasting Therapy in Patients with Type-2 Diabetes Mellitus and Metabolic Syndrome – A Randomized Controlled Explorative Study"

Chenying Li, Badri Sadraie, Nico Steckhan, Christian Kessler, Rainer Stange, Michael Jeitler, Andreas Michalsen (2017)

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Impact Factor: 1.685 (5-jähriger IF: 1.537)

Publication 2:

"In-Patient Treatment of Fibromyalgia: A Controlled Nonrandomized Comparison of Conventional Medicine versus Integrative Medicine including Fasting Therapy"

Andreas Michalsen, **Chenying Li**, Katharina Kaiser, Rainer Lüdtke, Larissa Meier, Rainer Stange and Christian Kessler (2013)

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Publication 3:

"Fasting Therapy for Treating and Preventing Disease – Current State of Evidence"

Andreas Michalsen, **Chenying Li** (2013)

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Publication 4:

"Modified *Ling-Gui-Zhu-Gan* decoction combined with short-term fasting improves therapeutic response in type 2 diabetic patients"

Dingsheng Chen*, **Chenying Li***, Andreas Michalsen, Christian Kessler, Yingjuan Huang, Jun Meng, Bin Ke, Yuanyuan Wang, Junjie Zhang, Jian Qin (*These authors contributed equally to this work.) (2012)

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“Effects of A One-week Fasting Therapy in Patients with Type-2 Diabetes Mellitus and Metabolic Syndrome – A Randomized Controlled Explorative Study”

Chenying Li, Badri Sadraie, Nico Steckhan, Christian Kessler, Rainer Stange, Michael Jeitler, Andreas Michalsen (2017)

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“In-Patient Treatment of Fibromyalgia: A Controlled Nonrandomized Comparison of Conventional Medicine versus Integrative Medicine including Fasting Therapy”

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Research Article

In-Patient Treatment of Fibromyalgia: A Controlled Nonrandomized Comparison of Conventional Medicine versus Integrative Medicine including Fasting Therapy

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Fibromyalgia poses a challenge for therapy. Recent guidelines suggest that fibromyalgia should be treated within a multidisciplinary therapy approach. No data are available that evaluated multimodal treatment strategies of Integrative Medicine (IM). We conducted a controlled, nonrandomized pilot study that compared two inpatient treatment strategies, an IM approach that included fasting therapy and a conventional rheumatology (CM) approach. IM used fasting cure and Mind-Body-Medicine as specific methods. Of 48 included consecutive patients, 28 were treated with IM, 20 with CM. Primary outcome was change in the Fibromyalgia Impact Questionnaire (FIQ) score after the 2-week hospital stay. Secondary outcomes included scores of pain, depression, anxiety, and well being. Assessments were repeated after 12 weeks. At 2 weeks, there were significant improvements in the FIQ ($P < 0.014$) and for most of secondary outcomes for the IM group compared to the CM group. The beneficial effects for the IM approach were reduced after 12 weeks and no longer statistically significant with the exception of anxiety. Findings indicate that a multimodal IM treatment with fasting therapy might be superior to CM in the short term and not inferior in the mid term. Longer-term studies are warranted to assess the clinical impact of integrative multimodal treatment in fibromyalgia.

1. Introduction

Fibromyalgia is a complex clinical pain syndrome. Patients typically suffer from widespread musculoskeletal pain, fatigue, insomnia, and impairment of physical and psychological quality of life [1, 2]. The international prevalence of fibromyalgia ranges from 0.7 to 3.3% in the general adult population with an increase in recent years and a continuous majority of female patients [2–4].

The etiology of fibromyalgia is still unclear, although research showed an abnormal pain processing and lowered mechanical and thermal pain threshold by fMRI [5] as well as dysfunction of descending pain modulatory systems, for example, in the rostral anterior cingulate cortex (rACC) [6] and distinct neurotransmitter activities in cerebrospinal fluid [7]. Further discovered dysfunctions of the neuroendocrine axis could explain concomitant complaints as fatigue, irritable bowel, and mood disorders that are predominant in most of the fibromyalgia patients [8]. An association with psychosocial stressors is most likely [1, 8, 9].

Recent guidelines recommend a multimodal, multidisciplinary therapeutic approach involving medication, exercise, patient education, and behavioral and psychosomatic therapy [4, 10]. Due to frequent unsatisfying results of conventional treatment a substantial proportion of patients use complementary and integrative approaches such as Mind-body medicine, supplements, acupuncture, massage, and various nutritional therapies [11]. Clinical experience and preliminary evidence from uncontrolled prospective studies suggest that an integrative approach including nutritional

and fasting therapies may help to decrease symptoms and increase the quality-of-life in inpatients with fibromyalgia [12, 13]. However, it would be useful to know how such an Integrative Medicine approach compares with conventional multimodal treatment which is established in specialized hospital units of rheumatology or pain medicine.

Prolonged modified fasting (Fasting cure, fasting therapy) with defined periods of voluntary abstention from solid food and a daily total energy intake <500 kcal has been found effective in several randomized trials on rheumatoid arthritis [14, 15]. The anti-inflammatory, pain relieving, antinociceptive, and mood-enhancing effects of fasting and caloric restriction have been well described in experimental and clinical studies [16–19]. Both, patients with rheumatoid arthritis and fibromyalgia frequently report that elimination diets and meal skipping alleviate their symptoms [13, 20, 21]. In a controlled nonrandomized study on the influence of a mediterranean diet or a fasting cure on the intestinal microflora the subgroup of patients with fibromyalgia experienced a greater improvement than nonfasters [13]. In another trial with a heterogeneous sample of chronic pain patients fasting led to an amelioration of mood and well-being [22].

In Germany, several academic hospital departments for naturopathic and integrative medicine have accumulated clinical experience in inpatient treatments of fibromyalgia. Within the treatment concepts of the integrative approach, modified fasting therapy is a mainstay of therapy. Notably, fasting treatments have been found to enhance health-promoting lifestyle modification [12], thus supporting a further key element of integrative therapy in fibromyalgia, mind-body medicine.

We conducted this first controlled nonrandomized pilot-study to compare an integrative treatment strategy including fasting cure with a conventional rheumatologic treatment strategy.

We investigated quality of life, pain intensity, and psychological outcomes before and after the treatment of fibromyalgia in inpatients of two different departments of Internal Medicine, Integrative Medicine, and Rheumatology, of the same hospital, which is a tertiary center for Rheumatologic diseases. We hypothesized that fasting and integrative treatment would lead to a beneficial add-on effect with regards to quality-of-life, pain, and further psychological outcomes at time of hospital dismissal.

2. Material and Methods

2.1. Study Design and Participants. The study was conducted as a prospective, controlled nonrandomized study. The study protocol was reviewed and approved by the Ethics Committee of the Charité-University Medical Center, Berlin, and all patients gave their informed consent to study participation. Collection of data was performed by trained study personnel.

All study subjects were inpatients from two departments of the Immanuel Hospital Berlin which is specialized in the treatment of rheumatic and chronic pain diseases, (1) patients of the Department of Integrative and Complementary Medicine and, (2) patients of the Department of Internal Medicine and Rheumatology. The primary diagnosis and reason for hospital admission of all participants was primary fibromyalgia. The study sample consisted of consecutively admitted inpatients during a 9-month period, who regularly stayed 14 ± 2 days in hospital for multidisciplinary treatment.

Inclusion criteria were a manifest fibromyalgia, as diagnosed by a rheumatologist, pain specialist, or internist, an age between 18 and 70 years, and a BMI between 20 and 45 kg/m^2. Patients with a start or change in drug therapy of their FMS less than 6 weeks ago, clinical relevant progressive or malignant diseases, current addiction or pregnancy, and inadequate cognitive abilities of cooperation were not included in the study. Further exclusion criteria were eating disorders, manifest liver disease, renal failure, gastric ulcer, and severe comorbidity including cancer and AIDS, premedication with immunosuppressive drugs (except corticosteroids) or coumarins, alcoholism, malnutrition, serious chronic infections, psychosis, epilepsy, type-1 diabetes, pregnancy, lactation, and a weight loss during the previous 3 months of >3 kg.

2.2. Interventions

2.2.1. Conventional Treatment. The conventional rheumatologic treatment approach consisted of a complex multidisciplinary treatment schedule with the following elements: group physiotherapy, hydrotherapy, thermal therapy, psychosomatic therapy, aerobic exercise, pool exercise, cognitive behavioral therapy, and education. The integrative and Complementary Medicine approach used the same treatment elements. In addition, fasting therapy and nutritional therapy supported by a group-based Mind-Body-Medicine concept was applied. The patients of both departments received a similar global amount of treatments with a total of 1600 to 2200 treatment minutes within the 2-week hospital period, according to agreements with health insurance companies in Germany.

The method of fasting was adapted from the technique described by Buchinger [23–26]. A fasting period with 7 to 8 days of subtotal caloric restriction (daily nutritional energy intake <500 kcal) was predefined. Fasting was preceded by one or two prefasting days, using a 800 kcal/day monodiet of fruit, rice, or potatoes according to patients' choice. Fasting then began the following day with ingestion of an oral laxative, Natrium sulfuricum ("Glauber's salt", 20–40 g). During fasting an enema or, if not wished by the patient, a mild laxative was applied every other day. The patients were recommended to drink 2-3 L of fluids each day (mineral water, small quantities of juice, and herbal teas). Vegetable broth was taken at lunch. The daily energy intake during the fast amounted to 350 kcal/day. For breaking the fast an apple was slowly eaten. The breakfast was followed by stepwise reintroduction of food with achievement of normocaloric intake by vegetarian meals on the third postfasting day. In the postfasting days a focus is set on reintroducing mindfulness to eating.

Both departments are well experienced with the treatment of fibromyalgia syndrome and patients are received in a general appreciating manner. Inpatient treatments for

fibromyalgia syndrome are recommended by German S-3 guidelines [1] and by health insurance companies for patients which do not respond adequately to outpatient care, including multimodal outpatient treatment. Patients are referred to both departments by internists, family practitioners, and rheumatologists comparably with patients' preference for Integrative Medicine and fasting treatment being the main criteria for choice of hospital department.

2.3. Measurements. All measures were assessed by trained study nurses at three study visits, at baseline, after 2 weeks (at dismissal from hospital) and at study week 12 (10 weeks after dismissal). The primary outcome measure was the change in the Fibromyalgia Impact Questionnaire (FIQ) score from baseline to the end of the in-hospital intervention. The FIQ is a validated, multidimensional measure to assess the severity of fibromyalgia as rated by patients. The total score ranges from 0 to 100, with higher scores indicating more severe symptoms [27]. The validated German version was used [28].

Global pain status was assessed additionally by asking the patients for the global severity of the disease-related pain by means of a self-rating 100 mm Visual Analogue Scale (VAS) with a value of 100 indicating maximum pain and 0 indicating no pain. Patients were carefully instructed before first self-ratings on the correct use of the VAS.

Prespecified other secondary outcomes included (1) a 100 mm visual analogue scale for self-rated global quality of sleep; (2) the German version of the Spielberger State-Trait Anxiety Inventory (STAI), which consists of 20 items relating to state anxiety and 20 items relating to trait anxiety [29]; (3) the Bf-S Zerssen well-being scale, which measures momentary emotional well-being and consist of three answer categories with higher scores indicating lower well-being [30]; (4) the German version of the Hospital Anxiety and Depression Scale (HADS) [31], a validated standard measure for anxiety and depression which uses a 14-item scale with seven of the items related to anxiety and seven related to depression [32]; (5) the German version of the Pain Perception Scale for Adolescents (SES), which assesses sensory pain perception in chronic pain patients [33].

Subjects height and body weight were measured following a standardized protocol while patients wore light clothing and no shoes after an overnight fast. BMI was calculated as weight (kg)/height^2 (m). Anthropometrical and clinical data were collected by trained study personnel. Seated blood pressure was measured after 5 min rest with a calibrated sphygmomanometer at the nondominant arm by trained nurses.

2.4. Statistical Analysis. As the study was designed as a nonrandomized pilot study no sample size calculation was conducted. However, we intended to include 60 patients and assumed a drop-out rate of 15%, giving a study sample of about 50 patients with full data sets.

Baseline differences were calculated by Kruskal-Wallis test. All outcome criteria were analyzed by intention-to-treat; including all subjects, irrespective whether or not they adhered to the protocol or gave a full set of data. For each outcome we fitted a generalized estimation equation (GEE), analysis of covariance (ANCOVA) which included treatment group (binary covariate), and the respective baseline value (linear covariable) as independent variables. Treatment effects were estimated within these models, and reported as adjusted group differences including their respective 95% confidence intervals (CI) and P values. All reported P values were based on two-sided tests, and a P-value < 0.05 was considered significant. All statistical computations were performed with SAS/STAT statistical software version 9.1 (SAS institute, Cary, North Carolina, USA).

3. Results

3.1. Baseline. During the 9-month study recruitment period we screened 56 screened patients with manifest fibromyalgia which were admitted to one of the two hospital departments. Of these, 48 volunteered to participate in our study; 20 in the department of Rheumatology and 28 in the department of Integrative and Complementary Medicine. Data assessments were complete for study visits 1 (baseline) and 2 (week 2). After 12 weeks data from 25 patients of the department of Integrative and Complementary Medicine and 17 of the department of Rheumatology were available.

Baseline characteristics of the study population revealed a middle-aged and predominantly female study population. Patients of the Department of Rheumatology showed a significantly greater impaired quality of life, the primary outcome, and had slightly higher pain scores and were more emotionally distressed with slightly higher scores for depression and anxiety compared to patients of the Department for Integrative and Complementary Medicine (Table 1). Use of medication prior and during the hospital stay, for example, with amitriptyline and other antidepressants, was not different between groups.

3.2. Primary Outcome. The FIQ score decreased substantially in the Integrative Medicine Group and to a significantly greater extent compared to the Rheumatologic group after 2 weeks (Table 2). At 12 weeks, the FIQ score increased again in both groups resulting in improvements of only 12% for the integrative and fasting approach and 6% for the control group, resulting in a nonsignificant difference between the groups.

3.3. Secondary Outcomes. At 2 weeks, the Integrative Medicine group had greater mean improvements in all secondary outcomes and most pronounced in the scores of quality of sleep, pain, pain perception, and anxiety (HADS, STAI) (Table 2).

At 12 weeks, the pain score and pain perception score only showed a trend towards a beneficial outcome for the Integrative Medicine group compared to the Rheumatology group. All psychological outcomes were better in the Integrative Medicine group compared to the Rheumatologic group, however group differences were reduced and no longer statistically significant with the exception of anxiety. All of the outcomes deteriorated again compared to the 2-weeks

Table 1: Baseline characteristics.

Characteristics	Integrative medicine group	Rheumatology group	P value
Male/Female, No.	0/28	2/18	
Age, years	53.6 ± 10.8	51.8 ± 10.1	0.516
Body mass index, kg/m^2	27.8 ± 4.5	30.3 ± 6.7	0.281
SBP, mm Hg	122.3 ± 13.2	128.5 ± 13.7	0.072
DBP, mm Hg	76.8 ± 7.8	78.8 ± 10.1	0.656
Physical well-being	7.1 ± 1.9	8.0 ± 1.2	0.089
Practice of exercise, No. /(%)	21 (75.0%)	13 (65.0%)	0.452
Practice of Relaxation, No. /(%)	8 (28.5%)	5 (25.0%)	0.784
FIQ score	54.3 ± 15.0	68.0 ± 8.9	0.004
Pain score	58.2 ± 19.6	66.5 ± 19.5	0.135
Quality of sleep	60.5 ± 26.7	68.3 ± 27.6	0.191
STAI state score	50.4 ± 11.2	58.4 ± 13.0	0.027
STAI trait score	51.1 ± 11.2	54.3 ± 12.0	0.341
HADS-Anxiety	10.4 ± 3.8	11.3 ± 5.1	0.607
HADS-Depression	8.3 ± 4.8	11.1 ± 5.2	0.055

Values are mean ± SD if not indicated otherwise. SBP: systolic blood pressure; DBP: diastolic blood pressure.
STAI: State and Trait Anxiety questionnaire, FIQ: Fibromyalgia impact questionnaire; HADS: Hospital Anxiety and Depression scale.

data resulting in mild mid-term treatment effects compared to baseline levels.

3.4. Safety. There were no serious adverse events in both groups. About 35% in each group reported some minor side effect. Within the Integrative Medicine group the first fasting days were frequently accompanied by dizziness, minor headache, and tiredness. Patients in the Rheumatology group reported frequently about muscle pain and tiredness, most likely due to exercise and physical therapies. 24 out of 28 patients in the integrative Medicine group declared that they would participate in fasting as again. 17 out of 20 patients in the Rheumatology group declared that they would like to repeat the treatment.

4. Discussion

In this controlled nonrandomized trial we compared the effectiveness of two time- and attention-balanced inpatient multimodal treatment strategies: an Integrative Medicine approach that included fasting therapy versus the conventional Rheumatologic therapy. While patients in the Rheumatologic group were more diseased at baseline, adjusted data analysis showed a more beneficial effect of the Integrative Medicine approach after 2 weeks for all of the clinical outcomes. At week 12, effects in both groups were reduced but still favored the Integrative Medicine approach, for example, for the psychological outcomes. The minimally clinically important difference of the FIQ is estimated to amount to 14%. In the present study the reduction of the FIQ at 2 and 12 weeks was 30.2% and 12.2% with Integrative Medicine versus 13.1% and 6.0% with multimodal Rheumatologic care. Thus, our results point to a relevant immediate effect of the Integrative Medicine approach while the long-term effects appear to be only mild.

We were surprised to see an only mild effectiveness of the Rheumatologic multimodal treatment approach although it combined several evidence-based treatment methods such as aerobic exercise, pool exercise, thermal therapy, psychotherapy, and cognitive behavioral therapy. However, it has to be noted that patients that are admitted to an inpatient treatment in Germany are highly selected as they have to be documented nonresponders to outpatient treatments according to requirements of health insurance companies and thus may be especially difficult to treat.

A recent study has evaluated the effects of a conventional multimodal inpatient treatment of 3 weeks within the setting of a specialized Rheumatologic rehabilitation hospital [34]. For the outcomes that were used (Pain, HADS) the results of the Integrative Medicine approach used in this study were also favorable, thus confirming our results.

Principally, treatment of fibromyalgia is still unsatisfying and most patients continue to be in considerable pain years after the first diagnosis and experience reduced quality of life. New approaches are needed and the majority of patients with fibromyalgia frequently also use methods of complementary medicine. Various types of exercise and mind-body medicine have been advocated, yet long-term adherence is limited. In Germany, nutritional therapies and fasting are very popular. Fasting treatments have found to be effective in the treatment of rheumatoid arthritis and pain syndromes, furthermore they may support motivation and self-efficacy in health-promoting lifestyle modification [12, 15, 21, 35]. In a preliminary study we observed a moderate pain-relieving effect of fasting in fibromyalgia [13].

Of note, we found a partially persisting mood-enhancing effect in the integrative medicine group which may be related to fasting therapy. Previous research has documented mood-enhancing effects of caloric restriction and fasting. Several mechanisms including increased central serotonin availability have been described experimentally [17].

Table 2: Outcomes in both groups at baseline, week 2 and 12 with group differences as indicators of change.

	Integrative medicine group			Rheumatology group			Mean diff		Mean diff (95% CI)	
	Baseline	Visit 2	Visit 3	Baseline	Visit 2	Visit 3	∇ 1-2 (95% CI)	*P* value	∇ 1–3 (95% CI)	*P* Value
FIQ score	54.3 ± 15.0	38.0 ± 17.3	47.7 ± 19.3	68.0 ± 8.9	59.1 ± 15.3	63.9 ± 20.7	−11.2 (−20.1, −2.3)	0.014	−6.7 (−17.5, 4.1)	0.223
Pain score	58.2 ± 19.6	37.4 ± 19.9	48.8 ± 26.1	66.5 ± 19.5	58.3 ± 22.8	64.4 ± 25.7	−17.5 (−28.8, −6.1)	0.003	−13.0 (−28.0, 2.1)	0.091
Quality of sleep	60.5 ± 26.7	43.6 ± 27.8	48.3 ± 26.4	68.3 ± 27.6	61.1 ± 29.0	67.4 ± 20.4	−15.5 (−30.6, −0.4)	0.044	16.5 (−30.0, −3.1)	0.016
HADS Anxiety	10.4 ± 3.8	6.9 ± 3.2	8.9 ± 3.9	11.3 ± 5.1	10.3 ± 5.0	11.6 ± 4.2	−2.9 (−4.6, −1.3)	<.001	−2.3 (−3.8, −0.9)	0.002
HADS Depression	8.3 ± 4.8	6.1 ± 4.2	7.8 ± 4.1	11.1 ± 5.2	9.3 ± 5.1	11.6 ± 4.2	−1.5 (−3.3, 0.3)	0.097	−2.0 (−4.0, −0.0)	0.046
SES Pain Perception	30.7 ± 9.1	22.1 ± 6.6	29.8 ± 10.2	36.4 ± 8.6	34.2 ± 9.1	37.0 ± 10.5	−10.1 (−14.7, −5.5)	<.001	−5.2 (−11.0, 0.5)	0.075
STAI State Score	50.4 ± 11.2	39.7 ± 10.2	48.2 ± 11.5	58.4 ± 13.0	51.4 ± 12.6	57.6 ± 11.5	−8.2 (−13.9, −2.4)	0.005	−6.1 (−11.8, −0.4)	0.036
STAI Trait Score	51.1 ± 11.2	43.9 ± 9.7	48.6 ± 9.3	54.3 ± 12.0	53.5 ± 10.0	55.5 ± 9.6	−8.3 (−12.3, −4.2)	<.001	−4.8 (−8.9, −0.7)	0.022
BfS Well-being	21.3 ± 11.6	17.5 ± 14.1	23.4 ± 11.8	27.2 ± 9.0	27.8 ± 8.2	26.0 ± 10.4	−6.8 (−12.5, −1.2)	0.018	−1.4 (−8.0, 5.2)	0.675

Values are mean ± SD if not indicated otherwise. SBP: systolic blood pressure; DBP: diastolic blood pressure.
STAI: State and Trait Anxiety questionnaire, FIQ: Fibromyalgia impact questionnaire; HADS: Hospital Anxiety and Depression scale;
∇ 1-2 = difference between groups from baseline to visit 2 at 2 weeks, ∇ 1–3 = difference between groups from baseline to visit 3 at 12 weeks,
*P values for between group difference of change, adjusted.

Only a few studies have investigated multimodal treatment programs for fibromyalgia that focus on Integrative and Complementary Medicine. A small uncontrolled study in 28 patients found an Ayurvedic program, also focusing on nutrition and mind-boy techniques, to be effective with a lasting effect up to 24 months [36]. However, the treatment was not compared to another intervention, thus selection bias and unspecific effects were most likely contributing factors to the effect.

In view of our documented effects and safety of the Integrative Medicine approach further research on the effectiveness of complex multimodal Integrative treatments and comparisons with standard care in fibromyalgia is warranted. Such a study should have a larger sample size, allocate patients randomly, and include an attention control for the fasting intervention. Here the conventional group could be deprived of some specific food ingredient without inducing fasting metabolism. As it is difficult to randomize patients into complete treatment settings due to patient preferences and obligations of cost coverage, also outcome research might be useful in benchmarking the best strategy in intensified treatment strategies of fibromyalgia.

Some limitations relate to our study. First, we used a nonrandomized study design as it is currently not possible to randomize patients to hospital departments when costs are covered by health insurance companies under usual care. Nonrandomized studies may introduce a bias by patient selection and different prognostic and response factors between the groups. In fact, baseline values found patients of the Rheumatologic department to be more diseased and more distressed. However, most of the baseline differences were statistically nonsignificant and all our data analysis included baseline values as covariates. Of note, Physicians can refer patients to both hospital departments only if they are documented nonresponders to intensive outpatient outpatient treatment. The selection of the department (Rheumatology or Integrative Medicine) is mainly influenced by patients' preference. Here a specific selection bias may be introduced as patients interested in integrative Medicine are possibly more likely to search for comprehensive treatments in less severe disease states. Second, our study population was of limited size. Smaller study populations hold the risk of overestimation of effects on the one side and nondetection of moderate treatment effects on the other side. However, if significant effects are found the magnitude of effects and the related possible clinical relevance of the intervention is emphasized, which our results reflect. A third limitation is the short observation period of 3 months. Further studies should include observation periods of 12 months and longer to assess long-term symptom control.

A strength of our study relates to the fact, that both departments are situated in the same hospital and that, beside fasting and mind-body medicine, all other treatments were comparable and applied by the same personnel. Thus setting effects, attention effects and other nonspecific factors that may otherwise introduce bias in comparative studies were minimized.

In conclusion, our preliminary findings indicate that a multimodal Integrative Medicine treatment approach that included fasting therapy might be superior to the multimodal conventional Rheumatologic approach in the short-term in patients with severe fibromyalgia. At 12 weeks neither of the studied interventions was significantly superior or achieved clinically relevant improvement. Longer-term studies are warranted to assess the clinical impact and potential of multimodal Integrative Medicine in fibromyalgia.

Conflict of Interests

The authors do not have any conflict of interests with the content of the paper.

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“Fasting Therapy for Treating and Preventing Disease – Current State of Evidence”

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Fasting Therapy for Treating and Preventing Disease – Current State of Evidence

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Keywords
Fasting · Salutogenesis · Chronic diseases · Complementary treatment

Summary
Periods of deliberate fasting with restriction of solid food intake are practiced worldwide, mostly based on traditional, cultural or religious reasons. There is large empirical and observational evidence that medically supervised modified fasting (fasting cure, 200–500 kcal nutritional intake per day) with periods of 7–21 days is efficacious in the treatment of rheumatic diseases, chronic pain syndromes, hypertension, and metabolic syndrome. The beneficial effects of fasting followed by vegetarian diet in rheumatoid arthritis are confirmed by randomized controlled trials. Further beneficial effects of fasting are supported by observational data and abundant evidence from experimental research which found caloric restriction and intermittent fasting being associated with deceleration or prevention of most chronic degenerative and chronic inflammatory diseases. Intermittent fasting may also be useful as an accompanying treatment during chemotherapy of cancer. A further beneficial effect of fasting relates to improvements in sustainable lifestyle modification and adoption of a healthy diet, possibly mediated by fasting-induced mood enhancement. Various identified mechanisms of fasting point to its potential health-promoting effects, e.g., fasting-induced neuroendocrine activation and hormetic stress response, increased production of neurotrophic factors, reduced mitochondrial oxidative stress, general decrease of signals associated with aging, and promotion of autophagy. Fasting therapy might contribute to the prevention and treatment of chronic diseases and should be further evaluated in controlled clinical trials and observational studies.

Schlüsselwörter
Fasten · Salutogenese · Chronische Erkrankungen · Komplementäre Therapie

Zusammenfassung
Zeiträume bewussten Fastens mit Beschränkung der Aufnahme fester Nahrung werden weltweit praktiziert, meist auf Grundlage traditioneller, kultureller oder religiöser Überzeugungen. Es gibt umfangreiche Erkenntnisse aus empirischen und Beobachtungsstudien die zeigen, dass medizinisch betreutes modifiziertes Fasten (Therapeutisches Fasten, Heilfasten, 200–500 kcal Nahrungsaufnahme pro Tag) in einem Zeitraum von 7–21 Tagen in der Behandlung von rheumatischen Erkrankungen, chronischen Schmerzsyndromen, Bluthochdruck und des metabolischen Syndroms wirksam ist. Die positiven Auswirkungen des Fastens mit konsekutiver vegetarischer Ernährung sind für das Indikationsgebiet der rheumatoiden Arthritis durch randomisierte kontrollierte Studien belegt. Weitere vorteilhafte Effekte des Fastens sind von Daten aus Beobachtungsstudien und zahlreichen Erkenntnissen aus der experimentellen Forschung gestützt. Demnach konnte festgestellt werden, dass die kalorische Restriktion und intermittierendes Fasten mit Verzögerung oder Vorbeugung der meisten chronischen degenerativen und chronisch-entzündlichen Erkrankungen einhergeht. Intermittierendes Fasten kann möglicherweise auch als begleitende Behandlung während der Chemotherapie von Krebserkrankungen zur Reduzierung von Nebenwirkungen nützlich sein. Eine weitere positive Wirkung des Fastens bezieht sich auf Verbesserungen in der nachhaltigen Lebensstilmodifikation und eine gesundheitsfördernde Ernährungsumstellung, was möglicherweise durch die stimmungssteigernde Wirkung des Fastens begründet ist. Verschiedene identifizierte Mechanismen des Fastens deuten auf dessen potenzielle gesundheitsfördernde Wirkungen hin wie z.B. die durch das Fasten induzierte neuroendokrine Aktivierung und hormetische Stressreaktion, die erhöhte Produktion neurotropher Faktoren, reduzierten mitochondrialen oxidativen Stress, die Inhibierung von Signalwegen, die mit Alterungsprozessen assoziiert sind, sowie die Förderung von Autophagie. Therapeutisches Fasten erscheint als vielversprechende Methode zur Vorbeugung und Behandlung von chronischen Krankheiten, die Wirksamkeit sollte in randomisierten kontrollierten klinischen Studien sowie Beobachtungsstudien weiter untersucht werden.

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Introduction

The evolution of mankind was characterized by frequent fluctuations of food availability varying between periods of fasting or starvation and feast or overfeeding. The ability to survive periods of fasting must have been of some survival value and contrasts the unfavorable health effects of continuous overfeeding of present times. Unsurprisingly, therefore the human body exhibits adaptive responses to the lack of food. When deprived of food, the human body employs various behavioral, biochemical, physiological, and structural responses to reduce metabolism, which prolongs the period in which energy reserves can cover all metabolic and physiological needs [1].

In current times, when overfeeding is the standard situation for many people in modern societies, the adaptation to a defined period of fasting may not only be seen as an ability to cover the acute needs of metabolism but also as an important opportunity to recover from the persistent overdrive and consecutive down-regulation of the physiological and biological systems, its receptors, and signal pathways.

Background and Fasting Methods

Fasting as a medical treatment has been claimed to be a valuable therapeutic method for chronic and acute diseases in a multitude of traditional and ethnomedical systems worldwide [2, 3]. In the last 2 decades, modified fasting gained growing popularity in the German public, i.e. as a self-care method for prevention and health promotion, particularly to initiate lifestyle modification [4, 5].

Historically, the reasons for fasting involved both religious/spiritual and medical aspects [6]. In traditional European medicine, fasting was an established treatment method since the ancient Greek Hippocratic school and thereafter recommended by most of older European medical schools for the treatment of several acute and chronic diseases [7]. The application of fasting in the context of medical treatment followed the empirical observation that infections and acute diseases are frequently accompanied by an anorectic response. In Europe, based on the works of physicians like Buchinger [8], Krauß [9], and Mayr, medical fasting attracted a growing number of patients from the 1950s on. Fasting cures were developed and successfully established in a couple of specialized fasting sanatoriums, thereby embedding defined periods of modified or subtotal fasting within holistic lifestyle modification programs, with focus on mind-body medicine and aspects of spirituality.

Physiologically, nutritional energy supply below a threshold of about 500 kcal/day leads to strong neuroendocrine responses accompanied by rapid mobilization of glycogen stores (phase I), followed by metabolism of fat mass via lipolysis after a fasting duration longer than 24 h (phase II), and finally the phase of late starvation with accelerated protein loss (phase III). A maintained daily intake of even few calories reduces protein catabolism by a significant amount [10]. Therefore, the daily intake of 200–500 kcal is established in clinical fasting and defines modified fasting being the currently most frequently used form of therapeutic fasting. Very low calorie diets (VLCD) allow a higher nutritional intake up to 800 kcal/day. Yet, whereas VLCD also lead to substantial weight loss, the adaptive physiological and psychological responses are reduced and the mind-body medicine approach is not included. Finally, caloric restriction is defined as a long-term reduction in energy intake without malnutrition, mostly consisting of a 30–40% reduction of daily nutritional energy intake [11]. Caloric restriction is commonly used in experimental animal research. As an alternative to traditional caloric restriction, intermittent or alternate-day fasting has also been established. Intermittent regimens usually involve a 'feast day' on which food is consumed ad libitum that alternates with a 'fast day' on which food is withheld [11, 12]. The feast and the fast periods are usually performed for 24 h and commonly weight is not changed by alternating diets. One of the most known religious fasting traditions in humans is the period of Ramadan. During the fasting month of Ramadan, Muslims abstain from food and drink from sunrise until sunset. Thus, Ramadan can be categorized as a short-period intermittent fasting regimen.

Beside the most frequently used fasting method according to Buchinger, there is a variety of other fasting methods and techniques [13]. In Germany, in 1982 the Physician's society for fasting and nutrition was founded, and in 2002 the first guidelines on fasting therapy were published by an expert panel of this society [14].

Buchinger's method of fasting includes the limited intake of vegetable or fruit juice and small amounts of vegetable broth with a total nutritional energy intake between 200 and 400 kcal/day [15]. Further components of Buchinger's method include the use of physical exercise, mind-body techniques, the defined application of enemas, and intake of laxative salts.

Other standardized methods of extended medical fasting were developed in the USA in the beginning of the 20th century by physicians like Tanner, Dewey, and Hazzard [6, 16]. Their mainly used method of fasting consisted of water-only fasting (partly with distilled water) and tea fasting, supported by enemas and physical exercise. Since that time and despite scientific documentation of its putative beneficial effects, little attention has been given to medical fasting in USA, and the method almost disappeared in medical care in Northern America.

Recently, renewed interest arose with the rapidly growing body of evidence from basic research consistently showing that caloric restriction, either by continuous restricted caloric energy intake or by intermittent fasting, may lead to substantial beneficial physiological effects and disease prevention. Notably, increases in lifespan and anti-aging effects mediated by caloric restriction and fasting were repeatedly described for a multitude of species, from the *Caenorhabditis elegans* up to

Table 1. Main types of fasting (selection)

Type of fasting	Nutritional profile	Further characteristic
Modified therapeutic fasting; 'fasting cure'	caloric intake 200–500kcal/day by fluids and water ad libitum	broad clinical indications. Rapid weight loss; strong neuroendocrine adaptation
Buchinger fasting	200–500 kcal by juice / vegetable broth	as modified fasting and holistic approach including mind-body methods (enhancing lifestyle change)
Very low calorie diet	caloric intake 600–800 kcal/day by formulated liquid meals; protein supplements	primary aim of weight loss
Calorie restriction		e.g., experimental evidence; long term adaption to underfeeding; decelerates age-related diseases
Continuous calorie restriction	daily reduced caloric intake by 30–40%	increase of lifespan; reduced degeneration; improved functional indexes
Intermittent fasting	alternate-day fasting (24 h); 5–2-days eating/fasting	increase of lifespan; reduced degeneration, improved functional indexes
Ramadan fasting	daytime fasting for 29 days; meal skipping	health-related effects unclear or only mild
Total fasting	zero-diet (water/tea ad libitum)	pronounced protein catabolism; more adverse effects than modified fasting
Water-only fasting	fasting with distilled water-only	pronounced protein catabolism; more adverse effects than modified fasting

the rhesus monkey [1, 17–19]. These data were supported by description of defined molecular mechanisms that are responsible for these effects.

Renewed interest in fasting also came from another perspective, the research on medical effects of fasting rituals as practiced in religious traditions worldwide. Many religions have a component of fasting involved. The common belief is that fasting supports spiritual practice and focuses the mind. Up to now, the most common forms of fasting studied in this field are Ramadan fasting and the Daniel's fast, which are characterized by only moderate or short-term calorie restriction, in contrast to the stricter medical fasting cures [20]. The different main types of fasting are summarized in table 1.

So far, the effects of medically supervised fasting have been studied for few indications by means of controlled trials. Further evidence arises from epidemiological and experimental studies on different fasting practices and from clinical trials that used very-low calorie diets with a comparable severely restricted energy intake, but without the supporting multimodal therapeutic elements that are typically used in traditional medical fasting. Experimental animal research on fasting, controlled underfeeding and starvation, which by definition are not voluntary, can be translated only to a limited extent to the condition of human medical fasting. Hence, some uncertainty in the appraisal of these results with regards to voluntary medical fasting cannot be resolved. The existing evidence for the main indications as derived from clinical, observational or epidemiological research, and the putative mechanisms are summarized in the following.

Mechanisms of Fasting Effects

General Mechanisms

Prolonged fasting is a strong physiological stimulus equivalent to a mild-to-moderate biological stress and activates numerous endocrine and neurobiological responses from systemic levels up to molecular signal pathways. Regarding health-promoting mechanisms, several general hypotheses have been proposed.

Most prominent is the 1) stress-resistance hypothesis which suggests that after calorie restriction or fasting, increased stress resistance and cross-resistance to other types of stressors occur, permitting cells to better resist to genotoxic, oxidative or metabolic insults [21–23]. Such a beneficial action and compensation of low-intensity environmental stressors can be classified as a hormetic response or hormesis, which describes a biological dose-response phenomenon characterized by low-dose stimulation and high-dose inhibition [24, 25]. Other examples of moderate or intermittent stressors inducing hormesis are exercise, UV radiation, and ischemic preconditioning [26]. Interestingly, fasting promotes ischemic preconditioning itself [27].

2) The oxidative stress hypothesis proposes that fewer free radicals are produced in the mitochondria due to reduced energy utilization [28], which results in less cellular damage [1]. However, there is also some controversy about the role of oxidative stress in disease and longevity [29].

3) A third hypothesis suggests that fasting and calorie restriction induce intrinsic cellular and organismal programs for adaption to scarcity, thereby slowing down generally metabolic processes which contribute to degeneration and aging [30].

In this context, it is also described that any type of food intake activates the NF-KappaB (NF-κB) pathway, thereby promoting cellular inflammation. Furthermore, other signalling pathways have been implicated in mediating these fasting effects, e.g., the known lifespan-regulating sirtuin pathway, the insulin-like growth factor (IGF)-1 / insulin pathway, the target of rapamyin (TOR) pathway, and the adenosine-monophosphate (AMP) pathway [26, 31].

4) A fourth putative mechanism relates to autophagy, a catabolic pathway involving the degradation of cellular components through the lysosomal machinery. Autophagy acts as a survival mechanism under conditions of stress, maintaining cellular integrity by regenerating metabolic precursors, clearing subcellular debris, and thus preventing cell death [32]. Nutrient depletion and fasting are potent physiological regulators of autophagy [33], and regulation of a macromolecular complex, mTORC1, may be critically involved. An abundance of experimental research describes dysregulation and down-regulation of autophagy associated with the initiation or progression of cancer, immunological and neurodegenerative disease, metabolic and cardiovascular disease, and aging. Experimental evidence suggests that fasting and dietary restriction increases autophagy and cellular clearance [34], however, the impact of periods of fasting in humans on autophagy has not been studied.

5) A further hypothesis relates to the organismic accumulation of advanced glycation end products (AGEs) which are the derivatives of glucose-protein or glucose-lipid reactions and are mainly generated from diet [35]. Binding of AGEs to the AGE receptor (RAGE) results in cellular activation, i.e. increased expression of inflammatory mediators and oxidative stress. AGEs have been repeatedly linked to the pathogenesis and progression of inflammatory and age-related disease as well as to increased NF-κB activity [36–38]. There is some preliminary evidence that fasting may decrease AGE load in human bodies. In a small study in patients with rheumatoid arthritis (RA) [39], a 54-day regimen with consecutive cycles of fasting and calorie restriction resulted in decreased urinary excretion of the AGE pentosidin which was accompanied by a reduction of disease activity. Further studies should address the role of AGEs in anti-inflammatory effects of fasting. As the decrease of pentosidin levels was only evident after 25 days, these studies should consider that extended fasting periods or longer diet and fasting programs may be needed to show effects on AGEs.

Endocrine and Neurobiological Effects

Neuroendocrine responses of fasting have been investigated by numerous physiological and clinical studies. Initially, during fasting the hypothalamic-pituitary-adrenal (HPA) axis [40–43] is activated. The biological mechanisms of this activation are not fully understood but include the reduced availability of cerebral glucose, reduced insulin and leptin levels, and the sensation of hunger [40–45]. Fasting-induced leptin depletion has been identified as a strong signal for biological adaptation responding to starvation [46]. Further, a transcription factor has been described which acts as a metabolic sensor in neurons of the lateral hypothalamic area to integrate metabolic signals, adaptive behavior, and physiological responses [47].

In human clinical studies, the fasting-induced neuroendocrine activation is associated with increased urinary and serum concentrations of noradrenaline, adrenaline, dopamine, and cortisol. This early hypopituitary adrenergic activation is followed by decreased adrenergic levels in the medium term. In a prospective study with obese subjects [48], a fast over 16 days led to substantial weight loss, paralleled by decreased basal and exercise-induced serum concentrations of noradrenaline, adrenaline, and dopamine.

Interestingly, this early mild stress response with a subsequent adaption process supports the view that fasting may be a characteristic example of hormesis [24]. Extended fasting over at least 5–7 days is further associated with increases in concentrations of growth hormone, glucagon, and reductions of the blood levels of thyrotropin (TSH) and T_3/T_4 [49, 50]. Clinically, fasting leads to a pronounced initial (days 1–3) natriuresis and diuresis. The mechanisms of fasting-induced natriuresis remain partly unclear; however ketoacidosis and fasting-induced increases of blood levels of aldosterone, glucagon, and natriuretic peptides are involved [51]. Studies on VLCD demonstrated an enhanced blood pressure-reducing effect of natriuretic peptides, which points to improved receptor sensitivity following a fasting intervention [52].

Different studies have shown that fasting leads to rapid depletion of the adipokin leptin and reductions of insulin levels [53–55]. Leptin depletion likely plays a crucial role in the neuroendocrine signalling and induces adaptive actions in response to fasting [56]. Blood levels of insulin and IGF-1 are decreased by fasting with a concomitant increase of adiponectin. Further beneficial effects to the cardiometabolic system relate to plasminogen activator inhibitor (PAI) and decreased angiotensinogen.

Brain neurotransmitters may be implicated in the fasting-induced neurobiological and central responses. The central serotonergic system is strongly involved in the regulation of food intake, and it also serves as transmitter system that is readily affected by nutritional factors. Serotonin release and turnover are known to increase during extended fasting [57, 58]. Increased output of the serotonergic system is assumed to be responsible for some of the characteristic nutritional effects on certain brain functions such as elevated mood, increased sleepiness, and reduced pain sensitivity. Studies on rats have reported an increase in the availability of brain tryptophan and serotonin during fasting [59, 60]. Further experimental data indicate that semi-starvation is associated with down-regulation of cortical serotonin transporters in the frontal cortex of the rat and alteration of the serotonin output pattern that also affects projection fields of the central serotonergic system [61]. Thus, fasting-induced modulation of central sero-

tonin availability may be a potential mechanism and would also explain previously described effects of fasting treatments in migraineurs [62], as pharmacological 5-HT receptor inhibition has been proven effective in the treatment of migraine. The cerebral glucose decrease could promote neurogenesis and synthesis of neurotrophic factors as well as chaperone proteins [63–65]. For instance, intermittent fasting causes an increase in brain-derived neurotrophic factor (BDNF), which is involved in the regulation of serotonin metabolism, an increased synaptic plasticity, improves cognitive function, and increases the brain's ability to resist aging [63–66]. Duan et al. [67] further suggested that the increase in BDNF may partly mediate the observed lifespan extension by intermittent fasting. Recent research further indicates a reciprocal relationship between BDNF and serotonergic signalling, in which BDNF enhances serotonin production and release [68, 69].

Another potential mechanism of the frequently described fasting-induced mood enhancement relates to the release of endogenous opioids. Plasma levels of beta-endorphin in subjects undergoing fasting periods between 5 and 10 days were significantly increased during the fasting period, while there was no direct association with body weight changes [70]. Also differential regulation of the endogenous synthetic pathways of morphine in response to fasting has been described. Brain morphine levels in rats were elevated 5-fold after 24 h and 2-fold after 48 h of fasting [71]. Moreover, brain levels of the endogenous cannabinoid 2-arachidonoyl glycerol (AG) were found to be increased in fasting mice, while moderate dietary restriction had no influence [72].

Finally, the production of ketone bodies could be involved in improving mood, decreasing pain sensation, and promoting protection against hypoglycemia and different types of brain damage [73–75], possibly through anticonvulsant properties [76–79]. Interestingly, recent studies [79, 80] have pointed to promising therapeutic effects of the ketogenic diet, not only in seizure prevention but also in degenerative and inflammatory neurological diseases, such as Parkinson's disease, Alzheimer's disease, and multiple sclerosis. Results of another clinical trial investigating the comparative effects of medical fasting and ketogenic diet in patients with multiple sclerosis are expected in 2014.

Clinical Effects of Fasting

Rheumatic Diseases

Patients with RA frequently report that their symptoms are alleviated by elimination-specific nutrients or fasting [81]. Several early studies [82–84] found beneficial effects of fasting on symptoms as well as on inflammatory parameters in patients with RA. In a randomized trial [85] investigating an initially 7–10 days fast followed by an individually adjusted vegetarian diet, fasting patients obtained substantial reduction of disease activity including a variety of laboratory markers over the 1-year study period. A systematic review [86] pooling the results of the available controlled studies, which reported follow-up data for at least 3 months, found a clinically relevant beneficial effect of fasting. Thus, available evidence suggests that fasting followed by vegetarian diet is useful in the treatment of RA.

In clinical experience, fasting is not only beneficial in RA and collagenoses but also in osteoarthritis (OA). The effect of fasting in OA of the knee and hand was investigated for the first time in an uncontrolled pilot study with 30 patients [87]. After 4 and 12 weeks of observation, substantial pain relief, improvements in quality of life, and improved articular function were documented.

Chronic Pain Syndromes

The general pain-relieving effect of fasting is a frequent empirical observation made by fasting therapists. The analgesic and antinociceptive effects of caloric restriction have been confirmed experimentally [88], and reduced responses to experimental pain have been associated with changes in endogenous opioid system [89]. So far, mostly smaller or nonrandomized studies have investigated the effect of fasting on chronic pain. In a preliminary study [90] investigating the neuroendocrine mechanisms of fasting in patients with unspecific chronic pain, a pain-relieving effect was described by the majority of patients. Furthermore, results of a controlled trial [91] suggested fasting therapy to be beneficial compared to normocaloric diet in the complex treatment of fibromyalgia. In a further controlled nonrandomized trial [92], we found a beneficial effect of fasting over standard complex treatment in inpatients with fibromyalgia. An uncontrolled study from Germany [62] reported a beneficial effect of fasting on headache frequency and intensity of migraine. In a large observational study of inpatients with mixed diagnosis of chronic diseases [93], health-related and behavioral outcomes were compared in fasting patients and patients on a normocaloric Mediterranean diet. Fasting patients showed higher satisfaction ratings with their treatment success and a greater improvement of chronic pain, being the main complaint among the majority of patients. Furthermore, fasting patients showed higher attrition rates with recommended health-related lifestyle modifications in the follow-up assessments at 3 and 6 months after discharge from the hospital.

These findings, together with the evidence of the mood-enhancing effects [13], support the view that fasting might be a promising treatment approach in chronic pain syndromes. Clearly, further randomized studies are necessary to clarify the role of fasting in the complex treatment of pain.

Hypertension, Cardiovascular Risk, and Metabolic Disease

In experimental research and in a couple of observational and clinical (mostly uncontrolled) studies [94–97], the blood pressure-reducing effect of fasting has been consistently confirmed. In a study on 68 patients with borderline hypertension undergoing 10–14 days of water-only fasting [98], the mean blood pressure reduction amounted to 20/7 mm Hg. In a further uncontrolled study [99], the same research group reported

results of 10–11 days of medically supervised fasting in 174 consecutive inpatients with hypertension. Fasting led to an average blood pressure reduction of 37/13 mm Hg, and in patients with stage 3 hypertension to an average reduction of 60/17 mm Hg. Despite the initial fasting-induced activation of the HPA axis the pronounced natriuresis of fasting, the increased concentration of and sensitivity to natriuretic peptides, the lack of salt intake, and the orchestrated endocrine effects of fasting including pronounced decreases in insulin may mediate this clinically relevant blood pressure reduction [51, 52, 97]. The blood pressure-reducing effect of fasting has also led to the recommendation of fasting experts to strictly reduce or withdraw antihypertensive medication when initializing fasting therapy, in order to avoid symptomatic hypotension as well as hyponatremia. After reintroduction of food, an increase in blood pressure is common, however blood pressure commonly remains below the pre-fasting values for weeks to few months, depending also on the post-fasting nutritional and lifestyle habits. Moreover, weight loss and the subsequent benefits of a healthier diet after fasting may contribute to the lasting antihypertensive effects of fasting [93, 96, 100]. Notably, epidemiological studies showed that routine periodic fasting, as practised by religious groups, is associated with a lower risk of coronary artery disease in patients undergoing coronary angiography [101].

Experimental research further revealed that calorie restriction and intermittent fasting attenuate age-associated changes in the heart and vessels. The attenuation of these age-associated changes does not occur due to the lower body weight but to cellular mechanisms directly related to fasting. Furthermore, alternate-day fasting reduces the level of apoptosis in the peri-infarct area in experimental ischemia [102] and enhances ischemic preconditioning [27]. Reductions in heart rate were observed experimentally in the course of intermittent fasting [11] and are a common empirical observation in patients after prolonged fasting (after the initial HPA activation). Accordingly, it has been found that a 3-week fasting course in metabolic patients leads to a smaller exercise-induced increase of catecholamines [48].

Modified fasting is frequently successfully applied in patients with type 2 diabetes and metabolic syndrome. An early study [103] found glucoregulatory improvements in obese diabetic women after 3 days of fasting, already. In an own uncontrolled study in 30 outpatients, a 1-week Buchinger fasting led to pronounced decreases in triglycerides, LDL-cholesterol, insulin, and leptin. Furthermore, clinically relevant decreases in blood pressure and heart rate were observed, paralleled by increases of adiponectin levels [104]. In an observational study in 25 inpatients that participated in Buchinger fasting [105], a significant improvement of insulin sensitivity, as assessed by the homeostasis model (HOMA) measurements, was shown. Long-term effects of Buchinger fasting were also evaluated by an outcome research [100] in 599 obese patients of a German rehabilitation facility. With response rates of 55%, the effect sizes for change of subjective health outcomes at 12 months after discharge were large and the patients showed lasting weight reduction and improved cardiovascular risk. Against the background of the available experimental and clinical evidence, it can be suggested that fasting is beneficial in hypertension, as additive treatment in type 2 diabetes, and in risk reduction of cardiovascular disease, even more pronounced when followed of useful lifestyle changes.

Cancer

Until recently, fasting therapy was not considered to be a treatment option in cancer, related to the fact that a common therapeutic goal in palliative cancer treatment is to avoid weight loss and to counteract the wasting syndrome. On the other hand, calorie restriction with continuous reduction of calorie intake has been found protective against oxidative stress and aging, applying to a multitude of organisms. As the toxic chemotherapeutic side effects in the treatment of cancer are mediated by cellular stress, the ability of calorie restriction to promote stress resistance recently gained increasing interest in oncological research [106]. However, weight loss due to cancer or chemotherapy is negatively correlated with prognosis in advanced stages of cancer. Therefore, continuous calorie restriction with its regular subsequent weight loss is estimated not to be useful in cancer patients. In contrast, intermittent or short-term fasting can also protect organisms from toxic effects of oxidative and chemotherapeutic agents and does not cause chronic weight loss. Furthermore, fasting does reduce IGF-1, a key factor in cancer promotion, to a greater extent than calorie restriction [107]. In their pioneering research, Longo and coworkers [108] could consistently demonstrate beneficial effects of short-term fasting in cancer when performed during and around chemotherapy. For example, fasting for 48–60 h protected mice from the side effects of etoposide. It was further shown that fasting prevents reproduction and growth processes in normal body cells by reallocating energy toward maintenance pathways. This switch to a protected mode when nutrients are scarce occurs only in normal body cells, but not in cancer cells as oncogenes prevent the activation of this type of stress resistance, thus making cancer cells unresponsive to anti-growth signals. This inability of cancer cells to properly respond to extreme environment changes thus provides a mechanism to enhance cancer treatment by selectively increasing stress resistance only in normal cells (differential stress resistance, DSR) [108]. DSR in mice and cell lines is partly mediated by the reduction of IGF-1 [109].

Clinically, fasting for 2–3 days before and 24 h after chemotherapy is mostly well tolerated by cancer patients. After the fasting days, an increase in weight is common, thereby regaining baseline weight. Longo et al. demonstrated [108] that cycles of fasting were as effective as chemotherapeutic agents in delaying progression of some tumors and increased the effectiveness of these drugs against melanoma, glioma, and breast cancer cells. In some animal models, fasting cycles, when added to chemotherapy, but not either treatment alone, resulted in

long-term remission. Furthermore, fasted breast cancer cell lines appeared to compensate for the lack of nutrients by a paradox increased translation, thus consuming even more energy with subsequent promotion of cell death. However, in summary the current state of research does not support a role of fasting in healing cancer as stand-alone treatment, but as a potential additive, synergistic side treatment to chemotherapy, and possibly also to radiotherapy [110].

In a first human case series, cancer patients who voluntarily fasted for 4–5 days in combination with chemotherapy experienced significantly reduced side effects [111]. So far, it seems that the periods of fasting have to be maintained at least up to 24 h after chemotherapy to minimize enhanced toxicity of chemotherapy to normal cells in the phase of refeeding [108].

Further research to investigate the effect of post-chemotherapy fasting is necessary to clarify the optimum time period of fasting in cancer and chemotherapy. Currently, several trials are underway testing the effects of fasting periods in combination with chemotherapy (NCT009363364: Short-term fasting prior to platinum-based chemotherapy: feasibility and impact on toxicity, USC; NCT01175837: Short-term fasting before chemotherapy in patients with lymphoma, a pilot feasibility study, Mayo Clinic; NCT01304251: Effects of short-term fasting on tolerance to chemotherapy, Leiden University; NCT01954836: Effects of fasting during chemotherapy: a randomized trial in gynecological oncology patients, Charité Berlin).

Affective Disorders and Impact on Mood

Fasting is associated with increases in tryptophan availability and serotonin turnover in the brain and induces the release of endogenous opioids. The practice of fasting in numerous religions as renunciation of external rewards in an ascetic approach may further reflect the empirically and clinically observed increase in mental alertness, sense of calm, and improved mood during fasting periods. Mood enhancement during fasting may represent an adaptive mechanism promoting the phylogenetic struggle for survival and search for food. Thus, the human body may be programmed to better cope with famine than with overfeeding. Mood improvement that occurs during these first few days of fasting could be a direct consequence of this activation. In clinical studies, fasting is frequently accompanied by increased vigilance and mood-enhancement, a subjective feeling of well-being, and sometimes even a feeling of euphoria [53, 112–116].

For example, in a prospective uncontrolled trial on 52 inpatients with chronic pain and metabolic syndrome, more than 80% of fasters (Buchinger fasting 8 days) showed a rapid decrease in depression and anxiety scores. Fasting-induced mood-enhancement has also found to be partly dependent on genetic factors [113]. In an observational study on inpatients with mixed diagnoses of chronic diseases [93], (mostly pain and rheumatic diseases) modified fasting also induced beneficial effects on lifestyle modification with a better adherence to nutritional recommendations, exercise, and relaxation practice thereafter, which may also relate to the initial mood-enhancing effect of fasting. Principally, the experience of fasting and the voluntary renunciation of food intake can support motivation for lifestyle change. Most fasters experience clarity of mind, have a feeling of letting go past actions and experiences [117], and thus may develop a more positive attitude towards the future. The fasting-induced neurendocrine responses [90] may support the motivation for behavioral change.

Further Indications

In the expert consensus guidelines on fasting therapy [14] as well as in empirical practice, fasting is also indicated as promising treatment option for further diseases, such as IBS, food intolerances, skin diseases as urticaria or neurodermitis, and recurrent infections. Furthermore, diseases for which T-2 lymphocyte activation is involved are frequent empirical indications for fasting therapy, e.g., asthma, inflammatory bowel disease, multiple sclerosis, and allergies [14]. So far, for these indications only preliminary data from prospective trials or no data are available. Beneficial effects in IBS were reported by a Japanese working group [118]. Results from a first trial on fasting and ketogenic diet in multiple sclerosis are expected in 2014. Clearly, further clinical research on fasting in these indications is warranted.

Safety

Fasting may reinforce eating disorders. Therefore it is important to ask patients about any history of anorexia or binge eating disorder. As fasting reduces the basal metabolic rate, patients who return to unrestricted eating after fasting may experience a yo-yo effect and weight cycling. On the other hand, outcome data of the German fasting clinics found no evidence for a mean increased weight after 1 or several fasting therapies [93, 119, 120]. Practically, in patients with a BMI > 45 kg/m^2 fasting only should be recommended if there is no indication of eating disorder and furthermore a sufficient motivation for lasting lifestyle change is present.

Anecdotal reports of deaths during fasting are only reported in the context of liquid-protein diets and a fasting period of >2 months (prolonged starvation) in obese subjects [121–123]. Of note, deaths during these diets occurred frequently in the phase of refeeding. The pathophysiology of the 'refeeding syndrome' focusses on intracellular loss of electrolytes, in particular phosphate, due to protein catabolism in prolonged starvation. When refeeded, malnourished patients exhibit an insulin-induced cellular uptake of phosphate, which can lead to profound hypophosphatemia and subsequent rhabdomyolysis, respiratory and cardiac failure, and arrhythmias [124]. Of note, cases of refeeding syndrome have not been observed with the shorter-term modified therapeutic fasting.

Within the current practice, serious adverse effects of fasting relate to the interaction with medication, e.g., hyponatremia by diuretics or bleeding during anticoagulation; therefore it is indispensable to accompany fasting therapy by a specialized physician. Minor adverse effects of fasting are experienced by about 10–20% of patients, e.g., initial headache (mostly due to caffeine withdrawal), unspecific initial back pain or lightheadedness due to reduced blood pressure. Subjects with known Gilbert syndrome may experience increase of blood bilirubin during fasting with frequently related general discomfort.

To ensure safety, the contraindications to fasting therapy have to be checked before initiation of treatment. Main contraindications are eating disorders, malnutrition and cachexia, pregnancy and nursing, uncontrolled hyperthyroidism, dementia, advanced liver or kidney insufficiency, and porphyria.

Studies on fasting [114] as well as clinical experience show that hunger is only moderate during fasting. General slight discomfort may be felt especially in the initial phase of fasting, from the first to third fasting day, when metabolism is changing to lipolysis. Typical complaints in this context include tiredness, irritability, nausea, and changing sleep patterns. These complaints can be best managed by self-help measures. The concern over fasting-induced loss of protein reserves and related adverse effects is ever present in nutritional medicine. However, the large experience in fasting therapy and available existing evidence found supervised fasting to be a safe approach, not leading to relevant protein loss.

Practical Aspects of Clinical Fasting

Fasting is an established treatment method applied in specialized hospitals or hospital departments of naturopathic, integrative, and nutritional medicine in various central European countries and in USA. In expert consensus conferences [14] and an updated expert panel statement [125], quality criteria of fasting as well as contraindications to medical fasting have been defined.

Disclosure Statement

The authors declare that there is no conflict of interest concerning this manuscript.

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Modified *Ling-Gui-Zhu-Gan* decoction combined with short-term fasting improves therapeutic response in type 2 diabetic patients

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Abstract

Objective: To evaluate the effects of a Traditional Chinese Medicine herbal decoction (modified *Ling-Gui-Zhu-Gan* decoction) combined with short-term fasting/very-low-calorie-diet (VLCD) on the therapeutic response in type 2 diabetes mellitus (T2DM) patients.
Materials and methods: A randomized controlled pilot-study was conducted with 60 T2DM patients (age 52.1 ± 13.4 y, BMI 25.7 ± 3.7 kg/m^2) with a lack of glycemic control. Patients were randomly allocated to the intervention group ($n = 30$) or the control group ($n = 30$). All patients received in-hospital treatment for one week followed by lifestyle recommendation. Patients in the intervention group participated in a 5-day modified fasting/VLCD combined with an intake of *Ling-Gui-Zhu-Gan* decoction. Patients in the control group received standard treatment only. Outcomes were assessed at baseline and at 3-months.
Results: Fasting plasma-glucose, 2-h plasma-glucose after oral glucose tolerance-test, HbA_{1C}, and the use of anti-diabetic medication decreased significantly in the intervention group compared to the control group after three months. Body weight also decreased significantly.
Conclusions: A combined integrative treatment approach including fasting/VLCD and a Traditional Chinese Medicine decoction might be superior to standard treatment in T2DM patients. This therapeutic concept should be further evaluated.

Keywords: Very-low-calorie-diets; Fasting; Chinese medicine; Diabetes mellitus; Glycemic control; Herbal medicine

Introduction

Modified fasting and very-low-calorie-diets (VLCDs) had come to clinical researchers' attention since the 1990s due to their effects on weight loss and improvement of cardiovascular risk factors in patients with T2DM and metabolic syndrome (MS). In the management of obese patients with T2DM these dietary treatments are used to initiate lifestyle modification and to improve weight control. [1–8] On the other hand, we empirically found that Chinese T2DM patients, which numbers are growing rapidly, tend to be unable to distinguish mild tastes and frequently exhibit a greasy and thick tongue coating as well as other pattern signs of so-called "turbid mucus distressing the spleen" according to the principles of Traditional Chinese Medicine (TCM). Hence, we developed a new treatment, combining short-term modified fasting/VLCD with a TCM herbal treatment, i.e. modified *Ling-Gui-Zhu-Gan* decoction, including the herbs of Sclerotium Poriae Cocos (*fu ling*), Ramulus Cinnamoni Cassiae (*gui zhi*), Rhizoma Atractylodis Macrocephalae (*bai zhu*), Radix Glycyrrhizae Preparata (*zhi gan cao*), Radix Codonopsis Pilosulae (*dang shen*), Radix et Rhizoma Rhei (*da huang*). According to TCM the application of these herbs is postulated to warm and resolve mucus (*wen-hua-tan-yin*) as well as to strengthen the spleen and to remove turbidity (*jian-pi-xie-zhuo*). In preliminary clinical observations we found that this treatment approach may promote the acceptance of caloric restriction and, moreover, may improve glycemic control. We designed and conducted the present pilot-study in order to investigate the effects of a combined dietary and TCM herbal treatment on patients with T2DM.

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Materials and methods

Subjects and study design

All patients were admitted consecutively to the hospital department of the *First affiliated Hospital of the Sun-Yat Sen University* for intensified in-patient treatment of T2DM. A total of 60 eligible patients (34 male and 26 female) participated in the trial. The diagnosis of T2DM was based on the WHO criteria of 1999. Patients were considered for the trial if they presented with a manifest and previously treated T2DM, however, with no sufficient glycemic control ($HbA_{1C} > 6.1\%$).

The study was designed as a clinical randomized pilot study, all patients were allocated randomly to either the intervention group or to the control group. Each group consisted of 30 patients. Treatment group allocation was performed by a non-stratified block-randomization with varying block lengths. Random numbers were generated by a computer program (see Fig. 1).

The study protocol was approved by the institutional review board. Written informed consent was obtained from all study subjects.

Interventions and treatment protocol

All patients had received the same amount of diabetes mellitus education classes before the trial. Patients in the intervention group were treated internally with a modified *Ling-Gui-Zhu-Gan* decoction combination with a 5-day modified fasting/very low calorie diet (VLCD). The modified *Ling-Gui-Zhu-Gan* decoction contained Sclerotium Poriae Cocos (*fu ling*) 20 g, Ramulus Cinnamoni Cassiae (*gui zhi*) 12 g, Rhizoma Atractylodis Macrocephalae (*bai zhu*) 15 g, Radix Glycyrrhizae Preparata (*zhi gan cao*) 9 g, Radix Codonopsis Pilosulae (*dang shen*) 30 g, and Radix et Rhizoma Rhei (*da huang*) 9 g. According to the principles of TCM the decoction aims to warm and resolve mucus (*wen-hua-tan-yin*), to strengthen the spleen and to remove turbidity (*jian-pi-xie-zhuo*). As previously described [9], the dietary fasting/VLCD treatment consists of three phases: (1) the pre-fasting phase, (2) the 5-day strict modified fasting/VLCD phase and (3) the food reintroduction phase. The pre-fasting phase consists of 1–2 dietary "relief" days with an intake of fruits and vegetables only. The pre-fasting phase aimed to prepare patients for the fasting phase, to adapt digestion and to stepwise control subjective perception of hunger. The fasting/VLCD phase

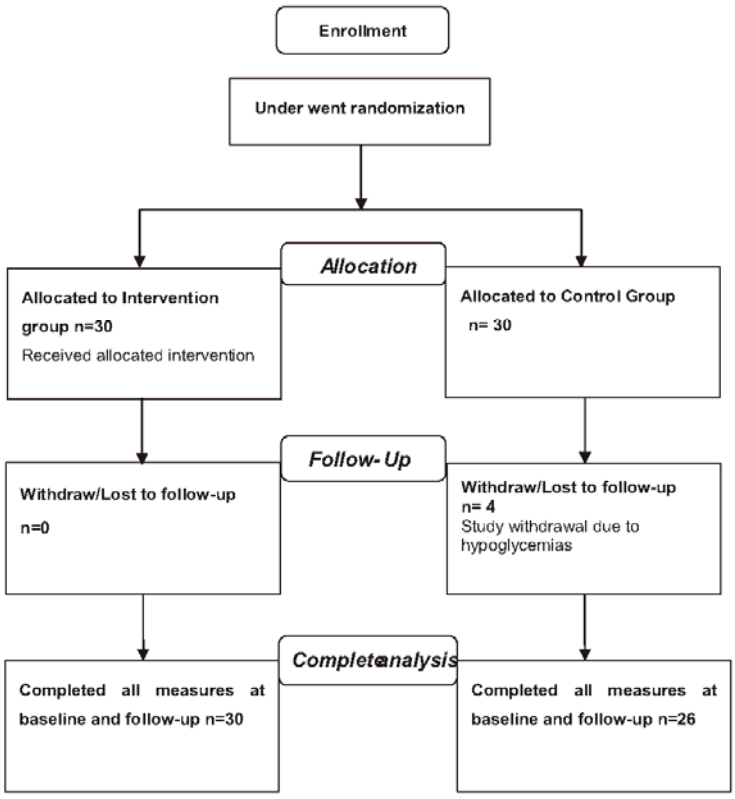

Fig. 1. Participant flow diagram.

followed throughout the subsequent 5 days started with the intake of 10–20 g thenardite powder for bowel-cleansing purposes. During fasting patients were advised to sip hot millet soup, which was prepared with ≤150 g millet and 1000 ml water, along with drinking 3 L of mineral water per day. Patients could also choose to drink moderate quantities of sugar-free sports beverages every day to maintain electrolyte balance. Solid food was refrained throughout the modified fasting phase. Nutritional energy intake was limited to <550 kcal/day. After the fasting phase patients reintroduced solid food items stepwise, increasing food intake gradually to an amount still smaller than standard diabetic diets. Ingestion of fluid diet to solid food was changed slowly. The in-patient treatment period comprised 7 days in both groups: in the fasting/VLCD group 5 modified fasting days and one day for relief and food reintroduction respectively; in the control group 7 days for continuous nutritional therapy and diet control, physical therapy and educational programs.

During the fasting phase the modified *Ling-Gui-Zhu-Gan* decoction was administered twice a day. Prescription of the *Ling-Gui-Zhu-Gan* decoction was continued for maximum one month, according to the condition of the patients.

After fasting, patients of both groups received dietary counseling and were asked to follow the suggested nutrition program. The recommended diet adapted the total energy intake to baseline BMI (kcal intake/kg body weight) and had a pre-specified proportion of carbohydrates, fats and proteins. According to these recommendations daily suggestions for menus and food items for a full day were given to patients. All patients were required to receive their decoction once a week in the out-patient clinic to ensure its proper administration. Detailed recommendations for preparation and intake were given repeatedly.

Patients in both groups received similar recommendations for physical activity and exercise. All patients were suggested to engage in moderate physical activity (walking) twice a day for 60 min.

Anti-diabetic drugs were not changed during the study, but physicians could adapt the dosage of the drugs according to patients' plasma glucose. No other drugs were added during the therapy. Within the following 3 months, all participants were required to re-visit the outpatient clinic once in two weeks in order to assess diabetic control and to supervise the implementation of recommended physical activities and diets as well as to adapt the oral dosage of anti-diabetic drugs. Reminders were given to all patients before the study visits by phone calls.

Outcomes

FG, 2hG, and HbA_{1C} were measured by standard methods. Plasma glucose was measured by the glucose oxidase technique and HbA_{1C} level was measured by Bio-Rad HPLC. Serum total cholesterol (TC) and triglycerides (TG) were measured by Olympus 2700 automatic biochemical standard analysis.

Documentation of oral dosage of anti-diabetic drugs and records of hypoglycemic events and symptoms of strong hunger, palpitations, cold sweats, tremor, pale face were based on interviews and semi-standardized inventories. FG levels of ≤3.9 mmol/L during monitoring were defined as hypoglycemic. All measurements were performed at baseline and at the 3-months study follow-up visit.

Statistical analysis

All normally distributed variables were expressed as mean ± standard deviation ($m \pm$ SD) and data were compared using a *t*-test. Group comparisons for discrete variables were performed using a chi-square-test. Differences were considered statistically significant at a $p < 0.05$ level. All data were analyzed with the Statistical Package for the Social Sciences (SPSS for Windows version 17.0). As this was an explorative pilot-study no adjustments for multiple testing were performed.

Results

All included participants presented with manifest T2DM and were on oral antidiabetic medication at baseline with most patients receiving Metformin 1000–2000 mg/day. Moreover, all patients showed a documented insufficient glycemic control with a mean HbA_{1C} value of ≥7.5 ± 1.15%. In addition, patients experienced adverse effects mostly in relation to oral anti-diabetic drug intake, including fluctuating levels of plasma glucose, hypoglycemia, abdominal distension and diarrhea.

There were no significant differences in demographic characteristics and laboratory tests between the two groups at baseline (see Table 1). All patients in the intervention group completed the trial. 4 patients of the control group stopped the trial prematurely because of repeated hypoglycemic events, most likely due to diet and exercise interventions. In the intervention group body weight decreased from 74.0 ± 15.5 kg to 71.5 ± 14.8 kg during in-hospital treatment and to 70.2 ± 12.8 kg at the 3-month follow-up. A similar decrease of weight was observed in the control group (baseline 74.3 ± 15.4 kg; hospital dismissal 73.3 ± 16.0 kg; 3-month follow-up 70.5 ± 13.9).

Glycemic control

Patients in the intervention group showed pronounced and clinically relevant decreases in the levels of FG, 2hG and HbA_{1C}. Patients in the control group only showed mild decreases of

Table 1
Baseline characteristics.

Groups	Age (y)	Disease course (y)	BMI (kg/m^2)	FG (mmol/L)	2hG (mmol/L)	HbA_{1C} (%)
Control (30 patients)	51.9 ± 13.7	3.9 ± 1.5	25.7 ± 3.41	6.5 ± 0.9	10.7 ± 3.9	7.47 ± 1.24
Intervention (30 patients)	52.3 ± 12.9	4.1 ± 1.9	25.6 ± 4.03	6.8 ± 1.2	10.9 ± 4.3	7.53 ± 1.19

Mean ± standard deviation. BMI, body mass index; FG, fasting plasma glucose; 2hG, mean 2-h plasma glucose after OGTT; HbA_{1C}, glycated hemoglobin A_{1C}.

glucose levels and HbA_{1C} resulting in significant group differences of FG ($p = 0.027$), 2hG ($p = 0.043$) and HbA_{1C} ($p = 0.024$). The course of the relevant diabetic control markers is depicted in Table 2.

Similarly, the intervention group showed significant greater reductions of TC and TG levels as compared to controls ($p = 0.041$ and 0.008, respectively).

Hypoglycemic events

During medical history taking before the beginning of the trial, 9 patients in the control group and 11 patients in the intervention group complained that hypoglycemia easily occurred if they would not eat food timely or after physical exercise. 4 patients in the control group dropped out because of repeated hypoglycemic events in the course of the study. Throughout the study, patients in the intervention group tended to be more capable of controlling appetite and no hypoglycemia event occurred. They also showed fewer symptoms of acute hunger, palpitations or tremors. Thus, hypoglycemic events decreased significantly in the intervention group compared to the control group ($p < 0.05$) (see Table 3).

Anti-diabetic medication

At three months, in control group one patient had stopped the oral antidiabetics and seven patients had decreased their oral dosage of antidiabetics. All other patients maintained their previous dosage. In the intervention group 9 patients stopped their intake of oral antidiabetics and 19 patients reduced the daily oral dosage of antidiabetics, the remaining 2 patients maintained their previous dosage ($p < 0.01$) (Table 4).

Discussion

In China, the prevalence of both diabetes mellitus and metabolic syndrome is increasing rapidly and large scale. However, because of the large variety of ethnic groups and related differences in dietary and lifestyle habits in China in comparison to Western countries, heavy obesity is rare and dietary treatments developed for Western populations might have to be modified. Modified fasting and very-low-calorie diets are established as intensified dietary approaches to initiate weight loss processes and to improve weight control. Preliminary data also suggest that periods of fasting might be useful in improving insulin sensitivity and diabetic control [1,3,10].

We previously observed that Chinese patients with metabolic syndrome and T2DM undergoing standard fasting or VLCD did frequently not tolerate the dietary approach for extended periods and presented signs like thicker tongue coating, subjective discomfort and chilliness, which indicates the TCM-pattern of mucus disturbing and Yang deficiency.

Hence, we adapted the European modified fasting therapy [11], combining a subtotal or modified fasting/VLCD (intake of 150 mg millet soup daily) with the prescription of a Traditional Chinese Medicine herbal decoction, the modified *Ling-Gui-Zhu-Gan* decoction. The decoction consists of subs-

Table 2
Levels of fasting glucose, post prandial glucose, HBA_{1C}, total cholesterol and triglyceride before intervention and after three months in both groups.

Groups	Baseline					3-Months follow-up				
	FG (mmol/L)	2hG (mmol/L)	HbA_{1C} (%)	TC (mmol/L)	TG (mmol/L)	FG (mmol/L)	2hG (mmol/L)	HbA_{1C} (%)	TC (mmol/L)	TG (mmol/L)
Control (26 patients)	6.6 ± 0.8	11.2 ± 4.0	7.51 ± 1.27	6.67 ± 0.99	5.01 ± 1.95	6.3 ± 1.0	10.1 ± 4.5	7.21 ± 1.33	6.18 ± 1.3	3.1 ± 1.85
Intervention (30 patients)	6.8 ± 1.2	10.9 ± 4.3	7.53 ± 1.19	6.98 ± 1.05	5.83 ± 2.06	5.5 ± 0.9*	8.1 ± 2.7**	6.23 ± 0.9***	5.12 ± 0.96#	1.74 ± 1.03##

FG, fasting plasma glucose; 2hG, 2-h plasma glucose after OGTT; HbA_{1C}, glycated hemoglobin A_{1C}; TC, total cholesterol; TG, triglyceride. Between-group differences after 3-months.
* *p*-Value = 0.027.
** *p*-Value = 0.043.
*** *p*-Value = 0.024.
Comparison to the baseline after the treatment.
\# *p*-Value = 0.041.
\## *p*-Value = 0.008.

Table 3
Frequency of hypoglycemic events during study phase in both groups.

	Control group	Intervention group
Patients with hypoglycemic events (*n*)	13	5
Absolute number of hypoglycemic events	33	5

Table 4
Course of antidiabetic medication within the 3-months study period.

Groups	Decreased dosage	Discontinued	Maintained dosage	Total
Control	7	1	18	26
Intervention	19	9	2	30

tances to warm and resolve mucus (*wen-hua-tan-yin*) and of Radix Codonopsis Pilosulae (*dang shen*) and Radix et Rhizoma Rhei (*da huang*) to strengthen the spleen and to remove turbidity (*jian-pi-xie-zhuo*). Moreover, Radix et Rhizoma Rhei (*da huang*) was administered to enhance bowl movements. According to the principles of TCM this decoction enhances spleen functions related to metabolic transportation and transformation. We evaluated the clinical effects of this combined integrative treatment approach for the first time by means of a randomized controlled pilot study.

The results of our study demonstrate a clear and clinically relevant effect of the combined integrative treatment approach on improving glycemic control, need of anti-diabetic medication and reduction of hypoglycemic events. Thus, T2DM patients with insufficient glycemic control may benefit from a combination therapy of a modified *Ling-Gui-Zhu-Gan* decoction and short-term modified fasting/VLCD.

Data from Chinese experimental studies suggest that single herbal extracts in the *Ling-Gui-Zhu-Gan* decoction are not capable of decreasing blood glucose, however, the combination within a multi-component and multi-target decoction might exert synergy suggesting that the effects of the present treatment resulted from an integrative modulation rather than from the effects of single herbs.

Since Mc Garry [12,13] named type 2 diabetes as a 'glycolipid disease' in 2001, the treatment of type 2 diabetes has shifted from a mere control of glucose levels to a control of glucose and lipids at the same time. Concomitantly, with improved glycemic control we found beneficial reductions in blood lipids in the patients of the intervention group. According to the knowledge of modern Chinese medicine [14,15], the pathogenesis of T2DM and hyperlipidemia is related to dysfunction of transportation and transformation of the spleen, resulting in insufficient metabolism of nutrients which then are thought to lead to an accumulation of mucus, fat and to dampness and turbidity. Hence, a combination of the modified *Ling-Gui-Zhu-Gan* decoction with fasting/VLCD may foster the renewing of the so called 'spleen function of transformation and transportation [16]. That is why this therapy could have curative effects in the treatment group, even if we would not have applied different Chinese drugs to patients in the treatment group according to different causes stages of the diseases.

According to TCM, millet can strengthen the spleen and harmonize the stomach, and may be specifically suitable for people with deficient spleen and stomach constitutions. Modified *Ling-Gui-Zhu-Gan* decoction in combination with millet can effectively promote the recovery of spleen functions on transportation and transformation.

Of note, pharmacokinetics focus on drug mechanisms of absorption and distribution, pharmacokinetics and metabolism. Compared with the concept of spleen ruling transportation and transformation, pharmacokinetics has an analogous meaning. TCM emphasizes the notion of homology of Chinese Medicine and food; the function of the spleen is identical to the processes of pharmacokinetics, so in TCM it is believed that the spleen governs processes of pharmacokinetics in human bodies. If the spleen shows dysfunction, this will have detrimental effects on metabolism and pharmacokinetics will also show pathological characteristics [17]. Thus it might be the case that the TCM treatment also restores patients' therapeutic responses to drugs and increase insulin sensitivity by recovering spleen function [16].

The mean BMI of the included patients in this study was only slightly over 25 kg/m^2. However, all patients adhered to and well-tolerated the modified fasting treatment. Therefore, we regard the combined treatment approach as suitable for non-obese T2DM patients.

There are several limitations that apply to our study. Firstly, we cannot differentiate which of the large anti-diabetic effects would have been realized by each single treatment module. The First Affiliated Hospital of Sun Yat-Sen University is the first formal medical institution which is carrying out treatments for type 2 diabetes using fasting therapy in mainland China. Therefore, there are no research results from other medical institutions for the evaluation of the advantages of a modified *Ling-Gui-Zhu-Gan* decoction combined with short-term fasting/VLCD in the treatment of type 2 diabetes. Thus, further studies should compare this combined treatment approach. Secondly, we do not know up to what extend the results of this trial can be transferred to Western populations. Finally, as we did not adjust for multiple testing in this pilot trial an overestimation of the statistical difference is likely.

Conclusions

In summary, the results of the present study suggest that a combined treatment approach with a short-term modified fasting and Chinese herbal Medicine may be a highly effective and safe treatment approach to improve glycemic control in patients with T2DM.

The long-term effects and mechanisms need to be evaluated in further studies. Given the urgent need of extended treatment possibilities in T2 DM further studies evaluating the combined fasting/TCM approach are warranted.

Conflict of interest

None.

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Poster:

Li C, Li S, Michalsen A, Qin J. Effects of caloric restriction combined with traditional Chinese phytomedicine on the glucolipid metabolism in Wistar Rats with insulin resistance. Poster at *International Research Congress on Integrative Medicine and Health* 2012 Portland, USA

Manuscripts in progress

„Fasting induces global changes in gene expression in patients with metabolic syndrome" (in revision, Sep 2017, PLoS One)

„The influence of a lifestyle modification program on hairsteroids of patients with cardio-metabolic risk" (in cooperation with AG Biopsychologie TU Dresden; Prof. Kirschbaum, T. Stalder)

„The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with gynecological cancer: a randomized cross-over pilot study"

„Intensified dietary and lifestyle modification in patients with hypertension and cardiometabolic risk constellation - a two-center randomized-controlled intervention study over 6 months"

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