

Metabolic and Psychological Response to 7-Day Fasting in Obese Patients with and without Metabolic Syndrome

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Keywords

Adipokines · Caloric restriction · Fasting · Metabolic syndrome · Mood

Summary

Background: Extended modified fasting is a frequently practiced tradition in Europe. It is claimed to improve the cardiometabolic state and physical and psychological well-being by an evolutionary co-developed adaptation response. We aimed to investigate the cardiometabolic and psychological effects of a 7-day fast and differences of these responses between patients with or without metabolic syndrome (MetS). **Methods:** We investigated 30 female subjects (49.0 ± 8.1 years, BMI 30.4 ± 6.7 kg/m²) with ($n = 12$) and without ($n = 18$) MetS. All subjects participated in a 7-day fast according to Buchinger with a nutritional energy intake of 300 kcal/day and stepwise reintroduction of solid food thereafter. Outcomes were assessed baseline and after fasting and included measures of metabolic and glucoregulatory control, adipokines as well as psychological well-being as assessed by Profile of Mood States (POMS) and Hospital Anxiety and Depression Scale (HADS). **Results:** Mean weight decreased from 85.4 ± 18.8 kg to 79.7 ± 18.2 kg accompanied by systolic/diastolic blood pressure (BP) reduction of -16.2 mm Hg (95% CI: $-9.1; -23.3$ mm Hg) and -6.0 mm Hg (95% CI: $-1.8; -10.3$ mm Hg), each $p < 0.001$ and $p = 0.005$. Fasting led to marked decreases of levels of LDL-cholesterol, leptin, and insulin and increases of levels of adiponectin, leptin receptors, and resistin. Fasting-induced mood enhancement was reflected by decreased anxiety, depression, fatigue, and improved vigor. Patients with MetS showed some greater changes in BP, LDL-cholesterol, triglycerides, adiponectin, leptin, and sleep quality. Fasting was well-tolerated. **Conclusions:** Our results point to marked beneficial responses to 7-day modified fasting and a potential role in the prevention of the MetS. Randomized trials with longer observation periods should test the clinical effectiveness of fasting in metabolic diseases.

Schlüsselwörter

Adipokine · Kalorienrestriktion · Fasten · Metabolisches Syndrom · Gemütszustand

Zusammenfassung

Hintergrund: Heilfasten in Form des modifizierten Fastens wird in Europa häufig praktiziert und verbessert aufgrund einer evolutiven umweltbedingten Anpassung insbesondere den kardiometabolischen Zustand sowie das physische und psychische Wohlbefinden. In dieser Studie wurde das Ziel verfolgt, die kardiometabolischen und psychischen Effekte 7-tägigen Fastens sowie die genannten Anpassungsunterschiede zwischen Patienten mit und ohne metabolisches Syndrom (MetS) zu untersuchen. **Methoden:** Untersucht wurden 30 Frauen ($49,0 \pm 8,1$ Jahre, BMI $30,4 \pm 6,7$ kg/m²) mit ($n = 12$) und ohne ($n = 18$) MetS. Alle Teilnehmerinnen unterzogen sich einem 7-tägigen Fastenprogramm nach Buchinger, das aus einer Energiezufuhr von 300 kcal/Tag und einem nachfolgenden schrittweisen Nahrungsaufbau bestand. Die Endpunkterhebungen erfolgten zu Beginn und nach dem Fasten und beinhalteten laborchemische Messungen des kardiometabolischen Profils, endokriner Parameter und Adipokine sowie des psychischen Wohlbefindens, erfasst mittels des «Profile of Mood States» (POMS) und der «Hospital Anxiety and Depression Scale» (HADS). **Ergebnisse:** Das durchschnittliche Gewicht sank von $85,4 \pm 18,8$ kg auf $79,7 \pm 18,2$ kg, begleitet von einer systolischen/diastolischen Blutdrucksenkung von $-16,2$ mm Hg (95% CI: $-9,1; -23,3$ mm Hg) und $-6,0$ mm Hg (95% CI: $-1,8; -10,3$ mm Hg), jeweils $p < 0,001$ und $p = 0,005$. Das Fasten führte zu einer deutlichen Senkung des LDL-Cholesterin-, Leptin- und Insulinspiegels und zu einem Anstieg des Adiponectin-, Leptinrezeptor- und Resistin-Spiegels. Das Fasten führte zu einer Verbesserung des psychischen Befindens, reflektiert durch reduzierte Scores von Angst, Depressivität und Fatigue sowie erhöhte Vitalität. Patienten mit MetS zeigten einige ausgeprägtere fasteninduzierte Veränderungen, insbesondere des Blutdrucks, des LDL-Cholesterins, der Triglyceride, des Adiponectins, des Leptins und der Schlafqualität. Das Fasten war gut verträglich. **Schlussfolgerungen:** Die Ergebnisse dieser Erhebung deuten auf relevante gesundheitsfördernde Effekte eines 7-tägigen modifizierten Fastens hin sowie auf die potenzielle Bedeutung des Fastens bei der Prävention des MetS. Randomisierte Studien mit längeren Beobachtungsperioden sind sinnvoll, um die klinische Effektivität von Fasten auf metabolische Krankheiten zu evaluieren.

Background

The metabolic syndrome (MetS) is characterized by insulin resistance, glucose intolerance, dyslipidemia, hypertension, and obesity [1]. It affects one-quarter of the American population [2] and is becoming increasingly prevalent in Europe [3]. In Germany the prevalence of MetS is estimated to amount to 40.4% [4]. Excess weight and weight gain during adult life increases the risk of several diseases including diabetes, cardiovascular disease, stroke, and dementia and can contribute to premature death. Although weight control is beneficial in reducing the incidence and progression of many of these diseases, the problem of poor compliance with weight loss programs is well known. Sustainable and effective energy restriction strategies are thus required. One possible approach might be intermittent fasting with severe calorie restriction (75–90% of energy needs) on 1 or 2 days per week [5]. Another traditional method is extended modified fasting [6]. In the recent past modified fasting attracted a growing popularity in German public as a self-care method for health and particularly to initiate lifestyle modification [7, 8]. Modified fasting may interrupt receptor resistances and modulate favorably the neuroendocrine regulation of metabolism, as has been shown for insulin and natriuretic peptides [9]. Furthermore, fasting may enhance adherence with health promoting lifestyle modification [7].

In a cultural context, periods of deliberate fasting with restriction to intake of solid food have been practiced worldwide, mostly on a traditional or religious background. Within the medical application different types of fasting can be differentiated. Clinically, fasting over 5–28 days with a daily intake of 200–500 kcal by fruits or juice is well established and defines the today mostly used form of modified medical fasting, fasting according to Buchinger. This fasting method is well described and methodological guidelines have been published previously [10]. The clinical effects of therapeutic fasting [10] have been investigated and confirmed by controlled trials in some of the traditionally claimed indications, e.g., rheumatoid arthritis [11, 12]. Some studies have further documented a relevant blood pressure (BP) reducing effect of total fasting [13, 14], and observational data pointed to lasting beneficial effects after 1–2 weeks of modified fasting in obese patients with MetS [15].

The human body exhibits a multitude of adaptive biochemical and physiological responses to extended periods of fasting which likely enabled mankind to survive in periods of food deprivation. Fasting leads to initial stimulation of the hypothalamic pituitary adrenal (HPA) axis as a characteristic physiologic equivalent of a stress reaction [16–18]. Leptin decrease following the initiation of fasting has been identified as strong signal and may play a crucial role in the neuroendocrine signalling in response to fasting [19]. So far, there are no data available comparing directly within one study and one protocol the cardiometabolic and psychological effects of modified fasting in patients with and without MetS. Furthermore, most

of the existing studies on fasting had observed patients during a hospital stay or a retreat situation, thus other factors than fasting may have contributed to the effects. Therefore, we aimed to investigate the metabolic and hormonal effects of a 7-day Buchinger fasting within a 2-week nutritional intervention in an outpatient setting while subjects maintained their daily life activities. With a fasting length of 7 days we chose a relative short period of Buchinger fasting. More recently, fasting periods of 5–7 days were more commonly applied.

This reflects the current need for concise interventions with consideration of health economic aspects, while maintaining a minimum time period to induce adaptation responses. We enrolled subjects with MetS and healthy subjects without MetS in order to analyze effects according to the metabolic state. Empirical observation indicates that specifically patients with MetS may frequently experience fasting-induced mood enhancement. Moreover, the previously observed beneficial effects of fasting on receptor resistances suggest that fasting may be specifically useful in MetS.

Methods

Subjects and Study Design

The study was planned and conducted as an uncontrolled prospective interventional study. The study period comprised 14 days. Assessments were done at a pre-study screening visit, in the morning of study day 4 (first morning of fasting), and on study day 8 (last day of fasting).

Subjects with MetS and healthy subjects without MetS were searched by means of advertisements placed in local newspapers. A total of 51 individuals responded and 30 were deemed eligible to participate after the screening assessment. As previous studies of our group found predominantly women to be interested in fasting cures, the study was pre-planned with female participants only to ensure the homogeneity of the population. The study was approved by the Ethics Committee of the Medical Faculty of the University Hospital Essen. All participants gave written informed consent to participate in the study. Key inclusion criteria were as follows: age 35–65 years, body mass index (BMI) 20–45 kg/m², and willingness to participate in fasting and the study examinations. Exclusion criteria were history of cancer, history of cardiovascular disease or other severe internal disease, history of eating disorder, psychosis, current addiction or pregnancy, current regular intake of medication, weight loss during the previous 3 months of > 3 kg, and inadequate cognitive abilities of cooperation. All enrollment criteria were reviewed in a screening telephone call and confirmed at the first study visit.

For data analyses the 30 patients were further divided into 2 groups, depending on the presence of a MetS. For diagnosis of MetS, patients were required to have 3 or more of the following criteria: 1) abdominal adiposity (≥ 88 cm); 2) low HDL-cholesterol(C) levels (≤ 50 mg/dl); 3) hypertriglyceridemia (≥ 150 mg/dl); 4) elevated BP ($\geq 130/85$ mm Hg); 5) impaired glucose homeostasis (fasting plasma glucose ≥ 110 mg/dl). Of the 30 participants 12 fulfilled the criteria for diagnosis of manifest MetS, the remaining 18 patients had no MetS and were free of severe disease as assessed by clinical examination by the study physician.

Fasting and Diet Protocol

The 2-week study and dietary intervention period consisted of 2 pre-fast days with moderate caloric restriction followed by 7 modified fasting days according to Buchinger [10] followed by gradual reintroduction of ordinary food intake over 3 days.

Table 1. Baseline values and changes in physiological and psychological variables before and after fasting for all patients (N = 30)

	Baseline	Fasting day 8	Change (95% CI)	p-value*
Weight, kg	85.4 ± 18.8	79.7 ± 18.2	-5.7 (-5.1, -6.2)	<0.001
BMI, kg/m ²	30.4 ± 6.7	28.3 ± 6.3	-2.1 (-1.6, -2.6)	<0.001
SBP, mm Hg	130.7 ± 25.0	114.5 ± 16.1	-16.2 (-9.1, -23.3)	<0.001
DBP, mm Hg	83.3 ± 13.3	77.3 ± 9.4	-6.0 (-1.8, -10.3)	0.005
Total C, mg/dl	208.4 ± 38.4	168.9 ± 27.7	-39.6 (-30.0, -49.1)	<0.001
HDL	61.0 ± 17.2	57.1 ± 14.1	-3.9 (-0.7, -7.1)	0.017
LDL	127.4 ± 34.7	96.7 ± 21.6	-30.7 (-22.1, -39.3)	<0.001
LDL/HDL ratio	2.3 ± 1.1	1.8 ± 0.6	-0.5 (-0.3, -0.7)	<0.001
Triglycerides, mg/dl	117.8 ± 45.0	106.8 ± 44.3	-11.1 (-23.3, 1.1)	0.075
Cortisol, ng/ml				
Morning	4.1 ± 4.5	7.2 ± 4.5	3.1 (0.6, 5.6)	0.015
Evening	5.4 ± 3.5	6.5 ± 3.3	1.1 (0.6, 2.8)	0.208
Adiponectin, µg/ml	12.4 ± 6.0	14.9 ± 5.1	2.5 (1.3, 3.8)	<0.001
Leptin, ng/ml	26.9 ± 20.3	9.7 ± 15.5	-17.1 (-11.7, -22.5)	<0.001
Receptors	21.1 ± 8.2	76.5 ± 28.2	55.3 (44.7, 67.5)	<0.001
Resistin, ng/ml	4.6 ± 1.6	6.9 ± 2.4	2.3 (1.7, 2.9)	<0.001
Insulin, µU/ml	14.0 ± 19.0	3.2 ± 4.0	-10.8 (-4.7, -16.8)	0.001
Hs-CRP, mg/dl	0.2 ± 0.2	0.5 ± 0.3	0.3 (0.1, 0.4)	<0.001
Sleep score				
Fatigue	4.8 ± 2.2	2.9 ± 2.1	-1.9 (-1.2, -3.5)	<0.001
Quality	4.5 ± 2.0	6.2 ± 2.8	1.7 (0.2, 3.3)	0.03
POMS				
Depression	1.1 ± 1.2	0.4 ± 0.7	-0.7 (-0.3, -1.2)	0.001
Fatigue	2.1 ± 1.5	1.0 ± 1.2	-1.1 (-0.5, -1.7)	0.001
Vigor	3.0 ± 1.1	3.4 ± 1.2	0.4 (-0.2, 1.0)	0.168
Anger/hostility	1.1 ± 1.0	0.2 ± 0.5	-0.9 (-0.5, -1.2)	<0.001
HADS				
Anxiety	7.2 ± 4.2	4.9 ± 3.2	-2.3 (-1.1, -3.6)	<0.001
Depression	5.3 ± 4.4	3.3 ± 3.0	-2.0 (-3.4, 0.5)	0.10

BMI = Body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; C = cholesterol; hs = high sensitivity; POMS = Profile of Mood States; HADS = Hospital Anxiety and Depression Scale; CI = confidence interval.
* Wilcoxon test *P*-values for within-group difference of change.

During the initial 2 pre-fast days subjects received a 3,350 kJ (800 kcal) / day, low-calorie, 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 afternoon at study day 11. During the fasting period subjects received unrestricted amounts of herbal tea (no black or green tea), 200 cl fruit juice, and small standardized quantities of light vegetable soup with a maximum total daily energy intake of 1,255 kJ (300 kcal). Fasting started with oral ingestion of a laxative salt (30–40 g sodium sulfate). While preparing to fast, it is common practice to achieve emptiness of the bowels by the most effective way. Bowel motility thus can be reduced once fasting has started, avoiding retarded and therefore unfavorable digestion of bowel contents present at the beginning. Patients were strongly advised to drink 2–3 l of fluids daily. The fasting period was followed by 3 low-calorie diet days with stepwise reintroduction of solid food. A mild calorie-restricted diet with intake of 1,800 kcal/day was reached again thereafter. Participants were strictly advised not to consume caffeine containing or alcoholic beverages.

Each day during the study period the participants had a group meeting within the hospital where the diet lunch and some fasting beverages were taken together.

Throughout the study, the subjects continued their usual daily and professional activities. No other therapies were delivered. Weekends were on study days 2/3 and 9/10. Compliance with the fasting procedure was controlled daily by measurements of urine pH and at the end of fasting period by a personal interview.

Measurements

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 (m)². Subjects' waist was measured with a soft tape midway between the lowest rib and the iliac crest. Anthropometrical and clinical data were collected by trained study personnel. Seated BP and pulse rate were measured after 5 min rest with a calibrated sphygmomanometer at the non-dominant arm by trained nurses.

Laboratory

Blood samples were drawn in the morning of study day 4 and study day 11. Assays for blood lipids and glucose were performed with standard methods. Serum concentrations of insulin and high-sensitivity(hs)-CRP were measured by immunonephelometric methods (BN-II-nephelometer, Siemens, Fernwald, Germany). Plasma adiponectin, leptin, and resistin concentrations were quantified using a high sensitivity enzyme-linked immunosorbent assay (ELISA). Salivary cortisol was measured by radioimmunoassay. Leptin receptor concentration (LepR-e) was measured with standardized and established methods of the laboratory. All analyses were performed at the Central Laboratory of the University Hospital Essen. Adverse events were monitored by diary and at the last study visit by interview.

Table 2. Metabolic parameters and risk factors, quality of sleep and psychological well-being: Change before and after fasting in patients with and without MetS. Mean values \pm SD, mean change (95% CI) before and after fasting with respective P-values

Variable	MetS				No MetS			
	baseline	day 8	change (95% CI)	p-value*	baseline	day 8	change (95% CI)	p-value*
Weight, kg	100.1 \pm 17.0	94.7 \pm 17.1	-5.6 (-4.8, -6.5)	<0.001	77.0 \pm 13.1	71.7 \pm 11.7	-5.3 (-4.8, -5.9)	<0.001
BMI, kg/m ²	35.5 \pm 6.4	33.3 \pm 6.1	-2.2 (-1.4, -3.0)	<0.001	27.0 \pm 4.4	25.0 \pm 4.0	-2.0 (-1.4, -2.7)	<0.001
SBP, mm Hg	146.3 \pm 29.8	126.4 \pm 16.4	-20.0 (-5.3, -34.6)	0.008	120.3 \pm 14.4	106.6 \pm 10.2	-13.7 (-6.8, -20.5)	<0.001
DBP, mm Hg	87.9 \pm 17.4	81.2 \pm 11.3	-6.7 (-16.0, 2.5)	0.151	80.3 \pm 9.0	74.7 \pm 7.0	-5.6 (-9.4, 1.8)	0.004
Total C, mg/dl	216.0 \pm 48.5	168.6 \pm 36.9	-47.4 (-30.7, -64.2)	<0.001	203.4 \pm 30.5	169.0 \pm 20.7	-34.4 (-23.3, -45.4)	<0.001
HDL	48.3 \pm 13.8	49.0 \pm 13.7	0.7 (-5.2, 3.8)	0.760	69.4 \pm 13.9	62.4 \pm 11.9	-7.0 (-3.1, -10.9)	<0.001
LDL	142.3 \pm 43.7	100.1 \pm 27.6	-42.1 (-26.2, -58.0)	<0.001	117.6 \pm 23.7	94.4 \pm 17.0	-23.2 (-14.9, -31.4)	<0.001
LDL/HDL ratio	3.1 \pm 1.3	2.1 \pm 0.7	-1.0 (-0.6, -1.4)	<0.001	1.8 \pm 0.5	1.6 \pm 0.4	-0.2 (-0.3, 0.0)	0.017
Triglycerides, mg/dl	155.3 \pm 43.7	136.1 \pm 51.1	-19.2 (-5.2, -43.6)	0.123	92.9 \pm 23.8	87.2 \pm 25.4	-5.7 (-17.9, 6.6)	0.364
Cortisol, ng/ml								
Morning	3.4 \pm 2.7	7.4 \pm 5.3	4.0 (0.2, 7.9)	0.038	4.6 \pm 5.5	7.0 \pm 4.1	2.4 (-5.7, 0.9)	0.150
Evening	5.9 \pm 3.1	6.9 \pm 3.2	1.0 (-3.5, 1.5)	0.433	5.1 \pm 3.7	6.3 \pm 3.3	1.2 (-3.6, 1.2)	0.331
Resistin, ng/ml	4.8 \pm 1.8	6.9 \pm 2.0	2.1 (1.4, 2.8)	<0.001	4.4 \pm 1.4	6.8 \pm 2.7	2.4 (1.6, 3.2)	0.038
Hs-CRP, mg/dl	0.3 \pm 0.3	0.5 \pm 0.3	0.2 (-0.4, 0.0)	0.114	0.2 \pm 0.2	0.5 \pm 0.3	0.3 (0.1, 0.5)	0.220
Sleep score								
Fatigue	5.1 \pm 2.3	2.9 \pm 2.8	-2.3 (-0.1, -4.2)	0.038	4.6 \pm 2.1	2.9 \pm 1.6	-1.7 (-0.5, -2.9)	0.004
Quality	3.6 \pm 1.6	5.8 \pm 3.5	2.2 (-4.5, 0.0)	0.052	5.1 \pm 1.9	6.5 \pm 2.2	1.4 (-2.7, 0.1)	0.065
POMS								
Depression	1.2 \pm 1.4	0.5 \pm 0.9	-0.7 (-0.2, 1.6)	0.122	1.1 \pm 1.1	0.3 \pm 0.6	-0.8 (-0.4, -1.2)	<0.001
Fatigue	2.1 \pm 1.7	1.1 \pm 1.4	-1.0 (-0.3, 2.2)	0.127	2.2 \pm 1.4	1.0 \pm 1.1	-1.2 (-0.5, -1.8)	<0.001
Vigor	3.1 \pm 1.3	3.2 \pm 1.5	0.1 (-1.2, 1.0)	0.873	3.0 \pm 1.1	3.6 \pm 1.1	0.6 (-1.2, 0.0)	0.040
Anger/hostility	1.1 \pm 1.1	0.3 \pm 0.6	-0.8 (0.1, 1.4)	0.024	1.1 \pm 0.9	0.1 \pm 0.3	-1.0 (-0.6, -1.3)	<0.001
HADS								
Anxiety	7.5 \pm 4.0	5.1 \pm 3.6	-2.4 (-0.3, -4.6)	0.027	7.1 \pm 4.4	4.8 \pm 3.0	-2.3 (-0.8, -3.8)	0.003
Depression	5.1 \pm 5.0	3.6 \pm 3.6	-1.5 (-1.8, 4.7)	0.373	5.4 \pm 4.1	3.1 \pm 2.6	-2.3 (-1.0, -3.6)	0.001

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; C = cholesterol; hs = high sensitivity;

POMS = Profile of Mood States; HADS = Hospital Anxiety and Depression Scale.

* Wilcoxon test P-values for within-group difference of change, unadjusted; CI = confidence interval.

Psychological Outcomes

Psychological outcomes were assessed by 2 validated self-report measures: 1) The German version of the Profile of Mood States (POMS) [20], which is a 34-item instrument that measures 4 domains of mood disturbance including vigor, fatigue, depression, anxiety, and anger; 2) The German version of the Hospital Anxiety and Depression Scale (HADS) [21], a validated standard measure for anxiety and depression which uses a 14-item scale with 7 of the items related to anxiety and 7 related to depression. Quality of sleep was assessed by 100 mm visual analogue scales (VAS) for self-rated global quality of sleep and day time sleepiness.

Statistical Analyses

If not indicated otherwise, results were expressed as means \pm standard deviation (SD). Changes of values before and after fasting were calculated by analysis of covariance models (ANCOVA). Missing values were replaced by multiple imputations. A p-value < 0.05 was considered as statistically significant. As this was an exploratory study we did not perform adjustments for multiple testing. All statistical computations were performed with the statistical software SAS version 8.2.

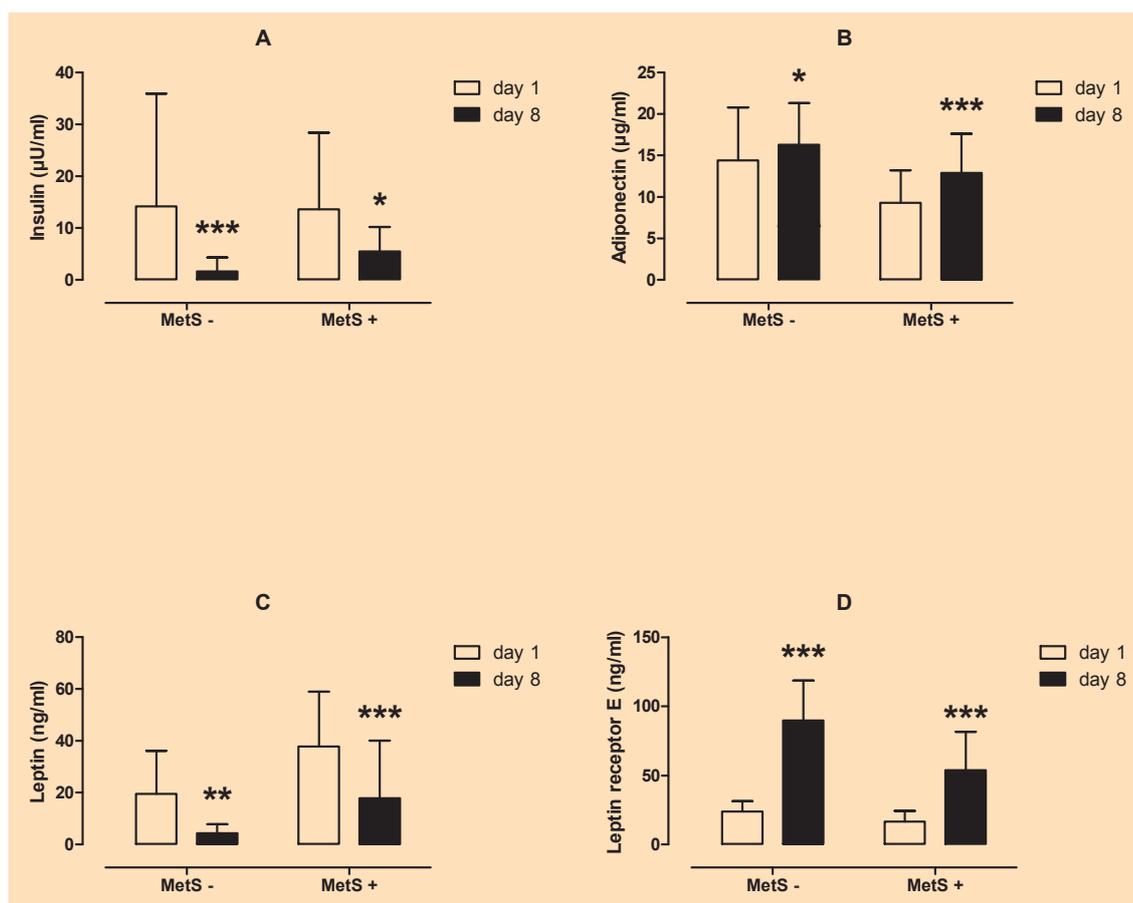
Results

A total of 30 subjects were enrolled in the study, with 28 completing the entire fasting period. 1 participant dropped out because of headache attributed to coffee withdrawal. 1 further participant stopped fasting due to gastric pain after the 3rd day. Of the 30 participants 12 fulfilled the criteria for diagnosis of MetS. Subjects' age ranged from 40 to 73 years with a mean age of 49.0 \pm 8.1 years and patients with MetS being slightly older (53.6 \pm 6.7 vs. 45.9 \pm 7.4 years). Baseline characteristics of all subjects and the 2 groups according to metabolic state are given in table 1. Subjects with MetS demonstrated typical clinical differences compared to subjects without MetS, however, subjects without MetS had higher blood insulin and salivary cortisol levels, yet differences were not statistically significant.

Fasting-Induced Changes in the Whole Study Population

During fasting mean weight of all patients decreased from 85.4 \pm 18.8 to 79.7 \pm 18.2 kg. Fasting was accompanied by a pronounced decrease in systolic, respectively diastolic BP of

Fig. 1. Blood concentrations of insulin, adiponectin, leptin, and leptin receptors before and after fasting in subgroups with or without MetS (mean and SD). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Mean changes were for MetS patients: adiponectin: 3.5 $\mu\text{g/ml}$ (95% CI: 2.1; 4.9 $\mu\text{g/ml}$); insulin: -8.1 $\mu\text{U/ml}$ (95% CI: -1.4; -14.6 $\mu\text{U/ml}$); leptin: -19.9 ng/ml (95% CI: -10.1; -29.7 ng/ml); leptin receptors: 44.7 ng/ml (95% CI: 32.1; 57.1 ng/ml). For patients without MetS as: adiponectin: 1.9 $\mu\text{g/ml}$ (95% CI: 3.8; 0.0 $\mu\text{g/ml}$); insulin: -15.3 $\mu\text{U/ml}$ (95% CI: -8.9; -21.6 $\mu\text{U/ml}$); leptin: -15.3 ng/ml (95% CI: -8.9; -21.6 ng/ml); leptin receptors: $\mu\text{58.6 ng/ml}$ (48.2; -71.0).



-16.2 mm Hg (95% CI: -9.1; -23.3 mm Hg) and -6.0 mm Hg (95% CI: -1.8; -10.3 mm Hg). Blood lipids showed significant decreases in LDL-C, HDL-C, and LDL/HDL ratio. We observed a significant increase of morning salivary cortisol through fasting period, while hs-CRP slightly but significantly increased. Fasting led to a marked drop of insulin and leptin levels with a concomitant pronounced increase in leptin receptors, adiponectin, and resistin (table 1).

The psychological assessments by the POMS documented a fasting-induced mood enhancement which was most pronounced and statistically significant for depression, fatigue, and anger/hostility. Both anxiety and depression as assessed by HADS revealed significant fasting-induced improvements. Concomitantly, quality of sleep increased and day time fatigue related to sleep decreased (table 1).

Fasting-Induced Changes in Subjects with or without MetS

The presence of MetS had some distinct influence on the fasting-induced changes of metabolic and endocrine outcomes (table 2, fig. 1). Mean systolic BP decreased by -20.0 mm Hg (95% CI: -5.3; -34.6 mm Hg) in patients with MetS group compared to -13.7 mm Hg (95% CI: -6.8; -20.5 mm Hg) in patients without MetS. Mean diastolic BP decreased by -6.7 mm Hg (95% CI: -16.0; 2.5 mm Hg) in patients with MetS compared to -5.6 mm Hg (95% CI: -9.4, 1.8 mm Hg) in patients without

MetS. LDL-C decrease was slightly pronounced in subjects with MetS who also showed no decrease of HDL-C decrease. Patients with MetS had lower levels of adiponectin and higher levels of leptin at baseline with more pronounced fasting-induced changes. At the end of fasting patients with MetS had reached baseline levels of the MetS without patients. Of note, leptin receptor concentrations increased markedly in both groups. Fasting-induced mood enhancement was observed in both subjects with or without MetS, however with a tendency to greater mood enhancement in subjects without MetS.

Discussion

This prospective study investigated for the first time the cardiometabolic, endocrine, and psychological effects of a 7-day modified fasting in a sample of middle-aged female outpatients with a 40% proportion of MetS. Fasting caused an average of 5.5% weight loss and led to pronounced beneficial effects on glucoregulatory control and the cardiometabolic and endocrine profile, e.g., the leptin-to-adiponectin ratio, which has been linked to insulin sensitivity [22]. Fasting was not associated with relevant hunger or adverse effects and had a significant mood enhancing as well as an antidepressant and anxiety relieving effect. Patients with MetS showed some

greater changes in BP, LDL-C, triglycerides, adiponectin, leptin, sleep fatigue score, and sleep quality. Our findings indicate that the response of the human body to a 7-day period of fasting can be regarded as a pronounced beneficial and health promoting adaptation process. This adaptation response is not restricted to metabolically diseased subjects.

In a recent trial, caloric restriction with an energy intake of 400 kcal/day quickly improved glucose control [23]. 1 observational and 1 experimental study from established clinical fasting centers in Germany also reported beneficial effects on metabolic and cardiovascular risk factors by fasting according to Buchinger [24, 25]. Some studies have further documented a relevant BP reducing effect of total fasting (water fasting) [13, 14]. Epidemiological studies further showed that routine periodic fasting with shorter fasting periods of 1–2 days, as practiced by specific religious groups, is associated with a lower risk of coronary artery disease in patients undergoing coronary angiography [26].

Studies on type 2 diabetes patients on a very-low-calorie diet (VLCD) found that after 12 weeks leptin levels decreased while adiponectin levels increased significantly. Similarly, VLCD in obese females induced weight reduction, which was associated with BP decrease and some improvement of metabolic parameters and leptin depletion by 30% [27, 28], however not to the same extent as in our study. Compared to the results of previous research 2 findings of our study seem important. First, we found marked and clinically relevant changes of important cardiometabolic and hormonal parameters. Second, these pronounced changes were already present after a 7-day fasting period while the traditional approach of Buchinger fasting usually favors longer fasting periods for achieving greater treatment effects.

The mechanisms behind the clinical effects of fasting are not fully understood. Clearly, longer periods of fasting represent a strong physiological stimulus and induce pronounced hormonal changes, e.g., stimulation of the HPA pointing to a mild stress reaction. The hypothalamus is critically involved in the regulation of feeding and fasting. Previous research has shown that glucose ingestion inhibits hypothalamic neuronal activity [29]. A transcription factor has been described which acts as metabolic sensor in neurons of the lateral hypothalamic area to integrate metabolic signals, adaptive behavior, and physiological responses [30]. Functional magnetic resonance imaging studies in diabetic patients undergoing a 4-day VLCD found a normalization of the hypothalamic responsiveness to glucose ingestion after the caloric restriction period [29].

The early hypopituitary adrenergic activation is followed by decreased adrenergic levels after some days. In a prospective study with obese subjects a fast over 16 days led to substantial weight loss paralleled by decreased basal and exercise-induced serum concentrations of noradrenaline, adrenaline, and dopamine [31]. Moreover, fasting is associated with increases in concentrations of growth hormone and glucagon and leads to pronounced initial natriuresis and diuresis [32].

Studies on VLCD demonstrated an increased BP lowering effect of natriuretic peptides after a 4-day diet period, which might point to effects of fasting receptor sensitivity [33]. Extending these findings, we could show that a 7-day fast largely increases the concentration of soluble leptin receptors. It has previously shown that leptin may play a crucial role in the orchestration of endocrine and metabolic effects of fasting [34, 35]. The cytokines and hormones derived from adipose tissue are referred to as adipokines. Leptin levels in the blood are dependent on the volume of adipose tissue, and caloric restriction significantly inhibits the expression of leptin mRNA [36]. Adiponectin is reduced in patients with obesity and type 2 diabetes and it has been shown experimentally that caloric restriction can increase plasma adiponectin levels [37]. In a randomized trial over 6 months Harvie et al. [38] compared the effect of continuous and intermittent caloric restriction on metabolic disease risk markers in younger overweight women. Decreases in circulating insulin and increases in adiponectin over 1–6 months were less pronounced than in our fasting period, however we do not know the long-term impact of our fasting intervention on insulin and adiponectin.

Surprisingly, fasting led to mild but significant increase in hs-CRP. Inflammatory biomarkers are frequently increased in obese subjects and weight loss through long-term caloric restriction reduces these biomarkers in women [39]. Reduction of inflammatory markers has been described in experimental studies [40]. To the contrary, shorter periods of fasting may lead to a mild stress or hormetic reaction [41] which is associated with increased circulating levels of catecholamines and thereby possibly leading to an acute phase response. Hormetic effects are characterized as an overcompensation of low dose stimulation and stress and are related to human health.

The mood enhancing effect of fasting has been described in earlier studies [16, 18]. Several mechanisms have been suggested, among them increased central serotonin availability, endorphin release, an increase in central catecholamines, and a modified sleep architecture. Furthermore, insulin and leptin signaling may impact on other central signaling pathways, such as the GABAergic and the dopaminergic system [42]. 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.

Fasting and VLCD have been criticized for resulting in weight cycling due to decrease basal energy consumption and thereby promoting weight gain when re-feeding [43]. In contrast, empirical and observational data [44] indicate that fasting may enhance lifestyle modification with longer-lasting improved behavioral nutritional habits. Accordingly, data from clinical centers that are specialized in fasting therapy could not confirm increased weight gain after fasting [10, 15].

Several limitations apply to our study. First, as this was an uncontrolled study we do not know the nonspecific effect of the intervention which may be due to the observation, atten-

tion, and the social effects through the group meetings. Furthermore, we tried to control compliance by interviews and by urine pH measurements, which, however, are not reliable in assessing fasting-induced acidosis. Yet, documented continuous weight loss in all our patients seems to support objectively the notion of good compliance of our study participants, as also confirmed in the interviews.

The conduction of randomized controlled trials (RCT) with a fasting intervention is difficult and faces logistical and motivational challenges. However, our results imply that such a RCT is warranted and should compare the long-term effects of extended fasting with other forms of caloric restriction, as alternate day fasting or continuous 20–40% energy restriction.

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Conclusions

Our results point to marked beneficial cardiometabolic and psychological responses to 7-day modified fasting with some distinct effects in patients with or without MetS. Pronounced adaptation responses on regulating hormones and its receptors indicate a potential role in the prevention of metabolic disease. Randomized trials with longer observation periods should test the clinical effectiveness of fasting in metabolic diseases.

Disclosure Statement

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