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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 serotonin 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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