Chapter 37 Fasting

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Introduction

Fasting is broadly defined as the voluntary practice of partially or completely abstaining from caloric foods and beverages.[1] Fasting methods differ based on the amount and type of calories consumed daily, time period for daily caloric consumption, fasting duration, as well as rationale.[1-6] Therapeutic prolonged water-only fasting is the protracted (i.e., ≥2 days) consumption of only water for purposes of health promotion.[1,2,7] Most humans have enough nutrient reserves to safely undergo a prolonged water-only fast (herein called "fast") for at least

40 days[8-10] depending on body mass index, fat and muscle percentages, activity levels, and state of health. Human survival during fasting is supported by our ability to enter ketosis and utilize ketone bodies as an alternate energy source for the brain and other organs.[11] Ketone bodies potentially modulate some of the molecular and cellular adaptations observed during nutrient deprivation.[12] Preliminary evidence correlating beneficial clinical outcomes with fasting[13-17] supports the continued research and clinical application of this method.

In this chapter, we briefly review various aspects of therapeutic fasting in humans including historical context, physiological responses, clinical research, and clinical application. Caloric restriction and intermittent fasting in humans and other organisms are reviewed in depth elsewhere.[3,4,6,18]

Historical Context

Evolutionary biologists speculate that *Homo sapiens* evolved with unpredictable access to food resources which likely became more unpredictable after the advent of agriculture.[19] Several evolutionary theories attempt to explain how periodic food scarcity shaped our fat storage capacity,[20] but there are fewer theories on how it contributed to our efficient utilization of ketone bodies as an alternate fuel. There is also limited understanding of how periodic food scarcity influenced our long-standing therapeutic, spiritual, and sociological relationship with fasting.[1] Historical texts indicate that, for millennia, people of nearly all cultures and religions have practiced various fasting methods.[21-23] Over the past 200 years, therapeutic fasting has gone in and out of fashion with both allopathic and alternative health practitioners. Therapeutic fasting has once again emerged as a potential tool to treat the pandemic of degenerative diseases largely caused by the overconsumption of highly processed foods.[1-4] The type of therapeutic fasting

currently practiced is based on the tenets of Natural Hygiene, which was founded by Isaac Jennings (1788-1874)[24] and later popularized by Herbert M. Shelton (1895-1985).[25-32]

Physiology

Humans gradually transition from the fed state through the fasted state, ultimately terminating in starvation. This transition is regulated by metabolic, endocrine, and neuronal adaptations that ensure whole-body energy requirements are continuously met[8,11] and appear to modulate molecular and cellular mechanisms associated with retardation of aging processes, at least in model organisms.[3,4,12,33,34] Early reports on human fasting physiology[9,35-37] as well as research by Cahill and colleagues[11,38-86] contributed substantially to our knowledge of human physiological responses to fasting. Metabolic processes were described in five stages based on the transition through the fed and fasted states that maintains physiological blood glucose levels.[11] Throughout this transition, metabolic states are often concurrent and have variable rates depending on an individual's age, sex, and nutrient reserves.[87] It should be noted that there appears to be marked differences between the metabolism of lean and obese individuals.[73,74,88,89] For example, lean individuals have increased concentrations of ketone bodies as well as an increased percentage of energy derived from protein oxidation while fasting.[73]

Stage I begins immediately following caloric ingestion, when carbohydrates, proteins, and fats are digested into sugars (primarily glucose), amino acids (single or peptides), and fatty acids (triacylglycerol, TAG), respectively.[11] All macronutrients are absorbed into the blood, transported to the liver for processing and/or storage, and transported back to the blood to maintain physiological processes. Glucose and amino acids are absorbed directly into the blood stream through the small intestine. TAGs are broken down into glycerols and free fatty acids, which form micelles that enter enterocytes where they are reconverted to TAGs and packaged in

chylomicrons. Chylomicrons are absorbed into the lymphoid system through the small intestine and then released into the blood stream. In the fed state, high blood glucose levels stimulate the pancreatic β cells to secrete insulin above basal levels. Insulin regulates the uptake and metabolism of glucose, amino acids, and fatty acids. At this stage, all tissues preferentially utilize glucose as fuel, except the liver and heart, which prefer α-ketoacids and fatty acids, respectively. Glucose is transported into cells where it is catabolized through glycolysis. During glycolysis, glucose is converted to pyruvate that is oxidized to acetyl-coenzyme A (CoA) that enters the tricarboxylic (TCA) cycle, ultimately producing adenosine tri-phosphate (ATP). Increased glycolysis in the liver results in an excess of acetyl-CoA that is used to synthesize TAGs, which are packaged into very low-density lipoproteins for storage and secretion when blood glucose is low. Insulin also regulates the uptake of glucose by adipocytes, where it is converted through glycolysis to glycerol 3-phosphate and acetyl-CoA, which are then synthesized into TAG. High levels of blood glucose enable hepatocytes and muscle cells to convert glucose to glycogen – the storage form of glucose – through glycogenesis. The liver and muscles store approximately 70 and 150 grams of glycogen, respectively.[8]

Stage II begins approximately 4-6 hours following final caloric intake.[11] Decreased blood glucose levels stimulate pancreatic α cells to secrete glucagon above basal levels. Glucagon is an insulin antagonist, which stimulates glycogenolysis of hepatic glycogen to glucose. Hepatic glycogen reserves are depleted within approximately 24 hours of fasting. Glycogenolysis also converts muscle glycogen to glucose 6-phosphate. However, muscle cells lack the enzyme glucose 6-phosphatase that is required to release glucose; therefore, muscle glycogen is not used to meet whole-body glucose requirements. During this early fasted phase, hepatic glycogenolysis

provides about 75% and gluconeogenesis accounts for the other 25% of daily glucose requirements of all tissue except the liver.[8]

Stage III lasts from approximately 24-48 hours following final caloric intake.[11] During this time, gluconeogenesis is the primary metabolic pathway supplying daily glucose requirements.[38-40,90] Gluconeogenesis, primarily in the liver, produces glucose from the non-carbohydrate carbon substrates glycerol, lactate, and amino acids.[8,91] TAG hydrolysis forms glycerol and fatty acids in adipose tissue. Glycerol is converted to dihydroxyacetone phosphate which used to produce glucose in the liver, after which it is exported to extrahepatic tissue. In skeletal muscle, when rates of glycolysis exceed the TCA cycle, excess lactate is produced and transported to the liver where it is converted to pyruvate and then to glucose through the Cori cycle. Glucose is then transported back to muscle cells or used to meet whole-body glucose requirements.[85] Amino acids are primarily used to make protein but when glucose is low, the breakdown of digestive and glycolytic enzymes, skeletal muscle, and other connective tissue provides amino acids for gluconeogenesis. In skeletal muscle, ammonium is produced as a byproduct of protein catabolism but it is unable to be converted to urea for removal through urine, as in the liver. Excess ammonium results in transamination of surplus pyruvate to ultimately form alanine. The glucose-alanine or Cahill cycle transports the glucogenic amino acid, alanine, from skeletal muscle to the liver to produce glucose that can then be used by extrahepatic tissue. Although all amino acids, with the exception of lysine and leucine, are glucogenic, alanine and glutamine are the predominate amino acids used in gluconeogenesis in the liver and kidneys, respectively.[92,93] Eventually, the renal cortex synthesizes more glucose through gluconeogenesis than does the liver.[64] During this stage, blood glucose begins to decline

but glucose is still utilized by all tissue with the exception of the liver.[8,91] In the fasted state, blood glucose levels routinely drop down to 40 mg/dL or lower.[11,90,94,95]

Stage IV begins approximately 48 hours after final caloric intake and lasts until approximately day 5-7.[11] At this stage, renal gluconeogenesis becomes progressively more important in the maintenance of blood glucose levels. Additionally, reduced blood glucose and increased glucagon levels induce adipocytes to increase lipolysis of TAGs into fatty acids and glycerol. Glycerol is converted to glucose through gluconeogenesis as described above. Fatty acids bound to albumin are transported to the liver, muscle, and other tissues. Fatty acids in the liver are broken down by β oxidation to form acetyl-CoA, when acetyl-CoA exceeds the capacity of the TCA cycle because of reduced oxaloacetate availability it is used to synthesize the ketone bodies acetoacetic acid (AcAc), acetone, and β-hydroxybutyric acid (βOHB) through ketogenesis.[8] The liver is unable to utilize ketone bodies for fuel which results in large quantities of ketones, primarily AcAc and βOHB, secreted into the blood stream. Within the mitochondria of extrahepatic tissue, βOHB is further oxidized to AcAc that is then transported to the TCA cycle. Increased ketones are typically identified through urinalysis by day three of the fasted state.[90] Except for red blood cells, the renal medulla, and the liver, all tissue, including the brain, are able to utilize ketone bodies for energy. By the end of stage IV, the brain's energy requirements are met primarily by ketone bodies.[8,11]

Stage V begins when rates of ketogenesis exceed gluconeogenesis and continues until starvation begins.[11] The length of this stage depends on an individual's body mass index, fat and muscle percentages, physical activity levels, and state of health. Studies on respiratory quotient and urinary nitrogen have demonstrated that adipose TAG stores meet the majority of whole-body energy requirements during prolonged fasting.[35,49,51,56,85] Meeting energy requirements

through fat metabolism decreases dependency on gluconeogenesis, thus sparing protein.[86,96] The brain begins utilizing ketone bodies, primarily βOHB, after approximately 4 days. This adaption is essential because brain glycogen content is very low (0.1%). The brain (40 g/day) and other tissues (40 g/day) still have an obligatory need for approximately 80 g/day of glucose, which is met through gluconeogenesis.[8,97] Starvation begins when essential protein is catabolized to meet energy requirements.[8] Based on average nutrient reserves, a 70 kg human can fast for 2-3 months before entering starvation (Table 37.1, 37.2).[8,35,49,51,97]

Although data in mammalian model organisms suggests that intermittent fasting has various effects on the neuroendocrine system such as increased synaptic plasticity and parasympathetic tone,[98] data on neuronal and endocrine adaptations during prolonged water-only fasting in humans is lacking. Preliminary research has shown that human growth hormone, reverse T3, adrenaline, noradrenaline, dehydroepiandrosterone (DHEA), sex hormone-binding globulin, and cortisol increase[94,95,99-102] whereas thyroid stimulating hormone, T3, luteinizing hormone, follicle-stimulating hormone, and testosterone decrease[94,95,99-101] during fasting. Specific details on fluctuations over the course of a prolonged fast; differences between individuals based on age, sex, and nutrient reserves; and the downstream effects of these changes remain to be elucidated.

It is well established that weight decreases in response to nutrient deprivation. During prolonged fasting, weight loss averages 0.9 kg/day during the first week and decreases to 0.3 kg/day by the third week.[90] Initial rapid weight loss is primarily due to water and sodium diuresis.[90] Other changes include decreased pulse rate[9,35] and blood pressure (BP)[9,35,37,103] as well as a transient small increase and then a slow drop in the basal metabolic rate by about 1% per day until stabilizing at about 75% of normal.[103] Electrocardiography often demonstrates cardiac

adaptations including sinus bradycardia, decreased QRS complex and T-wave amplitude, elongation of the QT interval, and shifts to the right of the QRS and T-wave axes, which normalize upon refeeding.[9,90,103,104] Physiological responses typically return to pre-fast levels upon caloric consumption.

Clinical Research

Research, primarily conducted in model organisms, has uncovered several potentially health-promoting cellular and molecular responses to nutrient deprivation, such as hormone modulation, reduced oxidative stress, and increased autophagy.[3,4] Additional research is needed to conclusively determine if fasting produces similar mechanistic responses or how these responses might affect clinical outcomes in humans. A century of fasting literature[1,105] and limited clinical evidence[15,17,106-109] suggests that the method has beneficial health outcomes, but the substantial amount of data is largely inconclusive due to methodological limitations. For example, there are essentially no randomized controlled trials (RCTs) on the efficacy of fasting in the treatment of any disease.

There is also an unsubstantiated perception that therapeutic fasting is unsafe.[5] The belief is associated with a period during which an extreme form of water-only fasting was used as to treat obesity.[110,111] During this period, there were several deaths[110,112-114] reported out of approximately one thousand documented fasting cases.[111,115-122] These deaths could likely have been prevented had unintentionally harmful fasting practices not been used. Until recently, there were no peer-reviewed assessments of adverse events during fasting. A recent retrospective study describes the adverse events (AEs; classified according to the Common Terminology Criteria for Adverse Events and MedDRA terminology) that occurred during prolonged water-

only fasting visits (2-40 days; n=768) at a medically supervised fasting center.[7] The study found that the highest grade AEs experienced during the majority visits (72%; n=555) were mild to moderate in nature and are known to commonly occur during fasting (e.g., nausea, back pain, headache, and presyncope). There were two serious adverse events (grade 4 hyponatremia and grade 3 dehydration), which resolved without further complication, and there were zero deaths. Overall, the data suggest that the method is safe, at least when conducted under medical supervision using the protocol described.

The following is a description of literature published on the effects of therapeutic fasting during which only water or, in some cases of early research, acaloric liquids and/or vitamin/mineral supplementation was administered. Unfortunately, in many early publications the fasting method was not adequately described, and these studies are not included here.

Case Reports

Case reports describe novel, informative clinical cases of 1-3 patients. They can inform clinicians and patients as well as guide the course of clinical research. In addition to the reports presented here, there are numerous case reports describing physiology and on the use of fasting to treat obesity.

Appendicitis

A 46-year-old male with an enlarged appendix accompanied by symptoms of appendicitis opted to undergo a medically supervised, water-only fast for 7 days with 4 days of refeeding rather than surgically remove his appendix. The patient fasted and refed for 7 and 4 days, respectively. There were no serious complications, and upon termination he had reduced abdominal swelling,

no pain or fever, and a normal white blood count. He remained symptom free at the 3-month, 1-year, and 2-year follow-up visits.[106]

Follicular Lymphoma

A 42-year-old woman with stage IIIa, low grade follicular lymphoma was reported in *BMJ Case Reports*. After a 21-day water-only fast followed by 10 days of supervised refeeding, her enlarged lymph nodes were no longer palpable and computerized tomography (CT) scans confirmed the size reduction. She did not undergo standard cancer treatment, has maintained a healthy lifestyle, and was symptom free at the 6-month follow-up visit.[15]

Chronic Posttraumatic Headache

A 52-year-old woman with a 16-year history of chronic posttraumatic headache presented with a constant headache that was described as "dull and achy" with a pain level of 6-8/10 that did not improve with standard pharmaceutical medications. She underwent two 40-day medically supervised, water-only fasts with a 6-month intervening period of an exclusively plant-foods diet. At the end of the second fast, she was free of headache symptoms with the exception of an occasional headache that lasted less than 10 minutes with a pain level 1/10. Her body mass index (BMI) reduced from 33.1 kg/m^2 to 18.8 kg/m^2. There were no serious complications, and her serological values remained normal with the exception of slightly increased liver enzymes, which resolved upon refeeding. At the five-year follow-up visit, she was still symptom free and had maintained a normal BMI.[109]

Clinical Studies

Studies on the clinical effects of fasting have been primarily observational in nature. Many studies lack the necessary sample size and controls to conclusively determine outcomes. There is a need for RCTs to draw conclusions about this method.

Cardiovascular Disease

Early studies suggest that fasting reduces serum triglycerides[123], blood pressure (BP)[9,35,90,124], and symptoms of congestive heart failure.[125] More recently, medically supervised, water-only fasting was shown to reduce borderline and high hypertension [REF].[14,108] In 68 consecutive patients with borderline high BP, an average of 13 days of water-only fasting reduced systolic BP by an average of 20 mm Hg, with 82% of patients achieving systolic BP below 120 mm Hg.[108] In 174 consecutive patients with high BP, an average of 10 days of water-only fasting resulted in more than 90% of patients becoming normotensive. In patients with systolic BP greater than 180 mm Hg, the average reduction in systolic BP exceeded 60 mm Hg.[107] Preliminary data also suggests that treatment of hypertension with a 14-day medically supervised, water-only fast could reduce combined medical and drug costs by almost $2700 per year per patient.[126]

Cancer and Chemotherapy

Preliminary research suggests that water-only fasting for approximately 2-3 days prior and/or following chemotherapy ameliorated commonly reported chemotherapy side-effects.[17,127] There is currently a randomized trial being conducted on the effects of 72 hours of water-only fasting in conjunction with chemotherapy.[127]

Diabetes Mellitus

Reports, as early as 1912, suggest that prolonged water-only fasting improves diabetes.[9,128,129] In obese diabetic patients, it was found that prolonged water-only fasting substantially improved most parameters of insulin function independent of weight loss.[130]

Epilepsy

Therapeutic fasting has been used since the early 1900s to treat seizures.[129,131] It was later found that ketosis, initiated by fasting, decreased the duration, severity, and number of seizures.[132]

Autoimmune Disorders

Several reports suggest that fasting has a beneficial effect on autoimmune disorders, such as chronic urticaria and colitis.[133,134] It was also found that fasting shortened the early stages of acute glomerulonephritis (reduced glomerular filtration rate, high BP, and edema) and improved prognosis.[135] Rheumatoid arthritis (RA) appears to respond particularly well to fasting. Studies have shown that fasting in arthritis patients results in decreased erythrocyte sedimentation rate (ESR), arthralgia, pain, stiffness, and need for medication.[136-143] Consistent with those findings, a study of 43 patients with definite or classic RA found that a water-only fast of 7 days significantly improved grip strength, pain, swelling of proximal interphalangeal joints, ESR, and functional activity.[144]

Obesity

It is thoroughly documented that fasting reduces weight. Therapeutic fasting as a treatment for obesity was popularized in the 1960s.[81,110-113,116-118,120,121,124,125,145-147] In general, fasting results in an initial weight loss of approximately .9 kg/day with a gradual decrease to 0.3 kg per day over 30 days.[148] The initial weight lost is primarily that of water, glycogen, and sodium. A study

monitoring 121 obese patients for approximately 7 years after fasting an average of 2 months found that after 2 to 3 years, 50% of patients returned to their pre-fast weights, and that by the end of the study, 90% weighed the same as before their fasts.[121]

Clinical Application

Although rigorous clinical research is lacking, there is substantial clinical anecdotal evidence supporting the use of medically supervised, therapeutic fasting as a safe and effective treatment for a variety of diseases. Since 1984, there have been more than 16,000 medically supervised fasting patients at TrueNorth Health Center (TNHC) alone. The vast majority of these patients have benefited from fasting with very few serious adverse events and no deaths. Clinicians at TNHC have observed improvements in diseases ranging from lupus to hyperhidrosis to follicular lymphoma. Several facilities, which follow the standards of care and principles of ethics established by the International Association of Hygienic Physicians,[149] now exist in the United States, Canada, England, and Australia, but TNHC is currently the only center in the United States that trains and certifies medical practitioners in water-only fasting.[150]

Therapeutic fasting conducted under medical supervision at an inpatient facility minimizes complications that can arise during fasting because clinical staff can monitor symptoms, order and analyze necessary clinical laboratory tests and procedures, approve adjunctive therapies, appropriately terminate the fast, and supervise post-fast recuperation. In most cases, fasting is therapeutically superior to a restricted diet because (1) hunger almost totally disappears,[9,124] (2) ketosis occurs more quickly and efficiently,[9,124] (3) famine edema does not occur,[9] (4) sodium diuresis is more pronounced,[111] (5) weight loss is greater and is typically from fat loss rather than protein catabolism, (6) healing time is shorter, and (7) patient strength

may be greater.[31] Restricted diets of vegetable broth or fruit and vegetable juices do not initiate fasting metabolic processes since they contain carbohydrates, protein, and/or fat. Nonetheless, restricted diets are often useful before and after fasting, for patients in whom a healing crisis (i.e., where chronic conditions/symptoms become acute) develops during a fast, and when a fast is contraindicated.[30]

Therapeutic fasting can be described in three clinical phases. Phase I, or early fasting, lasts up to 7 days during which patients can present with common detoxification symptoms of malaise, headaches, and muscle aches that are typically transitory. Patients often express concern for their health and a preoccupation with eating, but any desire for food is likely psychological and has nothing to do with physiological need. Phase II, or balanced fasting, is the most clinically significant fasting phase and can last for weeks to months. Patients often experience one or more "healing crises" and/or go through less significant detoxification reactions. Extending a fast beyond a notable healing crisis/detoxification reaction rather than stopping midcourse may result in more beneficial health outcomes. During this time, health should gradually return; if not, the patient should be given a thorough medical evaluation. Phase III, also called starvation, occurs when the body increases protein catabolism and can potentially damage essential tissue and, ultimately, terminate in death. Fasting should be discontinued before this phase begins. Predicting optimal fast length is difficult because it is based on many factors, including protein and fat reserves, individual metabolism, mental health, financial limitations, work and family obligations, severity of disease, age, and sex. Overall, "[the] doctor will look for good practical recovery where the patient is symptom free and signs of regeneration are present."[151] "Fasting to completion" (i.e., exhaustion of nutrient reserves) is no longer practiced

nor is it necessary, as consecutive fasting with intervening refeeding appears to be safer and as effective.[151]

Guidelines

The use of a whole plant-foods diet processed without added sugar, oil, and salt before and after fasting is beneficial for reducing symptom severity during fasting and avoiding complications during refeeding. This diet also promotes pre-fast bowel movements, which should occur at least daily prior to fasting, as well as post-fast bowel movements, which should quickly develop and pass without complication. It is necessary to adopt a health-promoting lifestyle, including diet, post-fast in order to to maximize and maintain any benefits obtained while fasting.

Consumption of 64 to 96 oz/day of pure water (distilled, filtered, or reverse osmosis) is recommended,[31,152] but upwards of 160 oz is commonly ingested without affecting serum sodium levels. Increased water intake appears to reduce detoxification reactions but excess consumption can cause electrolyte imbalances that are clinically significant and require refeeding. Physiologically, the body is able to modulate "available water" through reduced obligatory water excretion (owing to lower excretion of urea, the major osmotic solute) and by accessing water released from fat catabolism.[85] Upon refeeding there is a sudden shift from a low level of insulin and ketosis to a high level of insulin and glycolysis. As the plasma insulin rises, potassium, phosphate, and magnesium are driven intracellularly and sodium extracellularly, which dilutes the circulating concentrations. Thus, sodium restriction during refeeding should be emphasized to not precipitate dilution, edema, or acute heart failure.[78]

In addition to maintaining optimal hydration, rest is essential during fasting. Patients may nap throughout the day. It is also common to experience reduced sleep at night, possibly because

of decreased daily activity and increased daytime rest. Short walks or light stretching is permissible. Rigorous exercise while fasting is discouraged because fuel conservation is necessary to maximize healing and avoid unnecessary gluconeogenesis.[31,152] Even moderate activity can double caloric utilization.[59] In serious chronic disease, an excess of activity has been suspected as cause of death during fasting.[153] Sunlight is also important for general health during fasting, and patients should try to obtain 10 to 20 min/day. However, dehydration due to sun exposure can promote orthostatic hypotension and subsequent injury from falls. An increase in heart rate by 10 to 15 beats per minute may indicate excessive sun exposure.

Laboratory Values

Assessment of a fasting patient's progress is not based on a single sign or symptom, but on the total clinical picture. Therefore, vital signs, including blood pressure and pulse, should be checked daily. Laboratory tests such as a complete blood count and serum chemistry panel and urinalysis are performed weekly and other tests are performed as necessary. Laboratory values during fasting are typically unique to the individual and disease process, but some general observations have been made.[120,148]

Complete blood counts usually show no significant change. Low hemoglobin and hematocrit values[10,154] require that hemolysis or hemorrhage are ruled out, whereas elevations in hematocrit, hemoglobin, and red blood cell counts usually indicate reduced hydration.[78,155] White blood cell (WBC) counts are usually unchanged or decrease slightly with fasting. However, WBCs may increase if infection is present or if WBC counts are low before fasting.

Serum electrolyte levels are not good indicators of tissue stores, but they are considered the most important blood values during fasting because any significant change necessitates

immediate clinical management. All electrolytes reduce over the course of a long fast as mobilized stores are lost, but stores appear to be redistributed even when distilled water is used during prolonged fasts. Serum calcium and chloride concentrations are usually stable but can diminish, especially if vomiting or diarrhea is present. There is a tendency for serum potassium concentrations to decrease, although they can also increase, and values less than 3 mmol/L or higher than 6 mmol/L often require the fast to be terminated. Similarly, serum sodium concentrations can decrease and values less than 130mmol/L require immediate attention. The total body store of potassium is 115 to 131 g (of which 98% is exchangeable) and sodium is 83 to 97 g (of which 65% is exchangeable). The typical daily dietary intake of potassium is 3 to 5 g and sodium is 3 to 7 g. During early fasting, the body loses 1.6 to 1.8 g (40 to 45 mmol) of potassium and 3.5 to 5.8 g (150 to 250 mmol) of sodium, and these values eventually drop to 0.4 to 0.6 g (10 to 15 mmol) and 0.02 to 0.35 g (1 to 15 mmol), respectively.

Liver enzyme values may increase considerably if liver disease is present and may rise even if liver disease is not present. This is usually not a cause for concern as values typically return to normal post-fast. Triglyceride, cholesterol, and uric acid levels usually rise during fasting,[156,157] indicating mobilization of tissue stores. Post-fast values often show a decrease from pre-fast values[156,158] but lipid panels may not normalize until 4 to 6 weeks post-fast. Serum protein as well as pancreatic lipase and amylase values usually decline with fasting. A rise in blood urea nitrogen (BUN) value may occur but a decrease has also been reported.[9,10] Serum creatinine levels can increase,[158] remain stable,[159] or decrease. In cases of increased levels, prompt retesting and/or fast termination are required. Closely monitor creatinine for elevations, particularly in those with renal compromise. Blood glucose values drop in most patients.[128,160] In some patients, values below 40 mg/dL have been observed, and are not typically a cause for

concern in the absence of additional signs of hypoglycemia. If the blood glucose value is low before fasting, it may rise after fasting. ESR and C-reactive protein usually drop after fasting, although they may rise during the fast.[142,143]

Urinalysis is conducted weekly, but it might be difficult to interpret during fasting because the body discards considerable waste via the kidneys. It is not uncommon to see various types of casts, red blood cells, white blood cells (WBC), bilirubin (+1 to +2), protein (trace, +2), and ketones (+4), and, if liver disease is present, urobilinogen elevation. Trace leukocytes and blood are common incidental findings, particularly in women. Specific gravity is commonly elevated (possibly to 1.035), a finding that may reflect inadequate hydration.

Adjunctive Care

Dietary Supplements

During prolonged fasting, macro- and micronutrient imbalance is rare. Protein catabolism as well as vitamin and mineral excretion decreases as the fast progresses, and typically by day 10 is low enough to maintain homeostasis. Fast termination is preferred to supplementation. Problems such as nausea and indigestion have been reported when vitamin and mineral supplements were taken during fasting.[121,159] In a report describing vitamin deficiency during fasting, the actual fasting protocol was not described; in addition, the patient's physical activity was not restricted and oral medication for intercurrent illness was maintained during fasting.[121]

Enemas

Enemas are generally not administered or necessary if the fasting patient has daily, healthy bowel movements before fasting begins. To help prevent constipation, a raw and cooked plant

foods diet free from any additives, animal products, or refined carbohydrates for at least 2 days will help promote bowel movement pre-fast and prevent post-fast constipation. If bowel movements do not start early during refeeding then precautionary methods to avoid fecal compaction should be considered, including stewed prunes, enema, and/or colon hydrotherapy.

Hydrotherapy

Constitutional hydrotherapy and sitz baths have been implemented with fasting. Strong treatments, both in frequency and/or temperature interval size, should be limited to early fasting.

Intravenous Therapy

Intravenous administration requires much care and is best avoided entirely, except for emergent conditions. Saline should be avoided due to plasma expansion and edema, which has precipitated acute heart failure. Glucose, in contrast, should be accompanied by vitamin B_1 and B_6 co-administration to avoid acute thiamine deficiency and lactic acidosis.[161-163]

Pharmaceuticals

Pharmaceutical use is contraindicated during prolonged fasting. The primary concern regarding fasting medicated patients is the potentiation of drug action during the fasted state, urinary/hepatic metabolism, and known drug side effects and adverse events. Appropriately removing pharmaceuticals allows for ease of clinical assessment while ensuring patient safety. Successful fasts have been administered while maintaining some hormonal medications including insulin, thyroid, and reproductive hormones, often at reduced dosage.

Contraindications

Contraindications to fasting are few, and each case must be judged individually. For example, an inexperienced practitioner may assume that emaciated patients should not fast but in cases of extreme emaciation a short fast (1-3 days) or a series of such short fasts with longer periods of proper intervening feeding may be beneficial.[31] With regard to fasting contraindications Alec Burton stated:

> I have found few health problems which are absolute contraindications to fasting. In my experience, if the need is evident, the only genuine contraindication is fear.... As for the other conditions often mentioned, e.g. kidney disease, heart impairment, [tuberculosis], etc., they merely require extreme caution, because of the limits imposed by pathology, but they are not inexorable contraindications.*[151]*

Relative contraindications to fasting include severe anemia, porphyria, cachexia, anorexia, severe liver or kidney disease, medium-chain acyl-CoA dehydrogenase deficiency, advanced cerebral vascular insufficiency, higher-grade cardiac arrhythmias, certain cancers or psychological disorders, and active gastric ulcer disease.[164] Although fasting is contraindicated in severe renal insufficiency, patients with 65% renal function often normalize as a result of fasting and dietary management. Additionally, fasting pregnant women and children is controversial. Short, medically supervised fasts may be appropriate for pregnant women and children on an individual basis, but long fasts are typically strongly contraindicated and precaution is indicated. Ketosis in pregnant diabetic women is known to be associated with fetal damage,[165] but there are no studies on the effects of nondiabetic ketosis on fetal development. Doctors (e.g., Shelton, Benesh, Sidwha, and Burton) with considerable experience fasting pregnant women during all three trimesters have found no adverse effects with fasts of a few days to 2 to 3 weeks but there is insufficient data to conclude if the practice is safe. It is well recognized that fasting during

lactation is not generally advised, because milk flow is halted by fasting and is difficult to resume.[31]

Side Effects

Medically supervised, prolonged water-only fasting as a therapeutic procedure is generally safe.[7] Side effects of fasting are rarely serious, with the exception of electrolyte imbalance, but fasting may uncover disease and reveal weaknesses that were previously subclinical.[116,166] Discomfort during fasting may be due to withdrawal from stimulants, hypoglycemia, acidosis, elimination of wastes, and enhancement of repair. Patients may experience headaches, insomnia, nausea, back pain, dyspepsia, fatigue, skin irritations, presyncope, coated tongue, body odor, aching limbs, palpitations, mucous discharge, and visual and hearing disturbances. Hair growth is usually arrested, and skin may become dry and scaly. Most signs and symptoms are usually brief in duration. In certain cases, complications occur that may necessitate breaking the fast prematurely. Examples of such conditions are as follows:

- Sudden drop in BP (possibly due to peripheral circulatory collapse)
- Delirium
- Prolonged hypothermia
- Rapid, slow, feeble, or irregular pulse
- Extreme weakness
- Dyspnea
- Vomiting and diarrhea leading to dehydration
- Gastrointestinal bleeding
- Hepatic decompensation

- Renal insufficiency
- Severe gout
- Cardiac arrhythmias
- Emotional distress
- Severe electrolyte imbalance

Fasting also elevates serum uric acid values and uric acid excretion, and if fluid intake is insufficient, gout or renal stones may be precipitated.[167] A few reports have also discussed the development of Wernicke encephalopathy during prolonged fasting,[162,163] but it rarely occurs during therapeutic fasting. Therefore, it is difficult to determine whether the condition is related to methodology. Furthermore, the incidence of death at fasting institutions is low, and there is no evidence in the scientific literature to suggest that fasting itself can be considered a cause of death. Death during fasting indicates that the remedial efforts of the body have been overpowered by the pathologic process. This situation occurs in serious disease, whether the patient is eating or fasting. In examining the fallacy of attributing the cause of death to fasting, Stewart and Fleming wrote, "Fasting short of emaciation is not hazardous; if death results, reasons other than those of the fast should be considered before concluding that all supervised fasts should be discouraged."[168]

Conclusion

Prolonged water-only fasting conducted under medical supervision is increasingly recognized as a safe and effective therapy for a number of diseases, but the practice is not for everyone and post-fast lifestyle modifications are necessary to maintain any health benefits obtained from fasting. Preliminary research indicates that there is at least some degree of overlap between the

physiological responses induced by caloric restriction, intermittent fasting, prolonged fasting, and exercise, such as increased autophagy and insulin sensitivity.[3,169-173] Additional research is necessary to determine the extent to which these methods induce similar physiological responses in humans and if the responses result in clinical health outcomes. Nonetheless, used alone or in combination, these natural therapies could help reduce the overwhelming rates of chronic diseases that humans are experiencing globally. As it is more beneficial and cost effective to maintain rather than repair health, it will be important to determine the affect of these therapies on healthspan over the course of a life.

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Table 37.1 Fuel reserves in a typical 70-kg Man*

	Available Energy in kcal (kJ)		
Organ	**Glucose or Glycogen**	**Triacylglycerols**	**Mobilizable Proteins**
Brain	8 (30)	0 (0)	0 (0)
Blood	60 (250)	45 (200)	0 (0)
Liver	400 (1700)	450 (2000)	400 (1700)
Muscle	1,200 (5000)	450 (2000)	24,000 (100,000)
Adipose issue	80 (330)	135,000 (560,000)	40 (170)

Table modified from Biochemisty 5th edition.[8]

Table 37.2 Utilization of Energy Reserves

ENERGY SOURCE	RESERVE*
Blood Glucose	1 h
Glucose from Digestion	4-8 h
Glycogen	12 h
Amino acids	48 h
Protein	3 wks (if protein were the only fuel used for gluconeogenesis) 24 wks (obligatory loss only)
Triglycerides	8 wks

* These estimates are based on 100% utilization of each fuel. Data from Shils ME. Modern nutrition in health and disease, 9th ed. Philadelphia: Lea & Febiger, 1998; White A, Handler P, Smith EL. Principles of biochemistry, 6th

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