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Benefits of short-term dietary restriction in mammals

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Abstract

Dietary or calorie restriction (DR, CR), defined as reduced food intake without malnutrition, imparts many benefits in model organisms. Extended longevity is the most popularized benefit but the least clinically relevant due to the requirement for long-term food restriction. DR also promotes stress resistance and metabolic fitness. Emerging data in experimental models and in humans indicate that these benefits occur rapidly upon initiation of DR, suggesting potential clinical relevance. Here we review data on the ability of short-term DR to induce beneficial effects on clinically relevant endpoints including surgical stress, inflammation, chemotherapy and insulin resistance. The encouraging results obtained in these preclinical and clinical studies, and the general lack of mechanistic understanding, both strongly suggest the need for further research in this emerging area.

Introduction

Dietary or calorie restriction (DR, CR), defined as reduced food intake without malnutrition, is a potent intervention that increases lifespan and decreases incidence and severity of age-related disease in numerous model organisms from single-celled yeast to fruit flies to non-human primates (1). In addition to these aging-related endpoints, DR also improves metabolic fitness including glucose homeostasis, insulin sensitivity, serum lipid profiles and blood pressure, and improves resistance to a variety of acute oxidative stressors (1).

After early 20th century reports of DR's beneficial actions regarding cancer and longevity in rodents, hypotheses as to its mechanism of action focused on accumulated effects of reduced oxidative stress over time (2). An important implication of this viewpoint was that benefits of DR take a long time to accrue. Because long-term voluntary food restriction is impractical for most people, this made DR by dietary means (as opposed to pharmacological means in the form of DR mimetics) of little practical clinical value.

In the 21st century, it came with some surprise that near maximal changes in mortality rates could be achieved within days of food restriction in fruit flies (3). In mice, 40% CR initiated in 19 month old mice significantly increases lifespan and decreases the rate of age-associated mortality within 8 weeks. Changes in liver gene expression similar to those observed upon long-term CR occur in as little as 2 weeks (4).

The idea of a rapid response to DR runs counter to the idea of accrual of benefits (for example, a reduction in steady state levels of oxidized macromolecules) being important for onset of benefits. Instead, it supports the hormesis hypothesis of DR action focused on

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adaptive changes to the mild stress of food deprivation (5). Although the molecular nature of the “mild stress” associated with food restriction is not well defined, it may involve at least a temporary increase in oxidative free radical production driving pleiotropic adaptations in energy metabolism, stress resistance, and in multicellular organisms, immune function (6).

While the relative importance of these DR-dependent adaptations to increased lifespan/healthspan remain unclear, the speed at which these changes in immunological or metabolic fitness can occur is becoming readily apparent. This realization set the stage to ask which of the many known benefits of DR in mammals may also be realized within clinically relevant time frames. In this review, we will highlight existing evidence for short-term benefits of DR against clinically relevant endpoints. We will focus on planned stressful events with the most immediate translational potential, including elective surgery and chemotherapy. What little is currently known about underlying mechanisms will also be summarized. We begin with a definition of terms.

What is short-term DR?

The term DR is itself loosely defined, and its execution in experimental mammals varies widely among laboratories with respect to composition of diet, severity of restriction and timing of meals. For example, DR can consist of once daily or thrice weekly feeding over a range of restricted food amounts (7). Every-other-day (EOD) fasting is an alternate method of DR consisting of alternating days of ad libitum feeding and fasting generally resulting in reduced overall food consumption. DR is sometimes referred to as CR, implying the mechanistic importance of reduced calorie intake (8). When food is restricted, calories and nutrients are both reduced proportionately, yet the relative contribution of calorie vs. nutrient restriction remains unresolved. Total protein restriction or restriction of an individual essential amino acid such as methionine can both lead to organismal adaptations and functional benefits reminiscent of DR, but without enforced calorie restriction (9, 10). In this review, DR is defined broadly enough to include each of these dietary interventions, without implying a shared underlying mechanism amongst them.

In the context of DR, “short-term” and “long-term” also lack rigorous definitions in the experimental literature. Long-term DR in rodents is often associated with lifespan studies lasting years. Short-term DR, on the other hand, is used in conjunction with different experimental endpoints and ranges from days to months. For example, 3 days of 100% DR (water-only fasting) and 1 month of 30% DR both result in similar functional protection against renal ischemia reperfusion injury in mice (11). However, this does not imply that these two short-term DR regimens work by the same mechanism, or that either necessarily shares a mechanistic basis with long-term DR.

How then best to define “short-term DR?” With an eye toward clinical translation, we first considered setting an upper limit on the period of time that would be considered practical for a given clinical application, for example preconditioning prior to surgery or chemotherapy. However, what is considered practical is likely to depend on a number of variables including the severity of food restriction, motivation of the patient and his/her doctor, and evidence of potential benefit. Each of these variables is either currently unknown or difficult to ascertain. A different way to define short-term DR would be to equate it to a measurable biological phenomenon. In rodents, for example, the initial response to DR involves weight loss. At sustainable levels of DR such as 30%, initial weight loss is typically followed by a slight rebound before a new weight set point is established (12). Short-term DR could thus correspond to this period of time in which animals lose weight after initiation of food restriction but prior to rebound or weight maintenance (Figure 1).

Nonetheless, given the dearth of reports fitting this narrow biological definition of short-term DR, we instead took a practical approach and focused on the shortest reported DR periods available for a given experimental endpoint with potential clinical translation. Thus, our definition of “short-term” here ranges from one day to several months. However, in most cases the experiments highlighted in this review were not designed to find the minimum time of onset of benefits, so the potential clearly exists for shorter DR periods to demonstrate clinical relevance.

Protection from ischemia reperfusion injury and other surgical stressors in experimental models

Dietary Preconditioning

Surgery is inherently stressful. Incision, tissue dissection, cauterization and temporary stoppage of blood flow (ischemia followed by reperfusion) are standard techniques that engender local and systemic inflammatory as well as sympathetic nervous responses. Ischemic injury can also occur as an unintended consequence of vasoconstriction and/or arterial plaque rupture, resulting in such perioperative complications as heart attack or stroke (13).

The use of long-term DR as a preconditioning method to protect against stress, associated directly or indirectly with elective surgery, was first reported in a rat model of myocardial infarction. Twelve months of 40% daily food restriction reduces inflammation and infarct size associated with occlusion of the coronary artery (14). Three months of DR also protects against neuronal damage induced by occlusion of the middle cerebral artery (15) and other types of neuronal stressors, including MPTP toxicity (16). While these examples provided proof-of-principle that DR can lend protection in clinically relevant models, the long duration of the preconditioning period precluded any immediate practical translation to the clinic.

The first study to look specifically at the timing of onset of benefits of DR against surgical stress used models of ischemia reperfusion injury to the kidney and liver in mice (11). Two-four weeks of 30% DR or 1-3 days of 100% DR (water-only fasting) both ameliorate organ damage and dysfunction. Protection against death associated with renal failure is significantly reduced by as little as an overnight fast, while protection against organ dysfunction by fasting is dose dependent up to at least 3 days. Mechanistically, protection correlates with improved insulin sensitivity, reduced expression of Insulin-like Growth Factor (IGF)-1, and increased expression of cytoprotective genes including hemeoxygenase 1 and components of the glutathione detoxification system (11).

While this was the first study to place fasting in a mechanistic framework shared by DR with regard to protection from ischemic injury, it was by no means the first to show benefits of fasting in the context of clinically relevant models of surgical stress. Early studies in a rat model of focal brain ischemia showed that 48 hours of fasting prior to onset of injury reduces edema and neuronal necrosis in the striatum, neocortex and hippocampus (17). Mechanistically, utilization of ketone bodies was postulated to minimize lactic acidosis and its maladaptive neuropathological symptoms including seizures and mortality. In an isolated, perfused heart model of ischemia in rats, a 16 hour fast protects against damage, measured by release of cellular enzymes, and promotes functional recovery of heart rate and cardiac output following 15 minutes of total ischemia (18). In a rat model of liver transplantation following warm or cold ischemia, fasting of the donor animal for up to 4 days reduces organ damage and increases survival of the recipient for up to one week after transplantation. Interestingly, protection from warm ischemia by fasting increases in a dose dependent

fashion for up to at least 3 days, while protection from cold ischemia is significant only after 4 days of fasting, consistent with a threshold-based model of protection (19).

Although diets lacking essential macronutrients such as protein are incompatible with long-term survival, they can be used for up to 2 weeks to probe the nutritional basis of short-term DR. Two recent studies point to protein/essential amino acid deprivation as sufficient to induce protection from renal and/or hepatic ischemia reperfusion injury without restricting overall calorie intake. In one study, calories were supplied to mice for 3 days exclusively in the form of a saturated glucose solution (20). In the other study, mice had ad libitum access to chow lacking protein or a single essential amino acid (tryptophan) for 6-14 days (21). Both forms of protein/essential amino acid deficiency resulted in protection against renal and/or hepatic ischemia reperfusion injury. Furthermore, the latter study demonstrated a genetic requirement for the amino acid deprivation sensor General Control Nonderepressible (GCN)2. This protein binds to uncharged tRNAs and phosphorylates the translation initiation factor eIF2 α , thereby reducing general translation initiation but at the same time increasing translation of select mRNAs important for stress adaptations (22). Interestingly, although diets deficient in tryptophan mediate protection against renal ischemia in a GCN2-dependent manner, GCN2 itself does not appear to be activated in wild-type kidneys upon tryptophan deficiency, pointing to systemic mechanisms of protection. One of these may involve the circulating peptide hormone IGF-1, which is produced mainly by the liver but suppressed upon tryptophan deficiency in a GCN2-dependent manner (21). Mimicking deprivation of the non-essential amino acid proline with daily injections of the tRNA synthetase inhibitor halofuginone also induces GCN2-dependent protection from renal ischemia reperfusion injury within 3 days, consistent with rapid induction of adaptive stress resistance by activation of this nutrient deprivation sensing pathway (21).

Stroke and heart attack are two of the leading causes of physical and cognitive disability, as well as mortality, associated with ischemic injury. In addition to fasting-based protection in rodent models of brain and heart ischemia (17, 18), other short-term DR regimens impart significant protection. In a stroke-prone spontaneously hypertensive rat model, 2 weeks of 50% DR significantly delays onset of stroke and extends survival from 34 to 70 days (23). The ability of DR to dampen the inflammatory response is thought to be the primary mechanism of benefit. Restricted rats display reduced mRNA expression levels of inflammatory cytokines and chemokines such as IL-1 β , TNF- α , and MCP-1 in a range of tissues (liver, kidney, epididymal adipose tissue, and spleen); reduced adhesion molecule expression in cerebrovascular endothelial cells; and 20% fewer CD68 positive macrophages in the brain. In an isolated perfused rat model of global ischemia followed by reperfusion, short-term DR (11 days, 70% restriction) significantly improves cardiac function, ATP content recovery, and glucose utilization (24).

One reservation about using DR in a surgical setting is that reduced growth factor signaling can dampen cellular proliferation, potentially complicating wound healing. However, short-term preoperative DR followed by ad libitum refeeding after surgery in rodent models can protect against injury even in highly proliferative tissues such as the intestine. For example, although 1-2 days of fasting alone causes mucosal atrophy in the intestine, 2 days of fasting (but not 1) prior to ischemic injury preserves crypt depth and villus height (25). Dietary preconditioning is also beneficial in the context of non-ischemic types of injury, such as partial hepatectomy, that require massive proliferation for return to organ function. Fasting for 1-3 days prior to partial hepatectomy significantly increases survival and hepatic regeneration (26, 27). Taken together, the above studies demonstrate potential benefits of short-term DR in models of injury to tissues with ongoing or induced cellular proliferation. Nonetheless, detrimental effects of short-term DR also occur in various models of ischemia reperfusion injury, including occlusion of the superior mesenteric artery of the intestine (28).

Sixty percent DR for one week prior to 15 min ischemia decreases survival despite decreased myeloid cell priming and activation, possibly due to decreased glutathione levels.

Dietary postconditioning

While short-term DR is effective in preclinical models of elective surgical stress as discussed above, most heart attacks, strokes and traumatic brain injuries are unplanned and thus incompatible with preconditioning approaches. Nonetheless, recent data indicate that short-term DR may be beneficial even after certain injuries occur. For example, in rats, a 24-hr fast or the delivery of ketones can promote recovery following moderate but not severe damage in a controlled cortical impact (CCI) injury model (29). Post-conditioning with EOD fasting also protects against cervical spinal cord injury in a rat model (30). Improved behavioral recovery within 7 days of injury correlates with an increase in the receptor for Brain-Derived Neurotrophic Factor (BDNF) in the lesion area, consistent with increased BDNF-mediated survival signaling. This parallels evidence of increased BDNF-mediated survival signaling upon DR as a mechanism of protection against apoptosis resulting from neuronal injury (31).

Modulation of inflammatory response associated with infection or endotoxic shock

Modulation of the innate immune response is one mechanism by which DR may prevent damage from sterile inflammatory stressors, such as those resulting from ischemia reperfusion injury to various organs (14, 21). Mechanistically, this could occur by decreasing the ability of innate immune cells, including macrophages and neutrophils, to mount a pro-inflammatory response, and/or by increasing the ability of bystander cells to deal with such a response, for example by upregulating cytoprotective antioxidant mechanisms. DR can also prevent inappropriate activation of the immune system in response to infectious agents. For example, in an experimental model of malaria, mice on a mild DR regimen for seven days prior to inoculation with *Plasmodium berghei*-infected red blood cells are protected against the symptoms of cerebral malaria (break down of blood-brain barrier, seizures, death) without affecting parasite growth (32). While such work does not hold immediate translational promise for human malaria, in part due to the prevalence of malnutrition in affected populations, it does serve to illustrate the ability of host nutrition to rapidly affect host-parasite interactions and disease outcome.

DR also prevents inappropriate activation of the immune system in response to LPS, a model of endotoxic shock (33). Four weeks of up to 50% DR reduces signs of illness (fever, anorexia, cachexia) in a dose-dependent fashion in part by attenuating proinflammatory hypothalamic gene expression (COX-2, leptin) and increasing anti-inflammatory gene expression (SOCS3, IL-10). However, to the degree that reduced innate immune function could compromise resistance to potentially life-threatening bacterial infection, more studies are warranted to balance the appropriate level of caution with potential benefits when considering translation of short-term DR to humans.

Cancer, chemotherapy and calories

The anti-tumorigenic properties of DR on spontaneously arising tumors and in experimental cancer models have been known for over a century (34) and can occur rapidly. For example, 15 days of 40% DR significantly reduces the growth of orthotopic brain tumors of different origins in mice by reducing angiogenesis and increasing apoptosis of tumor cells (35). Although the mechanism of cell death differs according to tumor type, both pro-apoptotic and anti-angiogenic effects could be mediated in part through reduced levels of the pro-angiogenic, pro-survival factor IGF-1.

A hallmark of cancer is genomic instability, and how a given cancer responds to DR is in part dependent on its genetic makeup. Xenogenic tumors with constitutive activation of the phosphatidylinositol-3-kinase (PI3K) pathway (e.g. activating mutation in the PI3K gene itself or loss of tumor suppressor PTEN phosphatase) that proliferate independently of insulin or IGF-1 levels fail to respond to DR and continue to grow despite the reduction in nutrients and growth factors (36). Restoring normal PI3K or PTEN function in these tumors allows them to respond to DR with reduced growth in a 2-3 week time period. Thus differential activation of the PI3K pathway could be used to predict sensitivity of tumors to DR.

Short-term DR can also decrease the adverse effects of chemotherapeutic treatments on somatic cells. At the same time, DR can enhance the cytotoxic/cytostatic effects of these agents on cancer cells (37). While primary glia are protected from genotoxic agents by short-term DR, many cancer cell lines are sensitized to various chemotherapeutics including cyclophosphamide and etoposide. In mice, a 48-hour fast (resulting in a 20% weight loss) increases survival of the mice treated with these agents. Critical to differential protection of normal vs. cancer cells is the response to IGF-1. IGF-1 levels are significantly reduced upon short-term DR, conveying differential protection and sensitization of normal vs. cancer cells to chemotherapeutics (38). Two fasting cycles of 48 hours each is as effective as chemotherapy in reducing subcutaneous melanoma or glioma masses, and in other cases, combined fasting and chemotherapy retard the growth of human breast cancer tumors in mice (39). How the genetic makeup of different tumors, for example mutations in the PI3K pathway known to affect tumor growth upon DR (36), modulates differential stress resistance to chemotherapy upon DR remains to be tested.

Short-term DR may also be applicable to radiation therapy and more generally to radiation resistance. EOD fasting for the period of 2-3 weeks promotes optimal survival upon exposure to whole-body ionizing radiation, a model for treating blood-borne cancers (40). Interestingly, this protection occurs equally well on the fed or fasted day, but is rapidly lost upon a return to normal ad libitum feeding. It remains to be seen if other forms of DR can also give protection in a similar or shorter period of time in rodent models.

Mechanisms underlying benefits of short-term DR

As summarized above, the limited data available so far do not point to a single gene, pathway, or molecular mechanism underlying the benefits of short-term DR. Instead, these studies highlight a range of potential mechanisms. Three of these - altered metabolism allowing for differential or more efficient fuel usage (17, 24, 29), increased survival signaling resulting in less apoptotic cell death (30, 31) and upregulation of genes involved in cytoprotection (11) - are observed in the injured organs themselves, suggesting possible cell or organ autonomy. Systemic changes involving the innate immune system and endocrine hormones are also observed. These include immunomodulation via increased anti-inflammatory cytokine production and/or decreased expression of pro-inflammatory cytokines, chemokines and cell-surface adhesion molecules (23, 33); and reduced serum IGF-1 levels (21, 38). Reduced insulin/IGF-1 signaling is an evolutionarily conserved mechanism of longevity extension and stress resistance that could function through its pleiotropic effects on cytoprotective gene expression, granulocyte proliferation/priming and/or angiogenesis (11, 35, 38, 39). In the context of essential amino acid deprivation, reduced serum IGF-1 levels require the amino acid deprivation sensor GCN2 (21). Taken together, we conclude that very little is known about the molecular mechanisms underlying benefits of short-term DR, thus warranting further mechanistic studies. However, from what little we do know, functional benefits are likely derived from a complex range of organ autonomous and systemic mechanisms.

Short-term DR in humans

Does DR work in humans? Several recent randomized clinical trials indicate that humans on DR for 6 months to 2 years respond in similar ways to experimental mammalian models on long-term DR with respect to a variety of endpoints, including blood pressure, body weight, serum triglycerides and glucose metabolism (41, 42). Rigorous studies to probe the effects of short-term DR in humans have not been completed to date. Nonetheless, there are several reports suggesting feasibility and efficacy of short-term DR in the clinical setting, including in the contexts of surgery and chemotherapy.

In 1936, one year after McCay published his landmark findings on lifespan extension by DR in rodents (43), Hiram Studley published an influential paper concluding that preoperative weight loss of greater than 20% increases risk of perioperative mortality (44). Despite the lack of controls displaying pre-operative weight loss for reasons other than an underlying medical condition requiring surgery (gastric ulcer), the notion that weight loss prior to surgery is a risk factor took hold. Today, there are few dietary recommendations beyond the overnight fast, whose purpose is to avoid aspiration of regurgitated stomach contents while under anesthesia, and even this brief dietary restriction has its detractors (45).

Laparoscopic gastric bypass surgery is one of the few surgical procedures in which preoperative weight loss is routinely encouraged. The reason DR is used in this context is its ability to quickly and efficaciously reduce liver and intra-abdominal fat mass to facilitate the procedure, rather than intentionally to precondition the body against surgical stress (46). In a study of 298 patients, a 14-day very low-calorie diet (VLCD) before laparoscopic gastric bypass surgery reduced postoperative complications without affecting wound healing or infection rates (47). Interestingly, 4 days of a liquid VLCD can improve insulin sensitivity even in the absence of gastric bypass surgery (48).

While ischemia reperfusion injury underlying heart attack or stroke can be an unintended complication of almost any surgical intervention, it is a frequent co-morbidity of organ transplantation. In living organ donor transplantations, the only kind amenable to dietary preconditioning, short-term DR is feasible, safe and well tolerated by the donors (49). However because ischemia times are short and complications are rare in living organ donor procedures, large numbers would be required to observe any functional differences in a prospective clinical trial. Vascular surgeries have higher rates of complications, including heart attack and stroke, and thus may present a better opportunity in which to test the efficacy of short-term DR than living organ donor procedures (13).

In the context of chemotherapy, case studies show safety and efficacy of various fasting regimens (50). Fasting significantly reduces reports of fatigue, weakness, diarrhea and vomiting, but does not interfere with chemotherapeutic potency. Ongoing studies will demonstrate whether or not short-term DR will protect normal cells and sensitize tumors to chemotherapy.

Other examples of short-term DR

Stepping back from the DR experimental literature, we can find many examples of short-term DR practiced in the context of both religion and medicine. Ancient Greeks, the fathers of Western medicine, were practitioners of such techniques as therapeutic fasting. Although therapeutic fasting is still a common medical practice in some parts of the world, it has largely been lost from Western medical practice. However, fasting rituals remain a staple of most modern-day religions (51). What is the evidence, if any, of beneficial effects? During the month of Ramadan, adherents abstain from eating, drinking or smoking from sunrise to sunset. While some measures of lipid oxidation are improved in erythrocytes, most blood-

based measures of oxidative stress do not change (52). There could be numerous reasons for this, including detrimental effects of over-eating after fasting, or that the duration of the fasting periods are not long enough to induce benefits. Mormons have less heart disease than the Utah or US population in general. While protective lifestyle behaviors such as reduced tobacco use can explain some of the observed protection, routine fasting contributes to reduced coronary artery disease and diabetes (53). Such fasting is typically practiced one day per month, beginning as early as 8 years of age. Thus, at least under certain circumstances, repeated short-term DR can contribute to long-term benefits.

One final example of short-term DR comes from an unexpected area. In commercial hen houses, when egg production declines, birds may be induced to molt (lose their feathers) in order to increase subsequent egg production. One established technique to induce molting is to fast the animals, or to reduce their dietary nutrient intake, until their weight declines by approximately 30%, followed by refeeding. Data from small numbers of animals indicate that mortality rates decline upon nutrient deprivation in hens (54), resulting in increased survival for the duration of the study. Because commercial operations typically have very large numbers of hens of similar age under similar environmental conditions, there may be an untapped wealth of data to test the hypothesis that brief periods of DR have rapid benefits on health, including changes in the rate of increase in mortality.

Conclusions

Here we reviewed a growing body of evidence mostly in rodents and humans demonstrating that short-term DR has rapid, pleiotropic and largely beneficial effects on a number of metabolic, immunologic and stress-related endpoints. Much work remains to elucidate mechanisms underlying these effects in experimental models. However, given such immediate translational potential, why are clinical uses so rare? For a long time, the answer may have been that it takes too long for the benefits to accrue. Now we know that benefits can accrue rapidly in at least some contexts, and are thus faced with a new set of questions and challenges. For example, which systems benefit from total food deprivation, and which from protein withdrawal? What are the effects of the intensity of withdrawal, and of the duration? Many of these variables can be tested in experimental model systems, including rodents. However, moving to humans may require a “scaling factor” for such variables as duration and intensity of food restriction. Unfortunately, we don’t know what to base such a scaling factor on, nor do we have functional biomarkers of DR to help us cross species boundaries. Another non-mutually exclusive possibility is to test so-called DR mimetics, including metformin, rapamycin and resveratrol, for short-term benefits. These compounds elicit functional benefits also seen in DR without dietary alterations and could thus be more convenient in a clinical setting than even brief dietary interventions. Either way, clinical trials will be necessary. Yet despite these challenges, we seem closer than ever to translate short-term DR from the laboratory to the clinic.

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References

1. Speakman JR, Mitchell SE. Caloric restriction. *Mol Aspects Med.* 2011; 32:159–221. [PubMed: 21840335]

2. Gredilla R, Barja G. Minireview: the role of oxidative stress in relation to caloric restriction and longevity. *Endocrinology*. 2005; 146:3713–7. [PubMed: 15919745]
3. Mair W, Goymer P, Pletcher SD, et al. Demography of dietary restriction and death in *Drosophila*. *Science*. 2003; 301:1731–3. [PubMed: 14500985]
4. Dhahbi JM, Kim HJ, Mote PL, et al. Temporal linkage between the phenotypic and genomic responses to caloric restriction. *Proc Natl Acad Sci U S A*. 2004; 101:5524–9. [PubMed: 15044709]
5. Sinclair DA. Toward a unified theory of caloric restriction and longevity regulation. *Mech Ageing Dev*. 2005; 126:987–1002. [PubMed: 15893363]
6. Hine CM, Mitchell JR. NRF2 and the Phase II Response in Acute Stress Resistance Induced by Dietary Restriction. *J Clin Exp Pathol*. 2012; S4:004.
7. Weindruch R, Walford RL, Fligiel S, et al. The retardation of ageing in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake. *Journal of Nutrition*. 1986; 116:641–654. [PubMed: 3958810]
8. Masoro EJ. Subfield history: caloric restriction, slowing aging, and extending life. *Sci Aging Knowledge Environ*. 2003; 2003:RE2. [PubMed: 12844547]
9. Pamplona R, Barja G. Mitochondrial oxidative stress, aging and caloric restriction: the protein and methionine connection. *Biochim Biophys Acta*. 2006; 1757:496–508. [PubMed: 16574059]
10. Miller RA, Buehner G, Chang Y, et al. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. *Aging Cell*. 2005; 4:119–25. [PubMed: 15924568]
11. Mitchell JR, Verweij M, Brand K, et al. Short-term dietary restriction and fasting precondition against ischemia reperfusion injury in mice. *Aging Cell*. 2010; 9:40–53. [PubMed: 19878145]
12. Koubova J, Guarente L. How does calorie restriction work? *Genes Dev*. 2003; 17:313–21. [PubMed: 12569120]
13. Mitchell, JR.; Beckman, JA.; Nguyen, LL., et al. Surgery. Reducing elective vascular surgery perioperative risk with brief preoperative dietary restriction. in press
14. Chandrasekar B, Nelson JF, Colston JT, et al. Calorie restriction attenuates inflammatory responses to myocardial ischemia-reperfusion injury. *Am J Physiol Heart Circ Physiol*. 2001; 280:H2094–102. [PubMed: 11299211]
15. Yu ZF, Mattson MP. Dietary restriction and 2-deoxyglucose administration reduce focal ischemic brain damage and improve behavioral outcome: evidence for a preconditioning mechanism. *J Neurosci Res*. 1999; 57:830–9. [PubMed: 10467254]
16. Duan W, Mattson MP. Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease. *J Neurosci Res*. 1999; 57:195–206. [PubMed: 10398297]
17. Marie C, Bralet AM, Gueldry S, et al. Fasting prior to transient cerebral ischemia reduces delayed neuronal necrosis. *Metab Brain Dis*. 1990; 5:65–75. [PubMed: 2385215]
18. Schneider CA, Taegtmeier H. Fasting in vivo delays myocardial cell damage after brief periods of ischemia in the isolated working rat heart. *Circ Res*. 1991; 68:1045–50. [PubMed: 2009607]
19. Sumimoto R, Southard JH, Belzer FO. Livers from fasted rats acquire resistance to warm and cold ischemia injury. *Transplantation*. 1993; 55:728–32. [PubMed: 8475543]
20. Verweij M, van de Ven M, Mitchell JR, et al. Glucose supplementation does not interfere with fasting-induced protection against renal ischemia/reperfusion injury in mice. *Transplantation*. 2011; 92:752–8. [PubMed: 21926943]
21. Peng W, Robertson L, Gallinetti J, et al. Surgical stress resistance induced by single amino acid deprivation requires Gcn2 in mice. *Sci Transl Med*. 2012; 4:118ra11.
22. Wek SA, Zhu S, Wek RC. The Histidyl-tRNA Synthetase-Related Sequence in the eIF-2a Protein Kinase GCN2 Interacts with tRNA and Is Required for Activation in Response to Starvation for Different Amino Acid. *Molecular and Cellular Biology*. 1995; 15:4497–4506. [PubMed: 7623840]
23. Chiba T, Ezaki O. Dietary restriction suppresses inflammation and delays the onset of stroke in stroke-prone spontaneously hypertensive rats. *Biochem Biophys Res Commun*. 2010; 399:98–103. [PubMed: 20643106]

24. Yamagishi T, Bessho M, Yanagida S, et al. Severe, short-term food restriction improves cardiac function following ischemia/reperfusion in perfused rat hearts. *Heart Vessels*. 2010; 25:417–25. [PubMed: 20676965]
25. Langkamp-Henken B, Kudsk KA, Proctor KG. Fasting-induced reduction of intestinal reperfusion injury. *JPEN J Parenter Enteral Nutr*. 1995; 19:127–32. [PubMed: 7609277]
26. Verweij M, van Ginhoven TM, Mitchell JR, et al. Preoperative fasting protects mice against hepatic ischemia/reperfusion injury: mechanisms and effects on liver regeneration. *Liver Transpl*. 2011; 17:695–704. [PubMed: 21618690]
27. Sarac TP, Sax HC, Doerr R, et al. Preoperative fasting improves survival after 90% hepatectomy. *Arch Surg*. 1994; 129:729–33. [PubMed: 8024453]
28. Ueno C, Fukatsu K, Maeshima Y, et al. Dietary restriction compromises resistance to gut ischemia-reperfusion, despite reduction in circulating leukocyte activation. *JPEN J Parenter Enteral Nutr*. 2005; 29:345–51. discussion 351–2. [PubMed: 16107597]
29. Davis LM, Pauly JR, Readnower RD, et al. Fasting is neuroprotective following traumatic brain injury. *J Neurosci Res*. 2008; 86:1812–22. [PubMed: 18241053]
30. Plunet WT, Streijger F, Lam CK, et al. Dietary restriction started after spinal cord injury improves functional recovery. *Exp Neurol*. 2008; 213:28–35. [PubMed: 18585708]
31. Martin B, Mattson MP, Maudsley S. Caloric restriction and intermittent fasting: two potential diets for successful brain aging. *Ageing Res Rev*. 2006; 5:332–53. [PubMed: 16899414]
32. Hunt NH, Manduci N, Thumwood CM. Amelioration of murine cerebral malaria by dietary restriction. *Parasitology*. 1993; 107(Pt 5):471–6. [PubMed: 8295786]
33. MacDonald L, Radler M, Paolini AG, et al. Calorie restriction attenuates LPS-induced sickness behavior and shifts hypothalamic signaling pathways to an anti-inflammatory bias. *Am J Physiol Regul Integr Comp Physiol*. 2011; 301:R172–84. [PubMed: 21525175]
34. Kritchevsky D. Caloric restriction and experimental carcinogenesis. *Toxicol Sci*. 1999; 52:13–6. [PubMed: 10630585]
35. Mukherjee P, Abate LE, Seyfried TN. Antiangiogenic and proapoptotic effects of dietary restriction on experimental mouse and human brain tumors. *Clin Cancer Res*. 2004; 10:5622–9. [PubMed: 15328205]
36. Kalaany NY, Sabatini DM. Tumours with PI3K activation are resistant to dietary restriction. *Nature*. 2009; 458:725–31. [PubMed: 19279572]
37. Raffaghello L, Lee C, Safdie FM, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. *Proc Natl Acad Sci U S A*. 2008; 105:8215–20. [PubMed: 18378900]
38. Lee C, Safdie FM, Raffaghello L, et al. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. *Cancer Res*. 2010; 70:1564–72. [PubMed: 20145127]
39. Lee C, Raffaghello L, Brandhorst S, et al. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. *Sci Transl Med*. 2012; 4:124ra27.
40. Kozubik A, Pospisil M. Protective effect of intermittent fasting on the mortality of gamma-irradiated mice. *Strahlentherapie*. 1982; 158:734–8. [PubMed: 6761903]
41. Redman LM, Heilbronn LK, Martin CK, et al. Effect of calorie restriction with or without exercise on body composition and fat distribution. *J Clin Endocrinol Metab*. 2007; 92:865–72. [PubMed: 17200169]
42. Rochon J, Bales CW, Ravussin E, et al. Design and conduct of the CALERIE study: comprehensive assessment of the long-term effects of reducing intake of energy. *J Gerontol A Biol Sci Med Sci*. 2011; 66:97–108. [PubMed: 20923909]
43. McCay CM, Crowel MF, Maynard LA. The effect of retarded growth upon the length of the life span and upon the ultimate body size. *J Nutr*. 1935; 10:63–79.
44. Studley HO. Percentage of weight loss: a basic indicator of surgical risk in patients with chronic peptic ulcer. *JAMA*. 1936; 106:458–60.
45. Diks J, van Hoorn DE, Nijveldt RJ, et al. Preoperative fasting: an outdated concept? *JPEN J Parenter Enteral Nutr*. 2005; 29:298–304. [PubMed: 15961687]

46. Solomon H, Liu GY, Alami R, et al. Benefits to patients choosing preoperative weight loss in gastric bypass surgery: new results of a randomized trial. *J Am Coll Surg*. 2009; 208:241–5. [PubMed: 19228536]
47. Van Nieuwenhove Y, Dambraskas Z, Campillo-Soto A, et al. Preoperative very low-calorie diet and operative outcome after laparoscopic gastric bypass: a randomized multicenter study. *Arch Surg*. 2011; 146:1300–5. [PubMed: 22106323]
48. Isbell JM, Tamboli RA, Hansen EN, et al. The importance of caloric restriction in the early improvements in insulin sensitivity after Roux-en-Y gastric bypass surgery. *Diabetes Care*. 2010; 33:1438–42. [PubMed: 20368410]
49. van Ginhoven TM, de Bruin RW, Timmermans M, et al. Pre-operative dietary restriction is feasible in live-kidney donors. *Clin Transplant*. 2011; 25:486–94. [PubMed: 20718826]
50. Safdie FM, Dorff T, Quinn D, et al. Fasting and cancer treatment in humans: A case series report. *Aging (Albany NY)*. 2009; 1:988–1007. [PubMed: 20157582]
51. Trepanowski JF, Bloomer RJ. The impact of religious fasting on human health. *Nutr J*. 2010; 9:57. [PubMed: 21092212]
52. Ibrahim WH, Habib HM, Jarrar AH, et al. Effect of Ramadan fasting on markers of oxidative stress and serum biochemical markers of cellular damage in healthy subjects. *Ann Nutr Metab*. 2008; 53:175–81. [PubMed: 19011280]
53. Horne BD, May HT, Anderson JL, et al. Usefulness of routine periodic fasting to lower risk of coronary artery disease in patients undergoing coronary angiography. *Am J Cardiol*. 2008; 102:814–819. [PubMed: 18805103]
54. Webster AB. Behavior of white leghorn laying hens after withdrawal of feed. *Poult Sci*. 2000; 79:192–200. [PubMed: 10735746]

Highlights

- Short-term DR protects against multiple forms of acute stress
- Duration is typically up to a week in rodents
- Benefits may translate to clinical applications in humans

Figure 1.
Model for weight change characteristics upon initiation of DR.