Intermittent Fasting

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Fasting

Physiology

- Insulin secretion, which promotes the storage of glucose in the liver and muscle as glycogen, is stimulated by feeding in non-diabetic individuals.

- During fasting, circulating glucose levels fall, leading to decreased secretion of insulin.

- Concurrently, levels of glucagon and catecholamines rise, stimulating the breakdown of glycogen and gluconeogenesis.

- As fasting becomes prolonged for more than several hours, glycogen stores become depleted and there is increased fatty acid release from adipocytes.

Fasting

Physiology

- Oxidation of fatty acids generates ketones that can be used as fuel by skeletal and cardiac muscle, liver kidney and adipose tissue, sparing glucose for continued utilisation by brain and erythrocytes.

- result in ketogenesis
promotes potent changes in metabolic pathways and adaptive cellular responses that reduce oxidative damage and inflammation, optimize energy metabolism, and bolster cellular protection.

Fasting

Molecular mechanisms of its health promoting effects

- Prolonged fasting

-strong physiological stimulus

-activates endocrine and neurobiological responses

：neuroendocrine activation

: hormetic stress response

: increased production of neurotropic factors

: reduced mitochondrial oxidative stress

: decrease of signals associated with aging

: promotion of autophagy

Forschende Komplementarmedizin 2013;20:444-453

Several general hypothesis

1) stress-resistance hypothesis: adaptive cellular stress responses

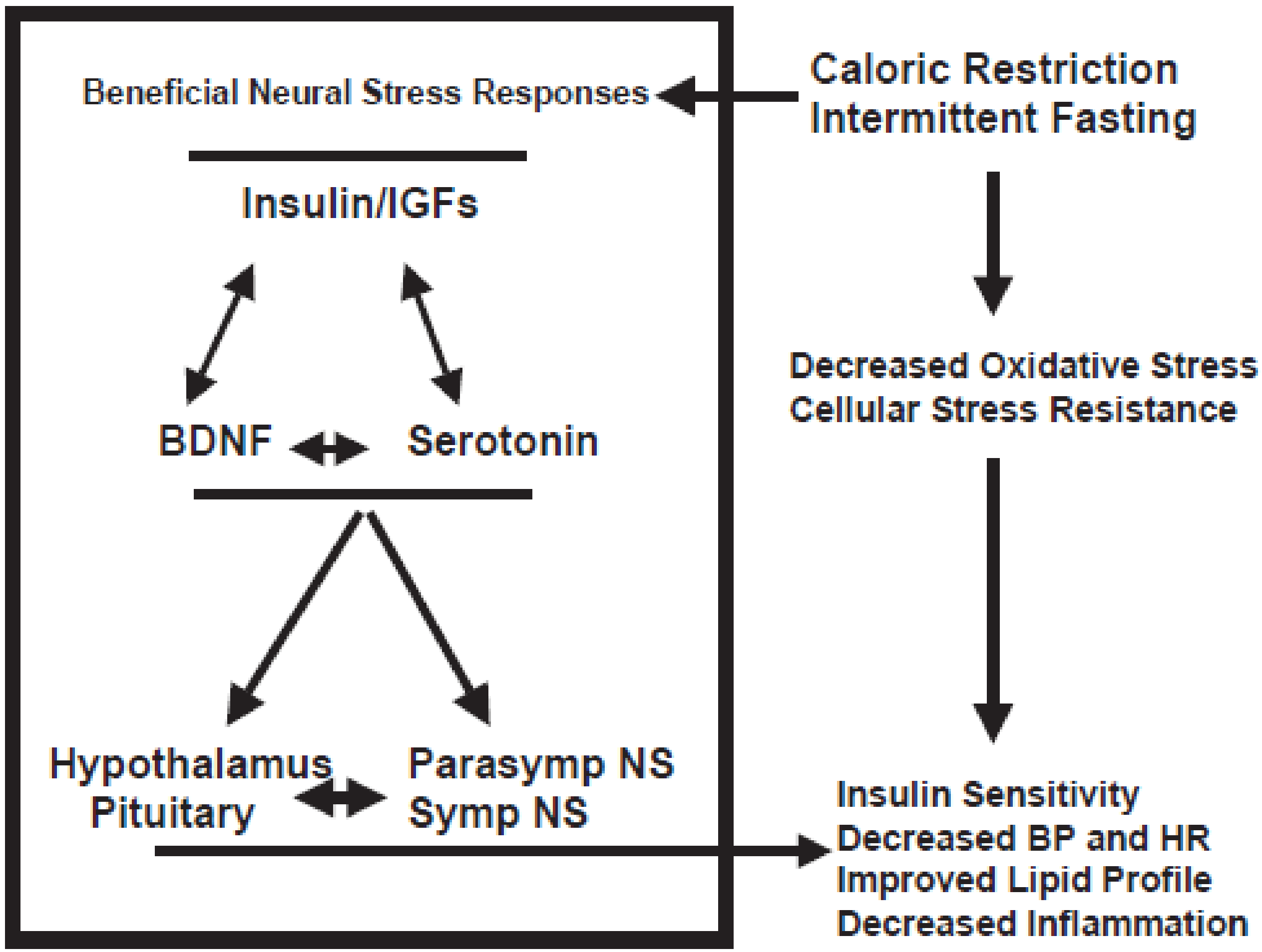
2) oxidative stress hypothesis

3) Induction of a scarcity program hypothesis

4) autophage

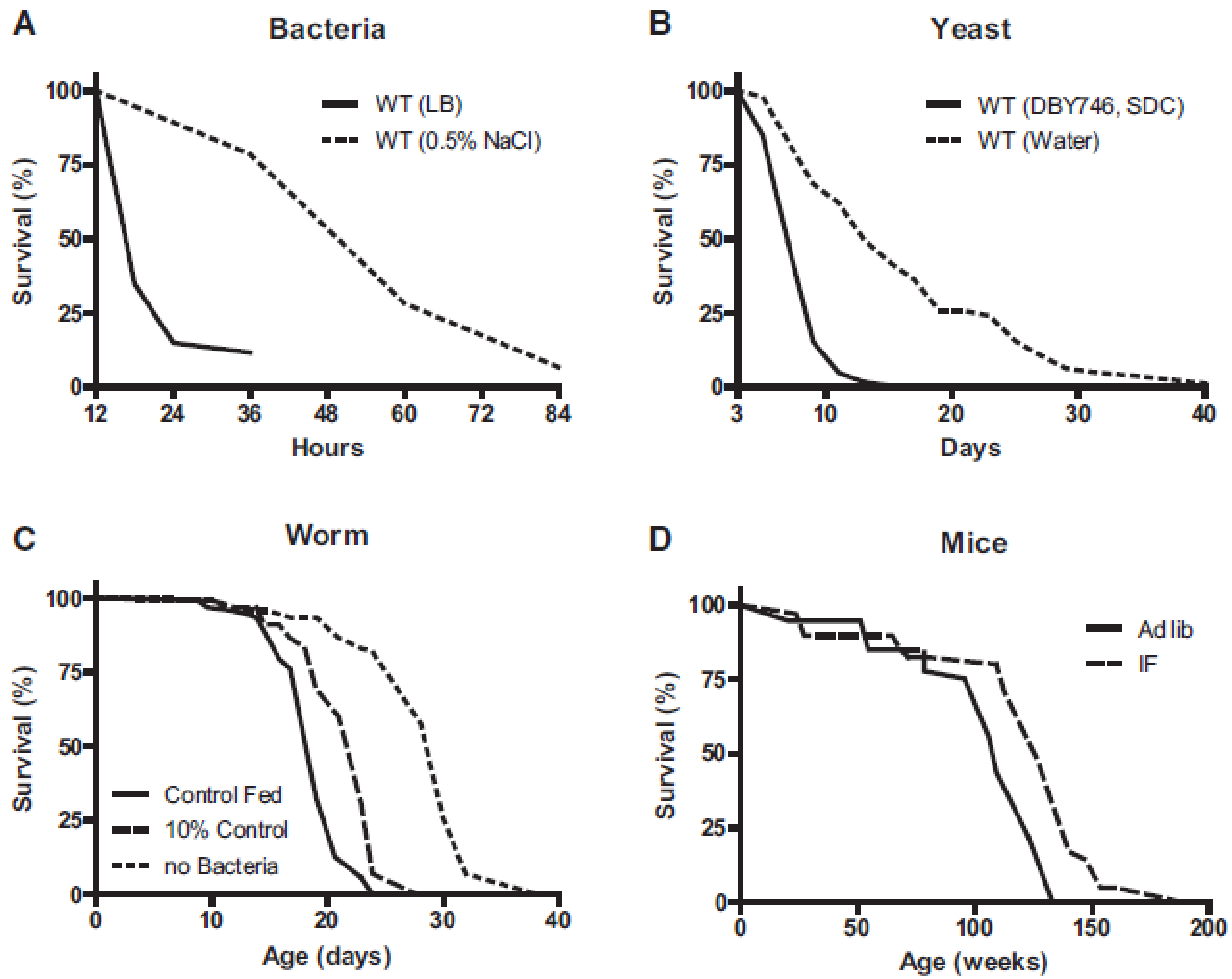
5) AGEs

Model of mechanisms by which DR may decrease the risk of CVD and stroke.



J Nutr Biochem 2005;16:129-137

Fasting extends lifespans of Bacteria, Yeast, Worms, and Mice



Cell Metabolism 2014;19:181

Fasting

: ingestion no or minimal amounts of food and caloric beverages for periods (from 12 hr to 3 wks)

: many religious groups

: in many clinics (water only or VLCD <200 kcal) for weight management and for disease treatment or prevention

Caloric restriction

: daily caloric intake is reduced chronically by 20-40% without malnutrition, but meal frequency is maintained

Starvation

: chronic nutritional insufficiency-extreme forms of fasting

: results in degeneration and death

Main types of fasting

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

Forsch Komplementmed 2013;20:444-453

Caloric restriction (CR)

- Only non-genetic intervention that has consistently shown to slow the intrinsic rate of aging in mammals
- Reduction in caloric intake while maintaining essential nutrient requirements
- Reduction in caloric intake by ~40%-which results in a 30-40% increase in maximum lifespan
- Many health benefits

  : prevents CVD, cancer, diabetes, neurogenerative ds, autoimmune disorders
- Despite the “magic” of CR, long-term CR in humans will fall short of the expectations as our “fountain of youth”

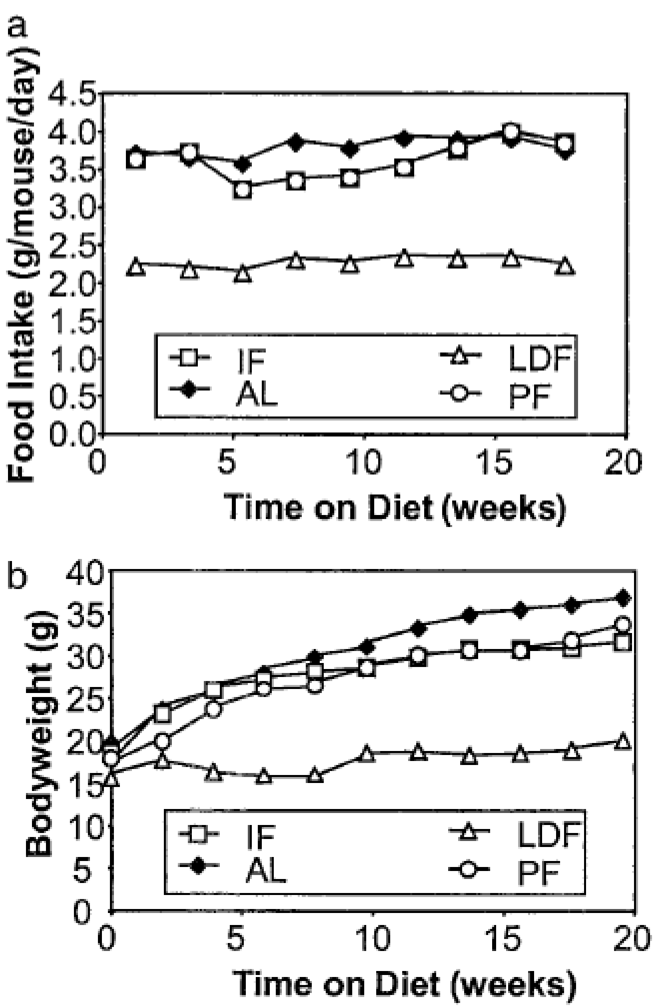
Health concerns of CR in humans

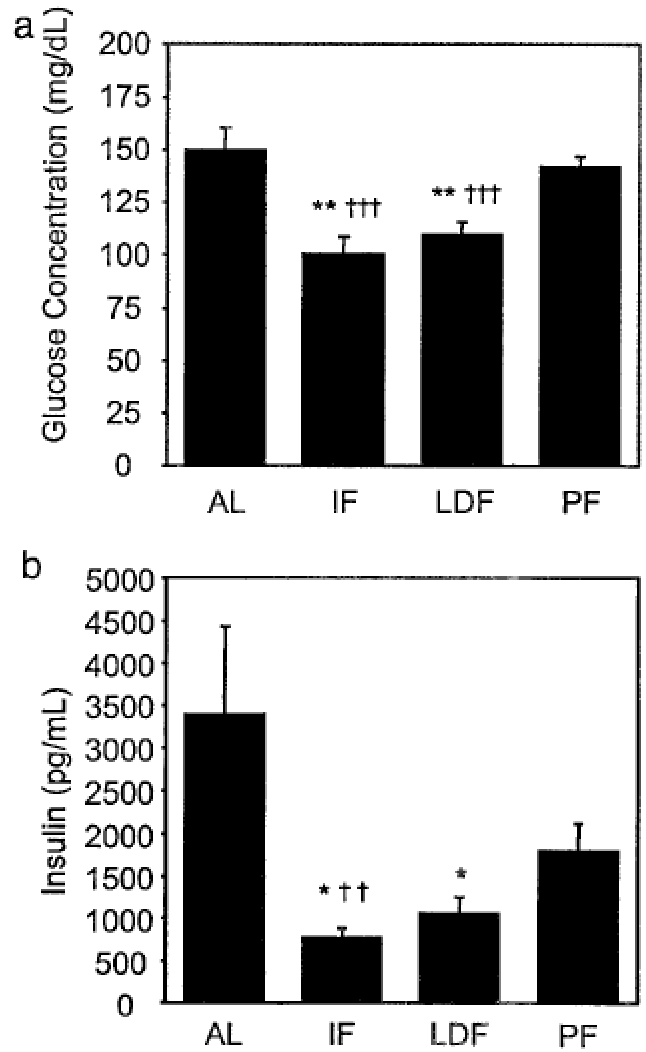
- Excessive loss of fat mass and muscle mass
- Experience hypotension, loss of libido, menstrual irregularities, infertility, bone thinning, osteoporosis, cold sensitivity, loss of strength and stamina, slower wound healing, depression, irritability

=>aside from the potential S/E,
classical CR is difficult for humans to maintain

- In animal models, intermittent energy restriction is superior or equivalent to daily energy restriction with respect to longevity, the reduction of cancers, and the reduction of CVD and dementia.

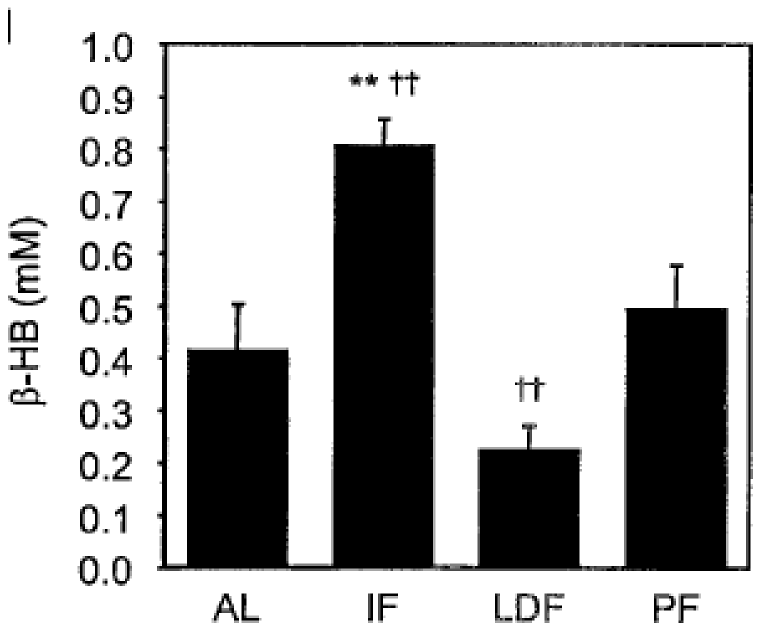
Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake

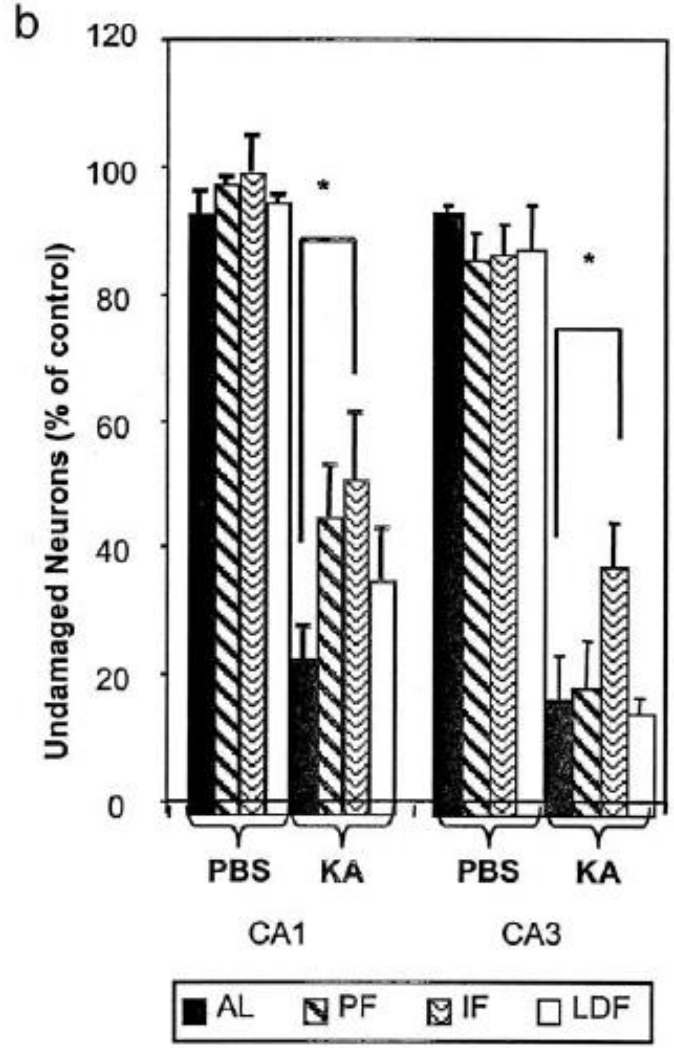




LDF; limited daily feeding

PNAS 2003;100:6216-6220





PNAS 2003;100:6216-6220

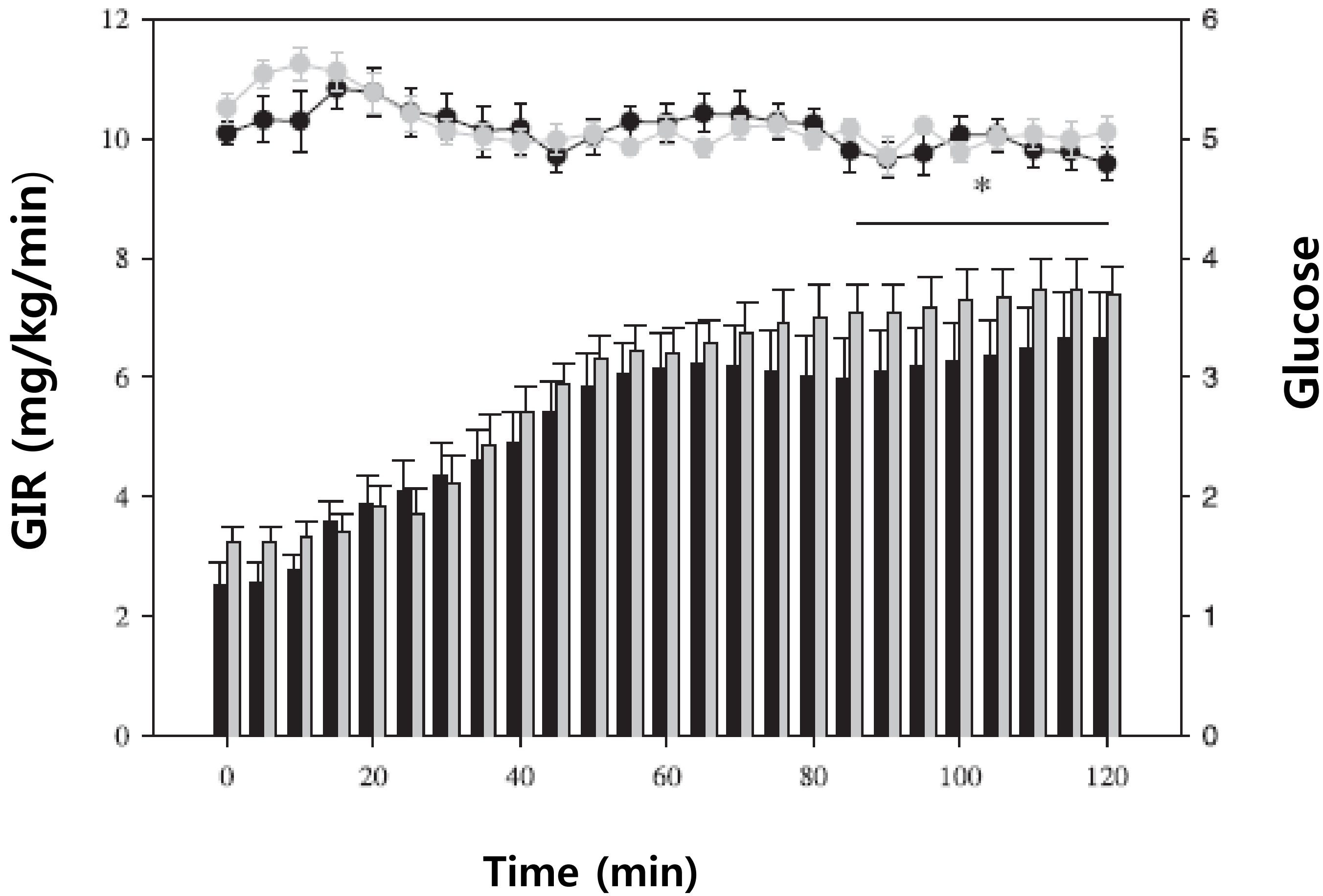
Effect of intermittent fasting and refeeding on insulin action in healthy men

Anti-MS effects of IF were also observed in healthy young men after 15 days of ADF: adiponectin 증가, whole body glucose uptake rates increased (Halberg et al 2005)

-8 healthy young men [25 years, BMI 25.7]
-IF every second day for 20 h for 15 days
-euglycemic hyperinsulinemic clamps before and after intervention period
-the first in human to show that IF increases insulin mediated glucose uptake rates
-no change in Bwt

J Appl Physiol 2005;99:2128-2136

Glucose infusion rate and glucose concentrations during the clamps before and after IF for 15 days



Alternate-day fasting in <u>nonobese subjects</u>: effects on body weight, body composition, and energy metabolism

Three weeks of ADF resulted in reductions in Body fat and insulin levels in normal weight men and women (Heilbronn et al 2005)

-Nonobese subjects 16 (8 women, 8 men; BMI 23)
-IF for 22 days
-fasting insulin decreased and fat oxidation increased
-Bwt decreased by 2%, TG decreased only in men
-But, hunger on fasting days did not decrease, perhaps indicating the unlikelihood of continuing this diet for extended periods of time.
-Adding one small meal on a fasting day may more acceptable

Am J Clin Nutr 2005;81:69-73

“fasting prescriptions”

Several variations of potential fasting-based interventions

- Alternate day fasting (ADF) diet
- “5:2” IF diet
- Modified Alternate day fasting (ADF) diet
- “Time-restricted feeding (TRF)”: 10-12 hour TRF window =Ramadan trials
- 4-5 day fast
- Low-calorie-but high nourishment fasting-mimicking diets once every 1-3 months followed by the skipping of one major meal every day

Typical intermittent fasting plan: 5:2 IF

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Normal	Normal	Fasting	Normal	Fasting	Normal	Normal
TDEE	TDEE	500 (female) 600 (male)	TDEE	500 (female) 600 (male)	TDEE	TDEE

Calories (per day)

TDEE = total daily energy expenditure

Brit J Diab Vasc Dis 2013; 13:68-72

Alternate-day fasting (ADF)

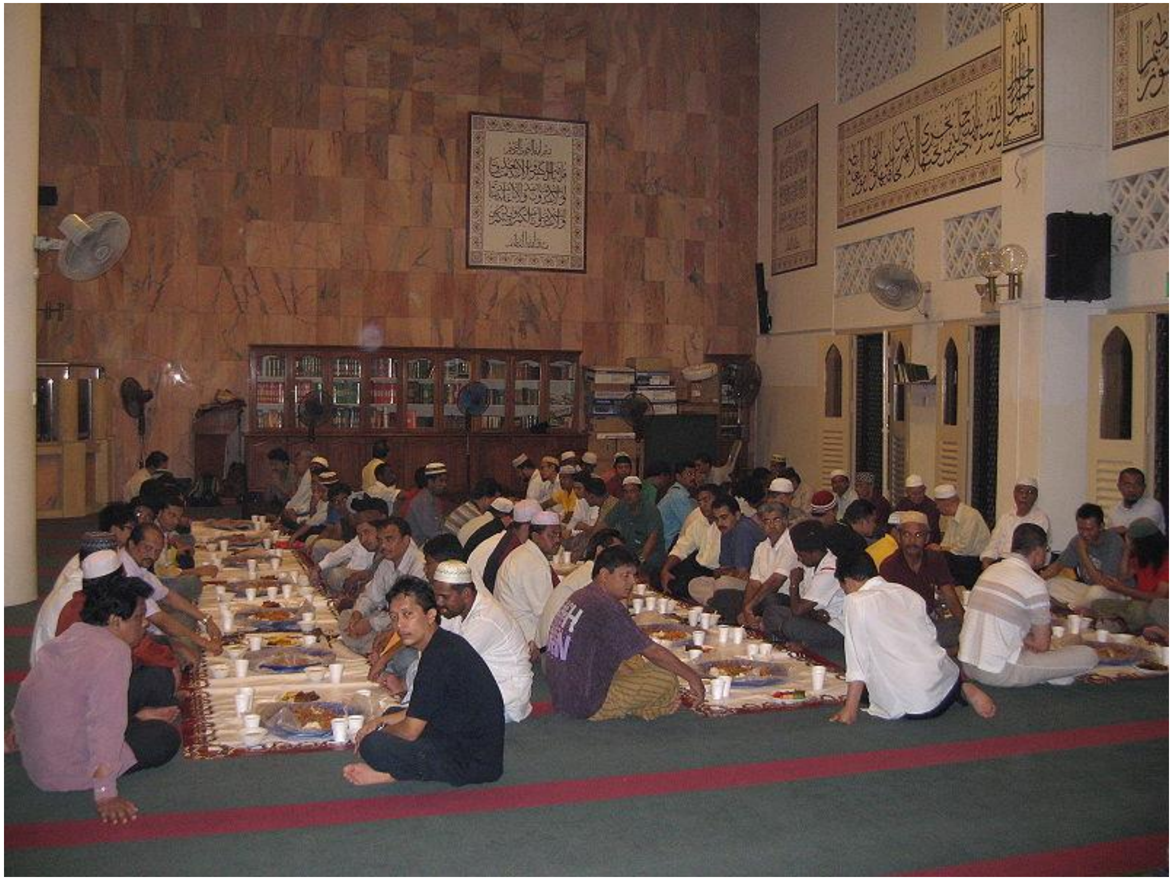
- Key point about the alternate-day fasting (ADF) approach is that overall calorie intake need not to be limited; instead, the frequency of food consumption is altered
- Consist of a “feed day” (ad libitum food intake for 24h) altered with a “fast day” (complete fast for 24h)
- Modified ADF regimens : allow for the consumption of 20-25% of energy needs on the fast day

10-12 hour TRF window

Reference	Subjects	Trial length	Intervention	Weight (% change)	Lipid factors (% change)				Change in glucoregulatory factors
					TC	LDL-C	HDL-C	TG	
4 h feeding window									
Halberg et al. (2005)[22]	n = 8, M 25 ± 1 y Overweight	2 wk	4-h TRF Every other day	Ø	–	–	–	–	↑ Glucose uptake* ↑ Insulin suppression of lipolysis*
Soeters et al. (2009)[23]	n = 8, M 20–30 y Normal weight	2 wk	4-h TRF Every other day	Ø	–	–	–	–	Ø Insulin sensitivity Ø Insulin suppression of lipolysis
7–8 h feeding window									
Ravanshad et al. (1999)[24]	n = 91, M 16–76 y Normal weight	4 wk	7-h TRF	Ø	Ø	–	–	Ø	↓27% Glucose*
Aksungar et al. (2007)[25]	n = 40, M & F 20–39 y Normal weight	4 wk	8-h TRF	Ø	Ø	Ø	Ø	Ø	–
Temizhan et al. (2000)[26]	n = 52, M & F 33 ± 10 y Normal weight	4 wk	8-h TRF	↓5% M* ↓5% F*	↓8% M* ↓10% F*	↓11% M* ↓12% F*	↑3% M* ↑2% F*	↓19 M* ↓29% F*	↑18% Glucose M* ↑22% Glucose F*
10–12 h feeding window									
Nematy et al. (2012)[27]	n = 82, M & F 29–70 y Overweight	4 wk	10-h TRF	↓2%*	↓5%*	↓12%*	↑11%*	↓19%*	Ø Glucose
LeCheminant et al. (2013)[28]	n = 29, M 23 ± 1 y Normal weight	2 wk	12-h TRF	↓1%*	–	–	–	–	–
Adlouni et al. (1997)[29]	n = 32, M 25–50 y Normal weight	4 wk	12-h TRF	↓3%*	↓8%*	↓12%*	↑14%*	↓30%*	↓14% Glucose*
Fakhrzadeh et al. (2003)[30]	n = 91, M & F 30 ± 4 y Normal weight	4 wk	12-h TRF	↓2% M* ↓2% F*	↓24% M* ↓29% F*	↓37% M* ↓35% M*	↑21% M* ↑31% F*	↓37% M* ↓19% F*	↓31% Glucose M* ↓27% Glucose F*
Zare et al. (2011)[31]	n = 32, M 23–37 y Healthy	4 wk	12-h TRF	↓2%*	↓6%*	↓9%*	↑15%*	↓4%*	–
Ziaee et al. (2006)[32]	n = 81, M & F 20–35 y Normal weight	4 wk	12-h TRF	↓2%*	Ø	↑4%*	↓9%*	Ø	↓10% Glucose*

Nutrition Review 2014;72:308-318

Ramadan



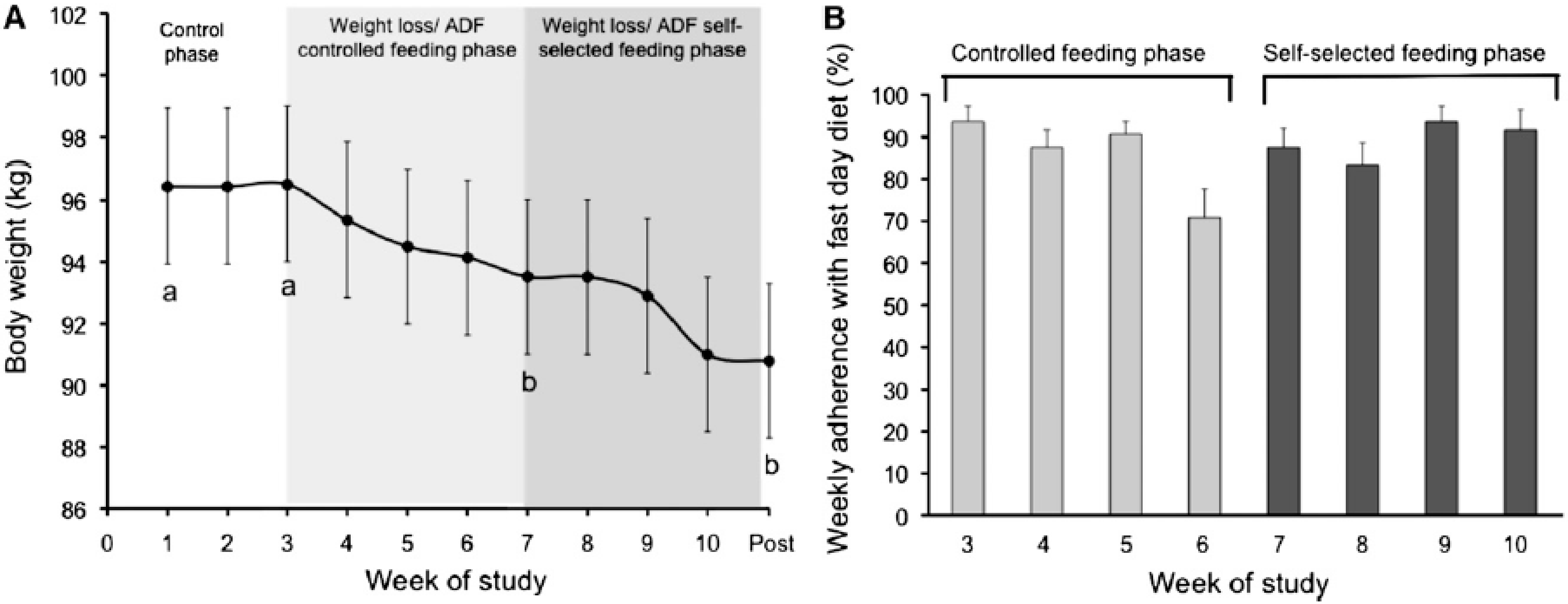
Short-term modified alternate-day fasting: a novel dietary strategy for weight loss and cardioprotection in obese adult

Body fat and BP were reduced and glucose metabolism improved in obese subjects in response to an ADF (Varady et al 2009)

-16 obese subjects (12 women, 4 men)
-Modified ADF : consuming 25% of energy needs on the fast day
-10 week trial, 3 phase
    A 2-wk control phase
    A 4-wk wt loss/ADF controlled food intake phase
    A 4-wk wt loss/ADF self-selected food intake phase
-Improve CAD risk factors (lipid profiles, SBP, HR)

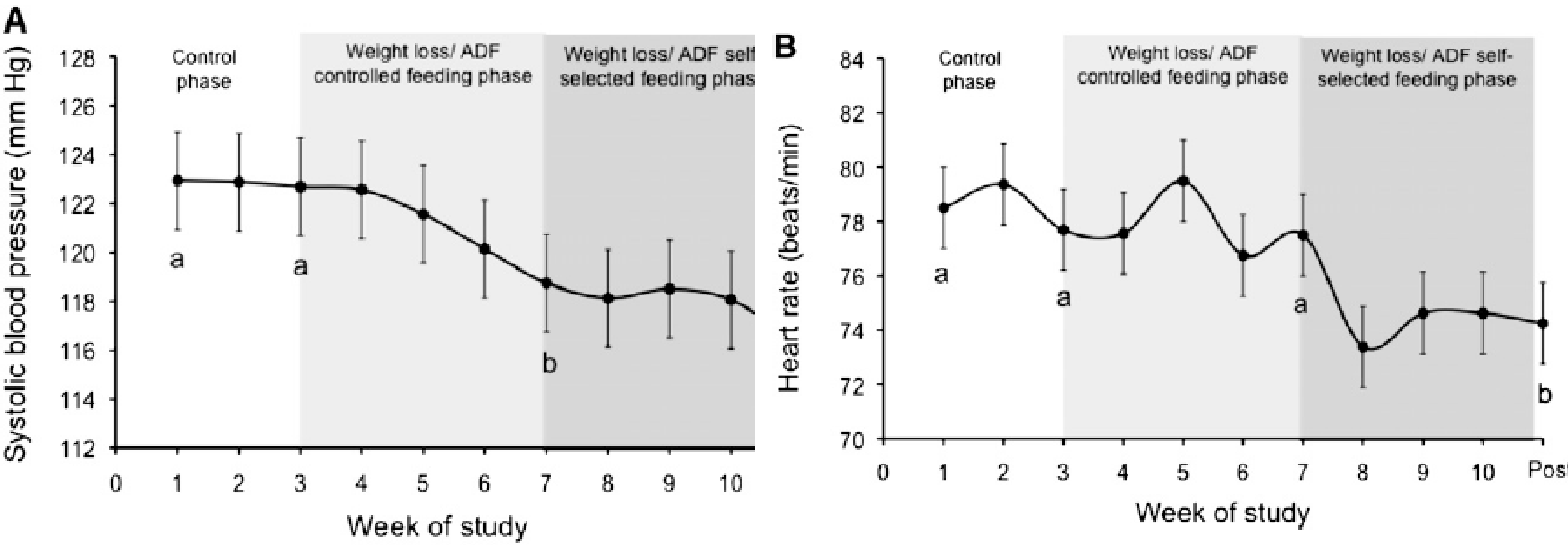
Am J Clin Nutr 2009;90:1138-1143

Mean body wt and percentage adherence during the 10-wk trial



Am J Clin Nutr 2009;90:1138-1143

Mean SBP and HR during the 10-wk trial



Am J Clin Nutr 2009;90:1138-1143

Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial

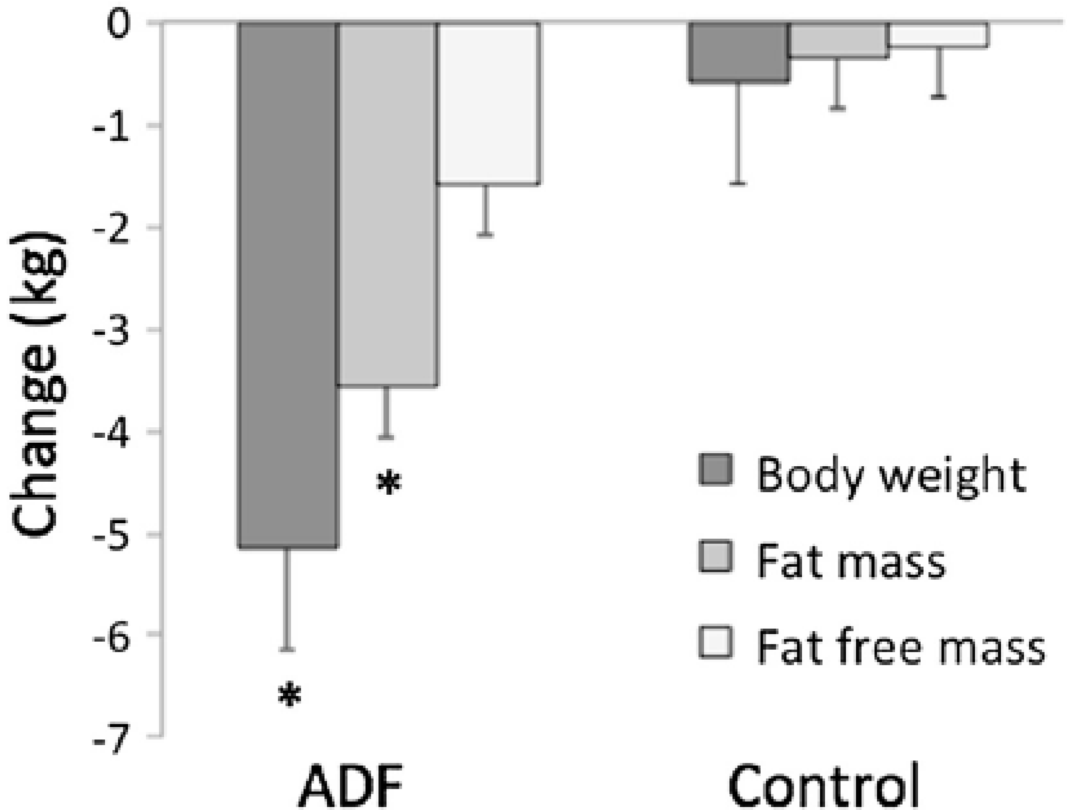
-32 subjects (BMI 20-29.9)

-ADF : consume 25% of their baseline energy needs on the fast day (400-600 kcal), ad libitum at home on the feed day

-In the ADF group vs control
: TG, CRP decreased,
LDL particle size increased, adiponectin increased

Nutrition J 2013;12:146

Body wt and body composition changes at week 12



Nutrition J 2013;12:146

Relative effects of Calorie Restriction and Weight Loss in NIDDM

-In obese T2DM subjets, a 7-day period of CR produces approximately half of the overall improvement in HGP, IS, and insulin secretion that is obatained after a substantial loss of weight.

-CR has an important regulatory effect on the metabolism of obese T2DM that is independent of wt loss

JCEM 1993;77:1287-1293

A Population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries : (EPIDIAR) Study -12,914 patients(8.7%T1DM)

RESEARCH DESIGN AND METHODS — This was a population-based, retrospective, transversal survey conducted in 13 countries. A total of 12,914 patients with diabetes were recruited using a stratified sampling method, and 12,243 were considered for the analysis.

RESULTS — Investigators recruited 1,070 (8.7%) patients with type 1 diabetes and 11,173 (91.3%) patients with type 2 diabetes. During Ramadan, 42.8% of patients with type 1 diabetes and 78.7% with type 2 diabetes fasted for at least 15 days. Less than 50% of the whole population changed their treatment dose (approximately one-fourth of patients treated with oral antidiabetic drugs [OADs] and one-third of patients using insulin). Severe hypoglycemic episodes were significantly more frequent during Ramadan compared with other months (type 1 diabetes, 0.14 vs. 0.03 episode/month, $P = 0.0174$; type 2 diabetes, 0.03 vs. 0.004 episode/month, $P < 0.0001$). Severe hypoglycemia was more frequent in subjects who changed their dose of OADs or insulin or modified their level of physical activity.

Diabetes Care 2004;27:2306-2311

Categories of risk in patients with T1DM or T2DM who fast during Ramadan

Very high risk

- Severe hypoglycaemia within 3 months
- Recurrent hypoglycemia
- Hypoglycaemic unawareness
- Poor glycaemic control
- Ketoacidosis within the 3 months
- T1DM
- Hyperosmolar hyperglycemia in preceding 3 months
- Acute illness
- Performing intense physical labor
- Pregnancy
- Chronic dialysis

High risk

- Moderate hyperglycemia
- Renal insufficiency
- Advanced macrovascular Cx
- Living alone and tx insulin or SU
- Old age with ill health
- Patients with comorbid
- Tx with drugs that may affect mentation

Diabetes Care 2010;33:1895:1902

Low risk

- Well controlled type 2 diabetes mellitus
  - Lowest risk in patients treated with
    - lifestyle therapy,
    - metformin,
    - acarbose,
    - thiazolidinediones and/or
    - incretin-based therapies

in otherwise healthy individuals.

Recommended changes to treatment regimen in patients with T2DM who fast during Ramadan

Before Ramadan	During Ramadan
Patients on diet and exercise control	Consider modifying the time and intensity of physical activity; ensure adequate fluid intake
Patients on oral hypoglycemic agents	Ensure adequate fluid intake
Biguanide, metformin 500 mg, three times daily	Metformin, 1,000 mg at the sunset meal, 500 mg at the predawn meal
TZDs, AGIs, or incretin-based therapies	No change needed
Sulfonylureas once a day	Dose should be given before the sunset meal; adjust the dose based on the glycemic control and the risk of hypoglycemia
Sulfonylureas twice a day	Use half the usual morning dose at the predawn meal and the usual dose at sunset meal
Patients on insulin	Ensure adequate fluid intake
Premixed or intermediate-acting insulin twice daily	Consider changing to long-acting or intermediate insulin in the evening and short or rapid-acting insulin with meals; take usual dose at sunset meal and half usual dose at predawn meal

Diabetes Care 2010;33:1895:1902

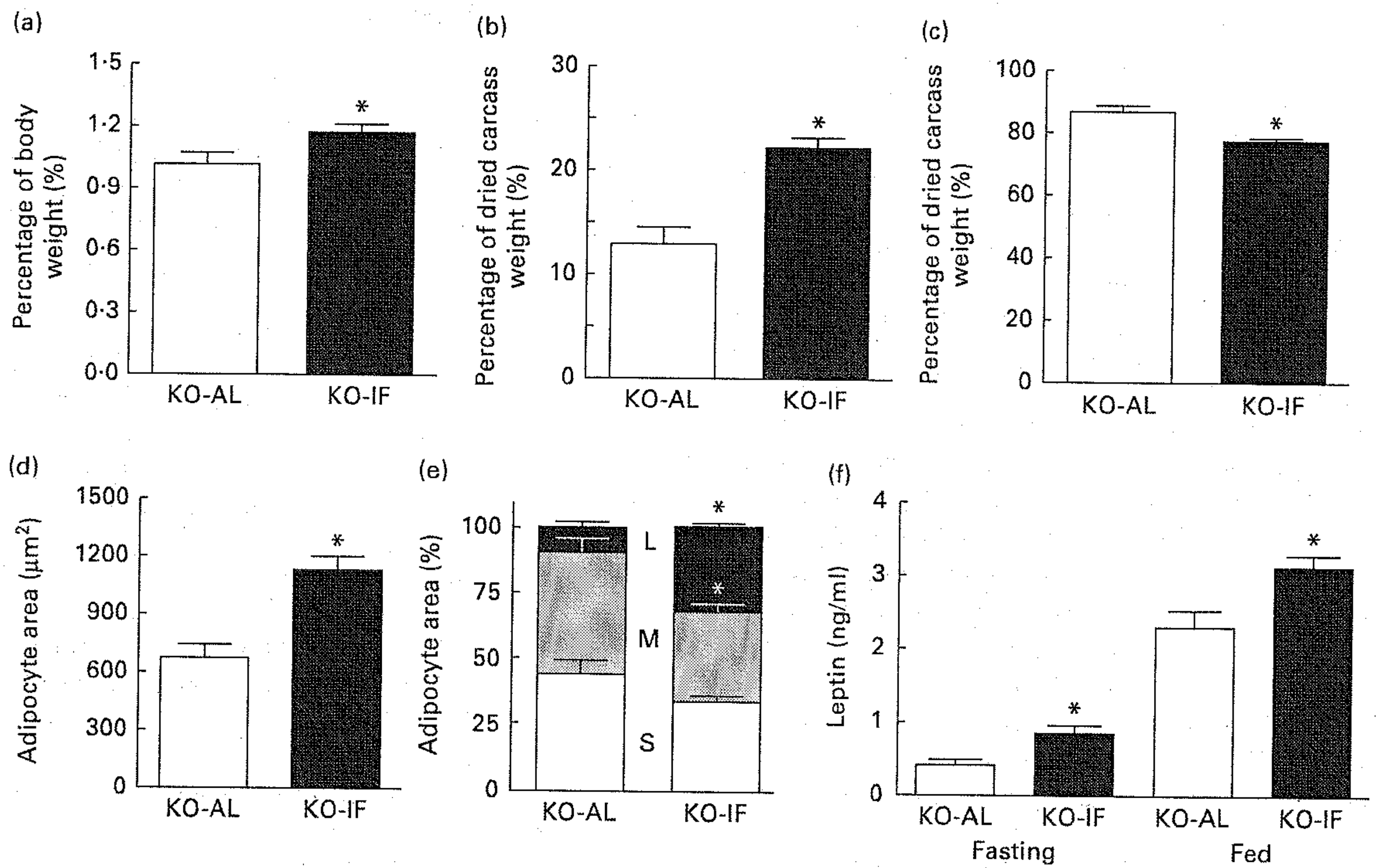
Effect of ADF on T2DM risk

Human trials

Reference	Subjects	Trial length	ADF protocol	DM
Heilbronn et al	n = 16 Normal-weight men and women Age 20–55 y	3 wk	Fast day: 24-h fast Feast day: ad libitum feeding No control group	Glucose clearance: ↓ (women), none (men) Insulin sensitivity: none (women), ↑ [2] (men)
Heilbronn et al	n = 16 Normal-weight men and women Age 20–55 y	3 wk	Fast day: 24-h fast Feast day: ad libitum feeding No control group	Fasting glucose: none Fasting insulin after 32-h fast: ↓ [2]
Halberg et al, 2	n = 8 Normal-weight men Age 25 ± 1.0 y	2 wk	Fast day: 20-h fast (2200–1800) Feast day: ad libitum feeding No control group	Insulin-mediated glucose uptake: ↑ [2] Insulin-induced lipolysis inhibition: ↑ [2] Fasting glucose: none Fasting insulin: none IMTG: none

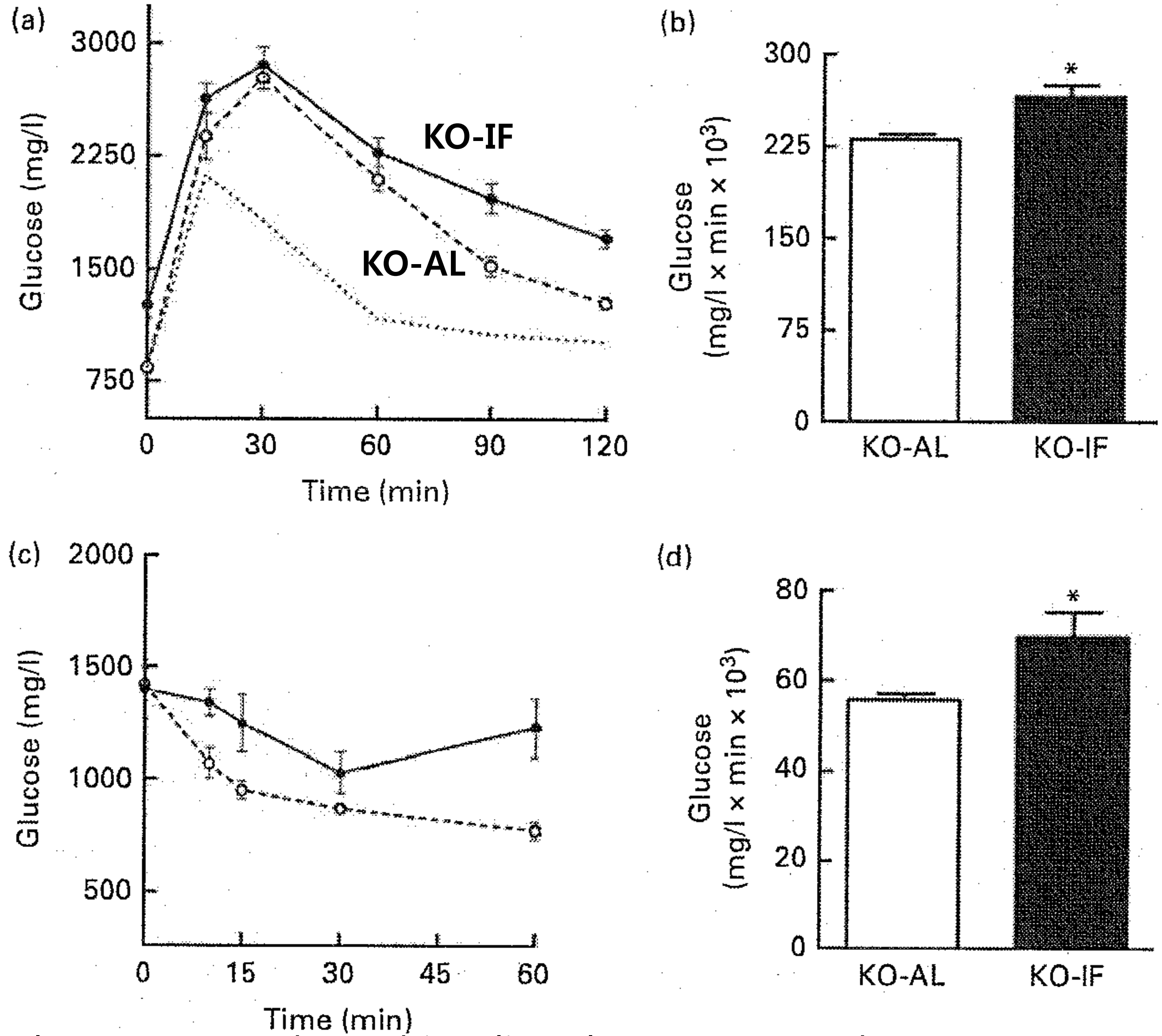
Am J Clin Nutr 2007;86:7-13

Food restriction by intermittent fasting induces diabetes and obesity and aggravates spontaneous atherosclerosis development in hypercholesterolaemic mice



KO: LDL-receptor knockout mice

Brit J Nutr 2014;111:979-986



Glucose tolerance test (a,b) and insulin tolerance test (c,d)

Meal frequency without CR

Despite a general perception among the public at large that it is important to eat ≥3 meals/d, no controlled studies have directly compared the effects of different meal frequencies on human health

Beneficial metabolic effects of regular meal frequency on dietary thermogenesis, insulin sensitivity, and fasting lipid profiles in healthy obese women

-Ten women [BMI 37], randomized crossover trial
-In phase 1 (14 d), regular meal pattern 6 occasions/d or
followed irregular meal pattern 3-9 meals/d
-In phase 2 (14 d), alternative pattern
-Regular eating : associated with lower EI,
greater postprandial thermogenesis,
lower total and LDL-C
lower peak insulin concentrations to the test meal

Am J Clin Nutr 2005;81:16-24

A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults

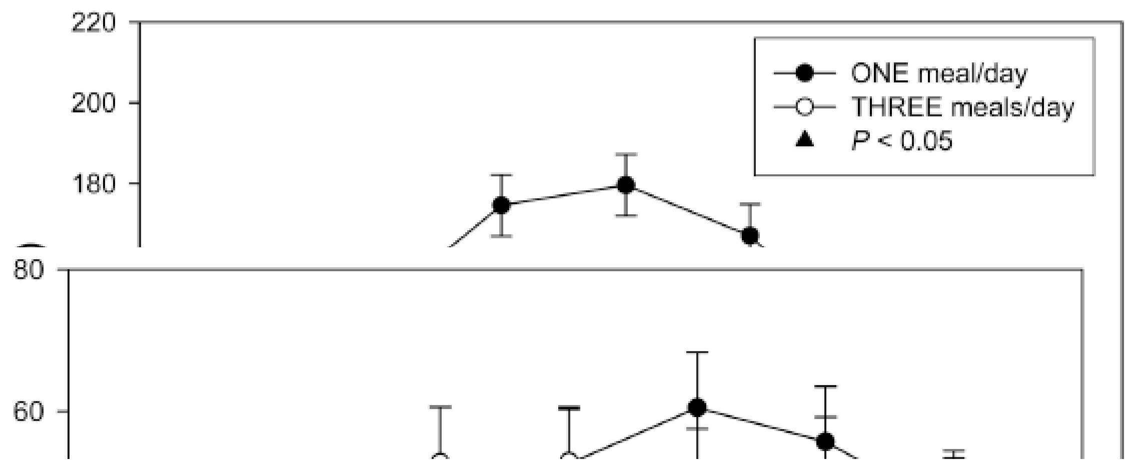
-randomized crossover design with two 8-wk treatment (n=21)
-consumed all of the calories needed for wt maintenance in either 3 meals/d (2429kcal), or 1 meal/d (2364kcal) (pm 5-pm 9)
-withdrawal rate : 28%
-1 meal/d : increase in hunger,
reduction of weight and fat mass
increases in BP, T-chol, LDL-C, HDL-C
-normal-weight subjects are able to comply with a 1 meal/d diet

Am J Clin Nutr 2007;85:981-988

Impact of reduced meal frequency without caloric restriction on glucose regulation in healthy, normal weight middle-aged men and women

-randomized cross-over design, two 8-wk treatment periods
-either 3 meals/d or 1 meal/d (pm 5-pm 9)
-n=15, BMI 18-25
-by OGTT; plasma glucose, insulin response, adipokine…
-1 meal/d : exhibit elevated fasting glucose levels
impaired glucose tolerance with a delayed insulin response not associated with alterations in the levels of adipokines

Metabolism 2007;56:1729-1734



	One Meal	Three Meals	P[2]
Glucose mg/dl	95.9 ± 1.7	85.4 ± 1.7	0.0002
Insulin µU/ml	5.0 ± 0.7	5.8 ± 0.7	0.4329
Glucagon pg/ml	66.5 ± 7.7	62.1 ± 7.4	0.6878
HOMA-IR	1.2 ± 0.2	1.3 ± 0.2	0.8718
OGIS	403.4 ± 14.0	458.8 ± 13.9	0.0114
ISI	0.1 ± 0.004	0.1 ± 0.004	0.6552
MCR	8.8 ± 0.3	9.2 ± 0.3	0.4011
β-cell function 1st phase	782.1 ± 66.0	1013.85 ± 66.1	0.0209
β-cell function 2nd phase	239.0 ± 19.0	253.7 ± 19.0	0.5894
Adiponectin pg/ml	13.5 ± 1.3	13.5 ± 1.3	0.9919
Resistin ng/ml	3.1 ± 0.3	2.8 ± 0.2	0.4147
Leptin ng/ml	20.2 ± 2.2	16.1 ± 2.1	0.18
Ghrelin pg/ml	163.2 ± 12.8	158.4 ± 12.8	0.7942
BDNF ng/ml	141.7 ± 26.7	148.1 ± 26.6	0.8175

Higher meal frequencies and regular breakfast consumption are inversely associated with obesity in youth….

Associations of meal frequency and breakfast with obesity and metabolic syndrome traits in adolescents of Northern Finland Birth Cohort 1986

Five meals/day including breakfast (regular)
Four meals/day including breakfast (semi-regular)
Four meals or less/day without breakfast (breakfast skipping)
: five meals/d pattern was robustly associated with reduced risk of overweight/obesity in both genders and abdominal obesity in boys [OR for boys; 0.41, girls;0.63, boys; 0.32]

Nutr, Metab & Cardio Dis 2013;23:1002-1009

Meal frequencies modify the effect of common genetic variants on BMI in adolescents of the Northern Finland Birth Cohort 1986

=regular five-meal-a-day pattern attenuates the effects of risk alleles on genetic susceptibility to increased BMI.

PLOS one 2013;8:e73802

Skipping breakfast and prevalence of overweight and obesity in Asian and Pacific regions: A meta-analysis

- 19 studies (93,108 total participants and 19,270 overweight or obese)

- The pooled OR of overwt or obesity for the lowest vs highest category of breakfast frequency was **1.75.**

- Promoting the eating of breakfast in all populations may be beneficial.

Preventive Medicine 2011;53:260-267

Int. J. Mol. Sci. **2013**, *14*, 6903-6919; doi:10.3390/ijms14046903

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Article

Beneficial Effects of the RESMENA Dietary Pattern on Oxidative Stress in Patients Suffering from Metabolic Syndrome with Hyperglycemia Are Associated to Dietary TAC and Fruit Consumption

Rocio de la Iglesia [1], Patricia Lopez-Legarrea [1], Paloma Celada [2], Francisco J. Sánchez-Muniz [2], J. Alfredo Martinez [1,3,*] and M. Angeles Zulet [1,3]

RESMENA (Metabolic Syndrome Reduction in Navarra) diet based on a different macronutrient distribution (30% proteins, 30% lipids, 40% carbohydrates), which was characterized by an increase of the **meal frequency (7 times/d),** low glycemic load, high antioxicant capacity and high n-3 fatty acids content.

Poor breakfast habits in adolescence predict the metabolic syndrome in adulthood

-Nothern Swedish Cohort, a longitudinal population-based cohort with 27-year f/u

-Poor breakfast habits were defined as skipping breakfast or only drinking or eating something sweet

-Adjusted OR for the MS at age 43 yrs was **1.68** for those with poor breakfast habits at age 16 yrs compared with breakfast eaters

Public Health Nutrition 2014

Fasting and MS

Overweight subjects maintained for 6 months on a twice weekly IF diet in which they consumed only 500-600 kcal on the fasting days, lost abdmoninal fat, displayed improved IS, and reduced BP (Harvie et al 2011)

Subjects undergoing coronary angiography who reported that they fasted regulary exhibited a lower prevalence of diabetes compared to nonfasters (Horne et al 2005)

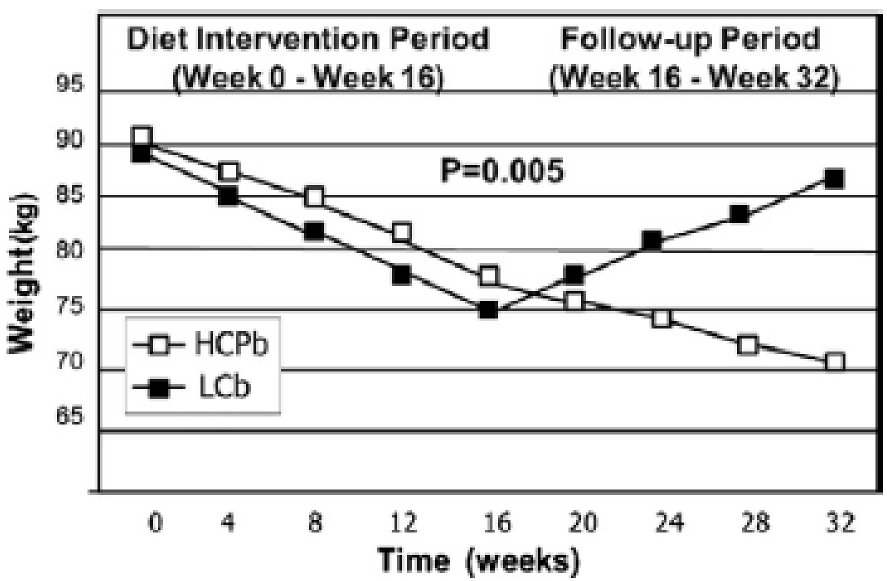
Ramadan fasting in subjects with MS resulted in decreased daily energy intake, decreased plasma glucose levels, and increased IS (Shariatpanahi et al 2005)

Meal timing and composition influence ghrelin levels, appetite scores and weight loss maintenance in overweight and obese adults

-193 obese [47 years, BMI 32.2], sedentary non diabetic adult men and women
-low carbohydrate breakfast (LCb)
isocaloric diet with high carbohydrate and protein breakfast (HCPb)
-DIP (week 16) and after a f/u period (week 32)
-HCPb may prevent wt regain by reducing diet-induced compensatory changes in hunger, cravings and ghrelin suppression

Steroids 2012;77:323-331

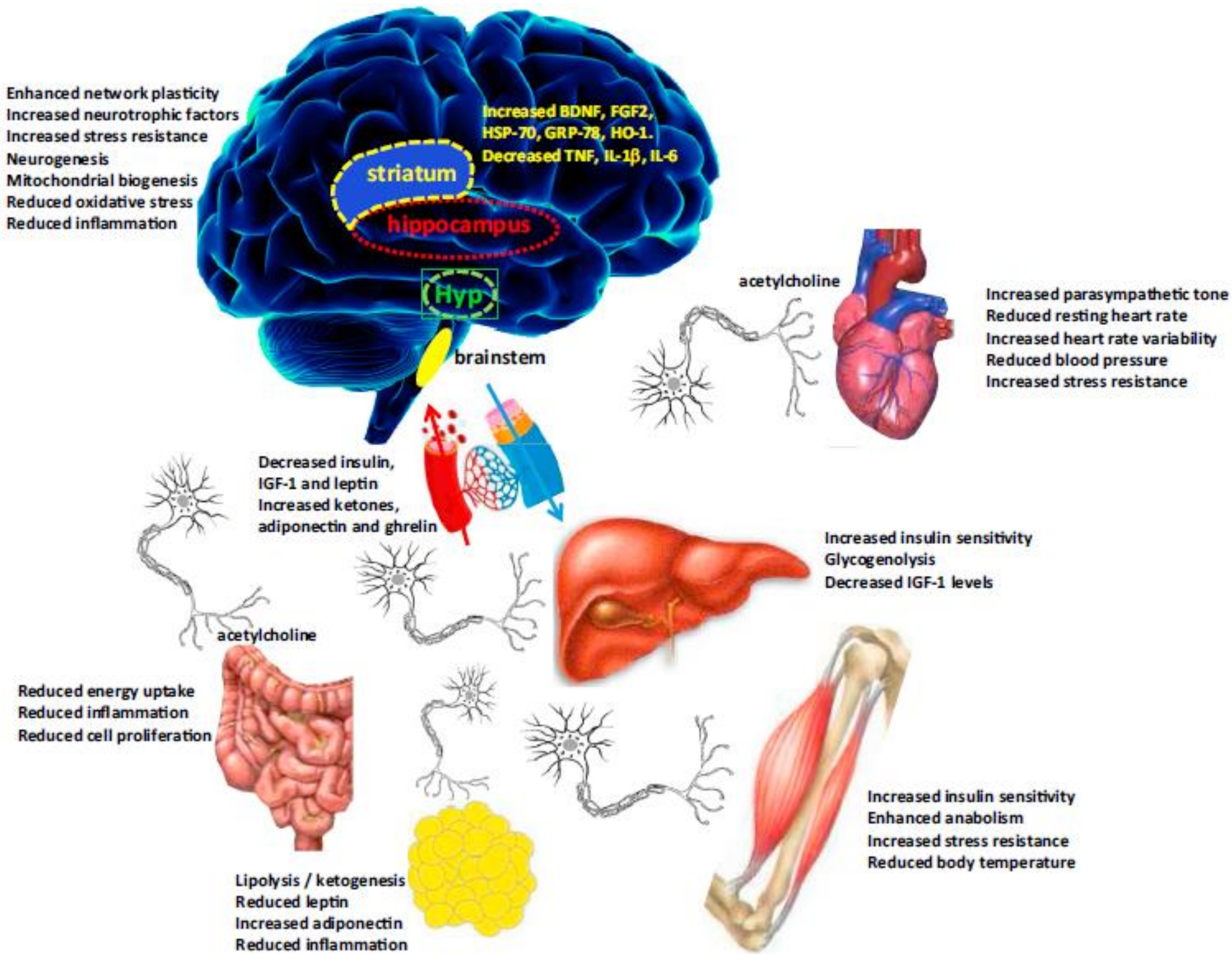
	HCb Women				LCb Women			
	Kcal	gCh (%)	gProt (%)	gFat (%)	Kcal	gCh (%)	gProt (%)	gFat (%
Breakfast	600	60 (40)	45 (30)	20 (30)	300	10 (13.3)	30 (40)	16 (48)
Lunch	500	10 (8)	70 (56)	20 (36)	500	10 (8)	70 (56)	20 (36)
Dinner	300	8 (10.7)	45 (60)	10 (30)	600	16 (10.6)	90 (60)	20 (30)
Total	1400	78(19.6)	160 (48.6)	50 (32)	1400	36 (10.6)	190 (52)	56 (38)
	HCb Men				LCb Men			
Breakfast	600	60 (40)	45 (30)	20 (30)	300	10 (13.3)	30 (40)	16 (48)
Lunch	600	12 (8)	84 (56)	24 (36)	600	12 (8)	84 (56)	24 (36)
Dinner	400	11 (10.7)	60 (60)	20 (30)	700	19 (10.6)	105 (60)	23 (30)
Total	1600	83 (19.5)	189 (48.7)	64 (32)	1600	41 (10.7)	219 (52)	63 (38)



HCPb: high carbohydrate, protein rich breakfast
LCb: Low carbohydrate

Steroids 2012;77:323-331

Pivotal roles of the nervous and endocrine systems as mediators of adaptive responses of major organ systems to CR/IF



Cell Metabolism 2014;19:181

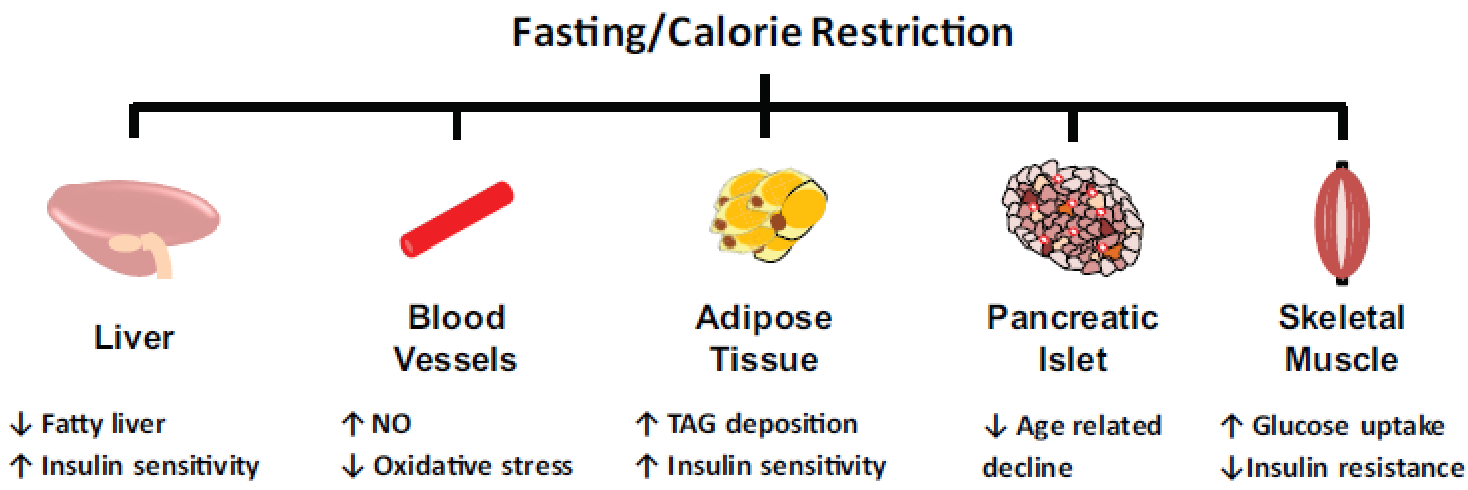


Figure 2. Tissue-specific effects of intermittent fasting and calorie restriction.
Research has identified several biological effects of intermittent fasting and/or calorie restriction on tissues that are central to metabolic and cardiovascular health. Key: NO: nitric oxide, TAG: triacylglycerides.

Conclusions

- A multitude of IF regimens (composition, frequency, duration) may hold promise in delivering similar benefits as CR.
- Whether the effects of IF are the results of CR rather than fasting is not clear yet.
- The optimal duration of restricted dietary periods within IF for wt loss and health benefits in human subjects is not known.
- Further studies are warranted to test the longer-term efficacy and safety of the IF.
- An unresolved issue is if and how changes in meal frequency affect energy metabolism and health in humans
- No single dietary approach will be appropriate and feasible for all, and there is unlikely to be a panacea given the complexity of wt management, but the addition of a further choice of intervention may be helpful.