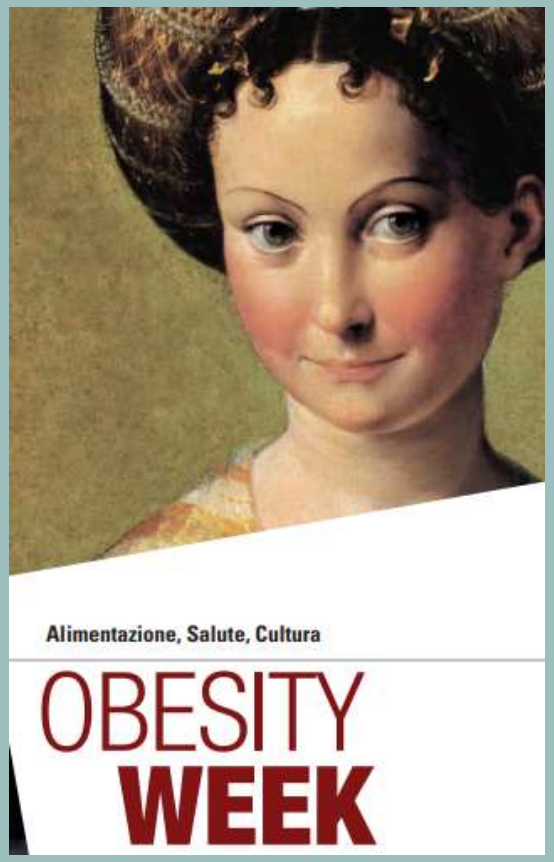
I MARTEDI DELL'ORDINE



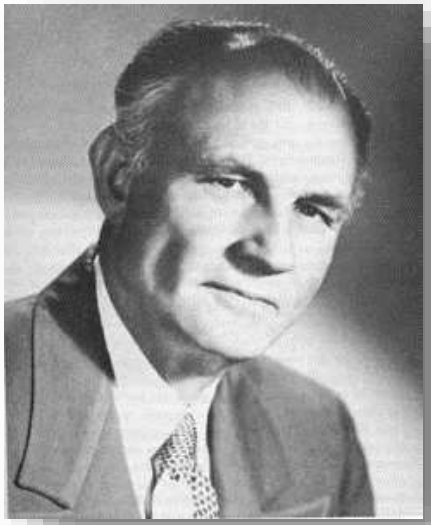
OBESITÀ, DIETE E DIGIUNO

Elisabetta Dall'Aglio
Malattie del Ricambio e Diabetologia
3 ottobre 2017

OBESITÀ E DIETE

- ✓ **L'obesità è una patologia cronica e necessita una terapia cronica, presenta un elevato tasso di recidiva.**
- ✓ **La restrizione energetica è difficile da raggiungere e da mantenere negli esseri umani !**
- ✓ **25-30% è l'aderenza ad un regime ipocalorico a 12 mesi**
- ✓ **20-40% raggiungono l'obiettivo di una riduzione >5% del peso dopo 12 mesi**
- ✓ **Gli effetti favorevoli sul metabolismo ottenuti con il calo ponderale si riducono con il ricupero ponderale.**

Dansinger et al . JAMA 2005;293:43-53.
Wadden et al Obes Res 7 170 – 178



1895 – 1985

Fasting is a complete voluntary abstinence from taking any kind of food for a definite period of time

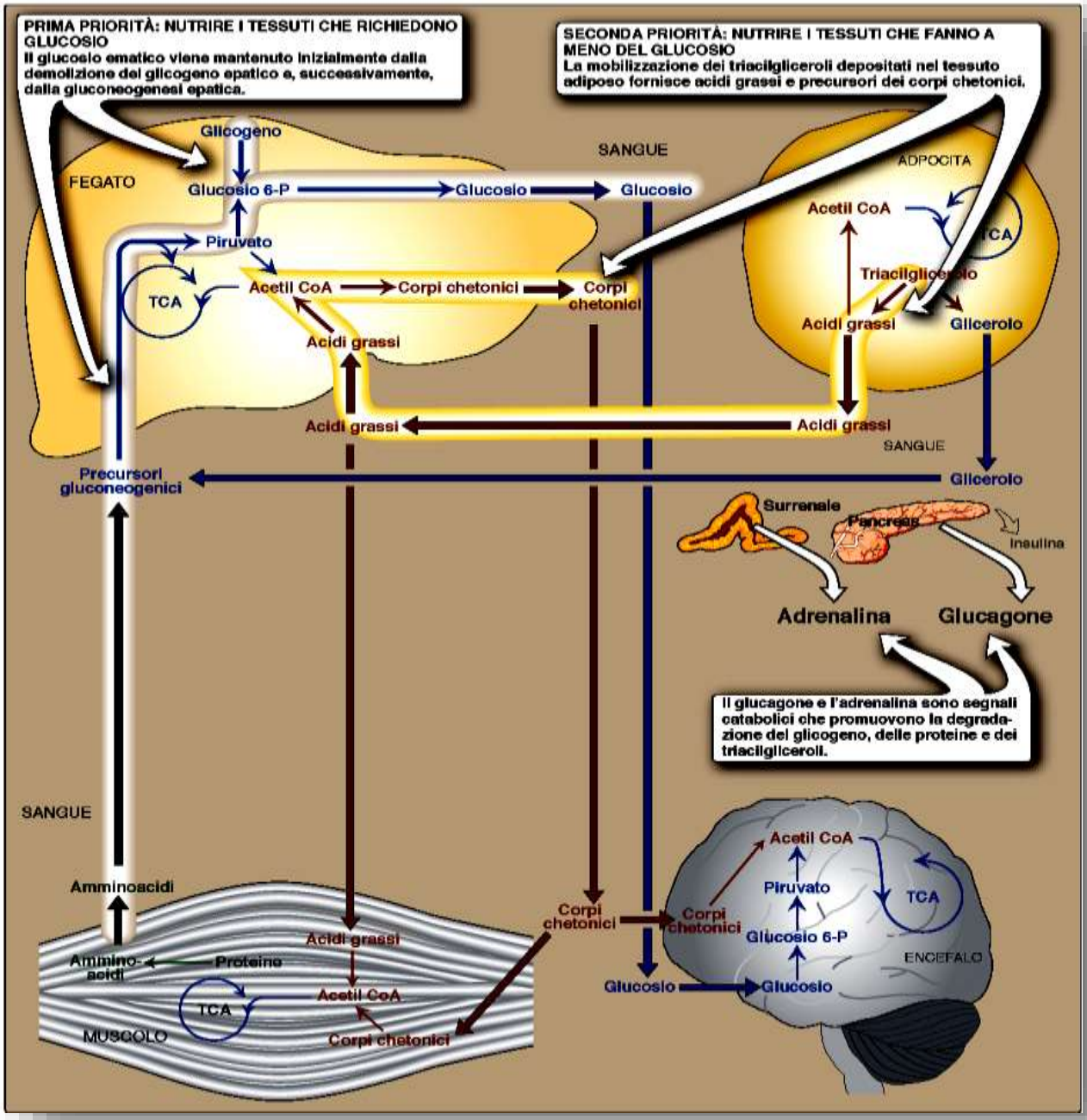
During a fasting body lives in reserve (dr Herbert M.Shelton)

Shelton afferma che la cottura altera il valore nutritivo dei cibi e che un corpo sano ha la capacità di ristabilirsi dalla malattia senza ausilio dell'intervento medico.
Aspramente criticato dai suoi contemporanei per il suo sostegno mostrato alla pratica del digiuno contro quella dei trattamenti medici.

Relazioni metaboliche tra i tessuti durante il digiuno

Organi coinvolti

- Fegato
- Tessuto adiposo
- Muscolo scheletrico
- Cervello
- Rene



DIGIUNO: TESSUTO ADIPOSO

Metabolismo dei grassi

Aumentato catabolismo dei TAG

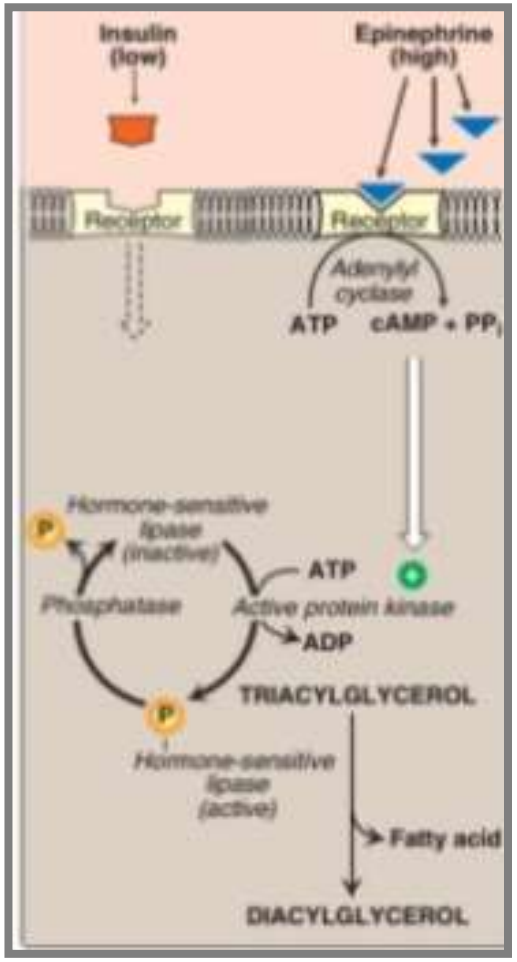
- Dovuto ad attivazione della lipasi ormono sensibile per aumento catecolamine e glucagone

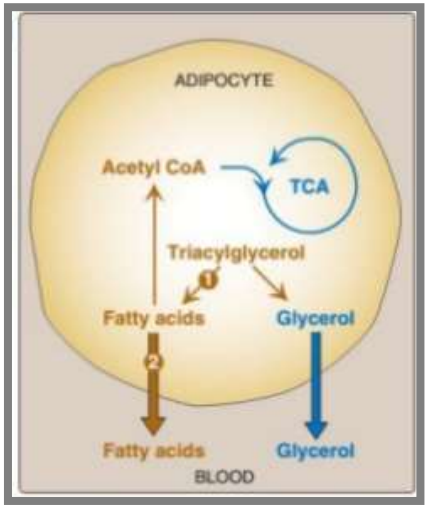
Aumentato rilascio di Ac Grassi FFA

- Idrolisi dei TAG liberazione di FFA
- Legame con albumina trasporto ai tessuti
- Glicerolo prodotto da idrolisi di TAG è utilizzato come precursore per neoglucogenesi epatica
- FFA convertiti ad Acetil-CoA che può entrare nel ciclo di Krebs per produrre energia per l'adipocita

Ridotta captazione degli ac grassi

- L'attività della lipoprotein lipasi è bassa





DIGIUNO: FEGATO

Metabolismo dei carboidrati

1° Glicogenolisi

- Mobilizzazione del glicogeno epatico

2° Gluconeogenesi

- Dal muscolo: amminoacidi gluconeogenici e lattato
- Dal tessuto adiposo: glicerolo

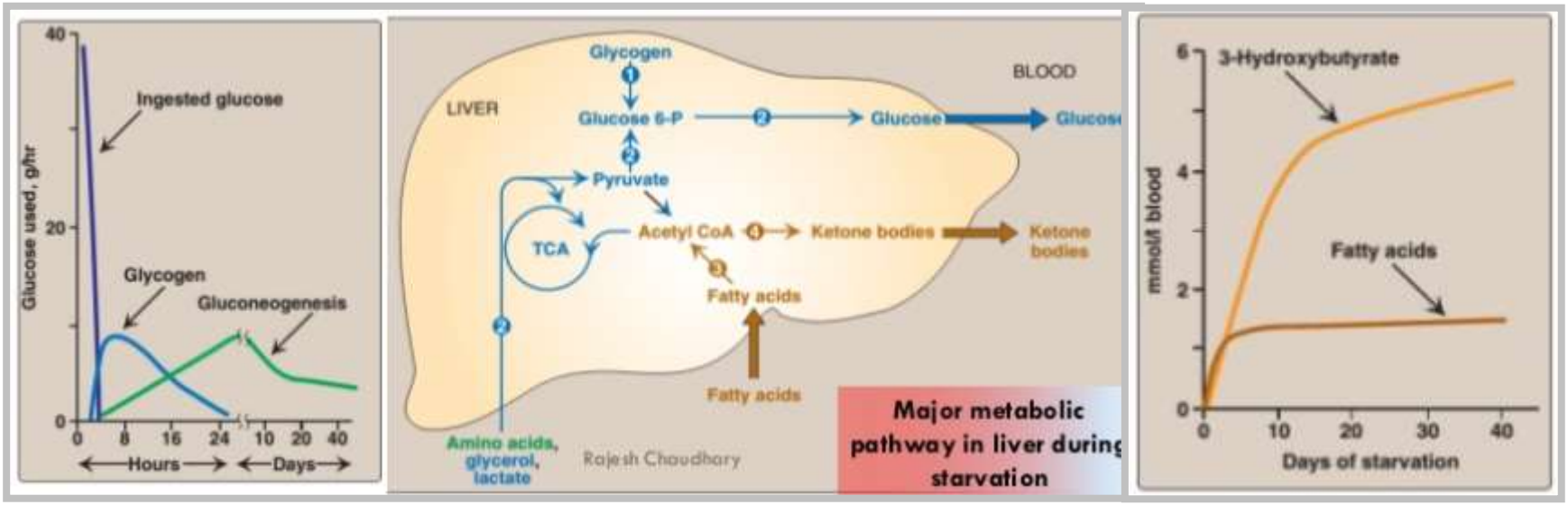
Metabolismo dei grassi

Aumento dell'ossidazione degli FFA

- Provenienti dall'idrolisi dei TAG nel tessuto adiposo
- Formazione di NADH ed ATP richiesto pe la neoglucogenesi

Aumentata sintesi dei corpi ketonici

- Quando la produzione di Acetil CoA è superiore alla capacità ossidativa
- Inizia dopo 1-2 giorni di digiuno
- Possono essere utilizzati da molti tessuti incluso il cervello



ENDOCRINE SYSTEM

- **Decreased insulin**
  - Caused due to low blood sugar and Increased glucagon levels
- **Increased glucagon**
  - Increased glycolysis
  - Increased gluconeogenesis
  - Increased transport of amino acid
  - Increased lypolytic and ketogenic action
  - Increased free fatty acid in blood
  - Increased ketogenesis
- **Increased growth hormone levels**
  - Mobilizes the fats from adipose tissue
- **Decreased thyroid hormones**
  - Decreased basal metabolic rate
  - Decreased erythropoisis rate
  - Decreased heart and respiratory rate
  - Increased drowzyness

- **Increased aldosteron**

Decreased sodium levels in body

↓

Increased aldosteron

↓

Increased retention of water and sodium

↓

Increased ECF

↓

Increased arterial blood pressure

↓

Increased ANP, BNP, CNP

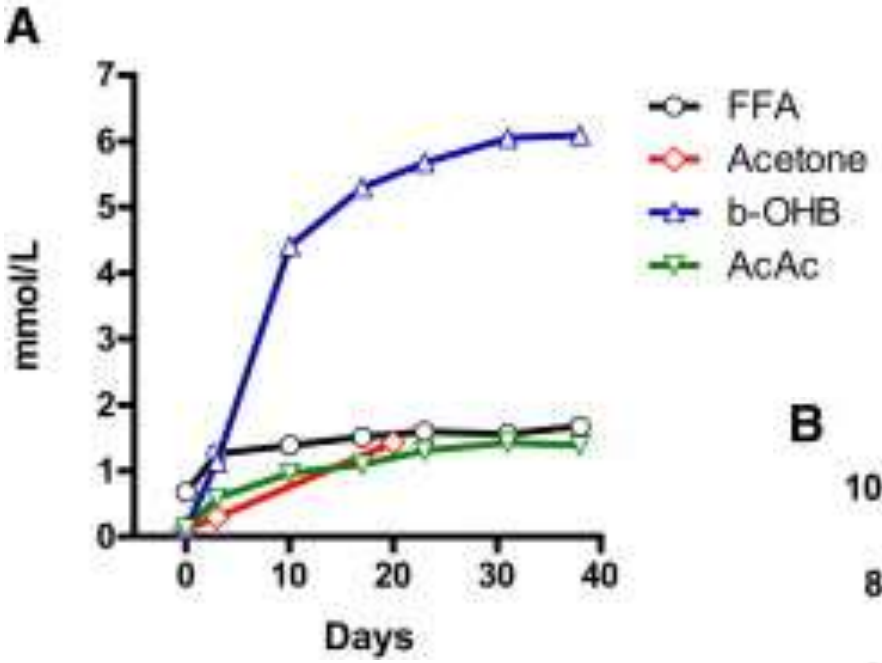
↓

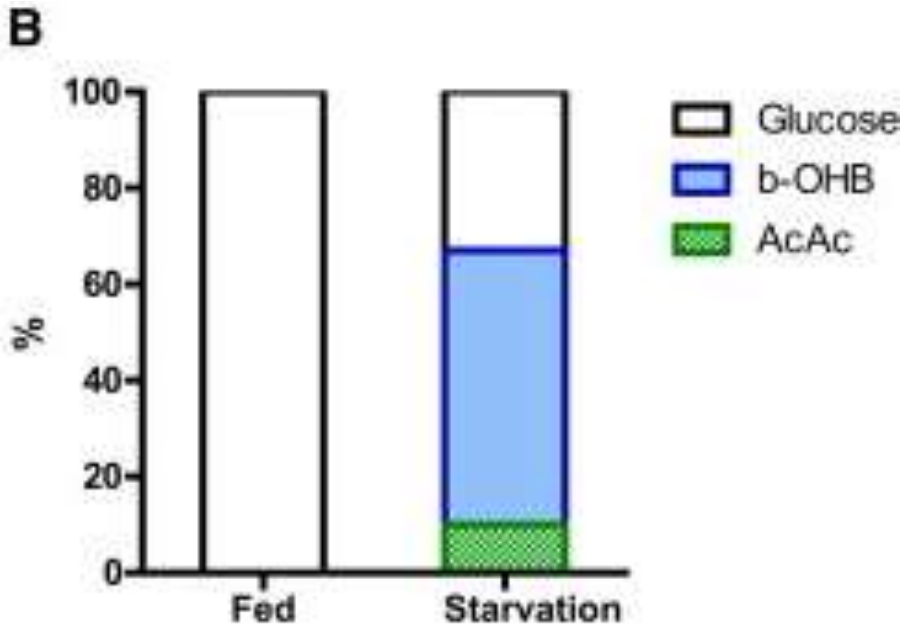
Excretion of water and sodium

- Increased cortisol
- Increased adrenaline and nor-adrenaine
  - Increased urination
  - Increased brain activity
  - Quick fatique
  - Increased sweating
  - Increased blood pressure(systolic)
  - Increased general vasoconstriction
  - Decreased blood coagulation

But in later stages all the functions alter,there is less sweating, urination,etc.

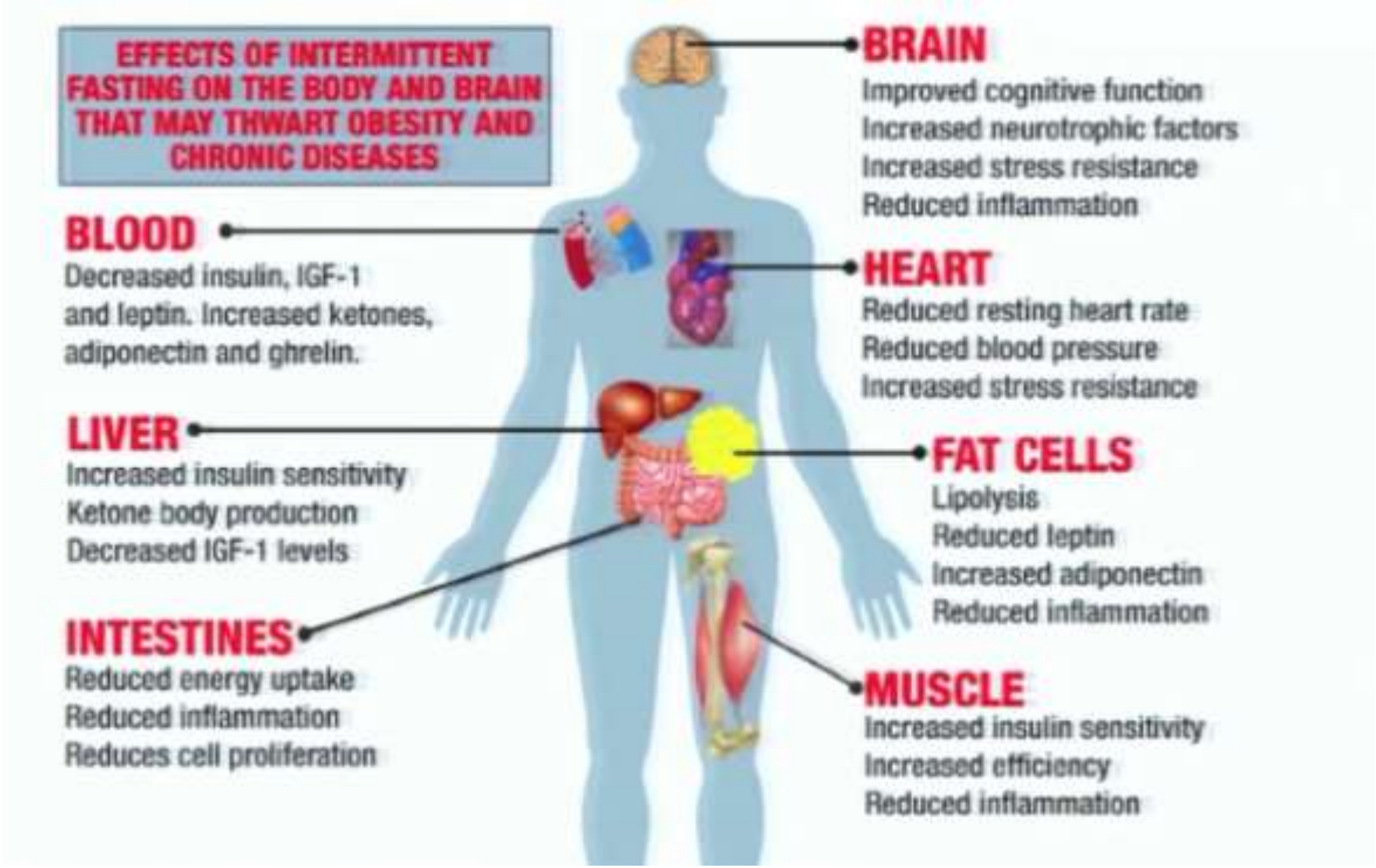
FASTING IN MAMMALS



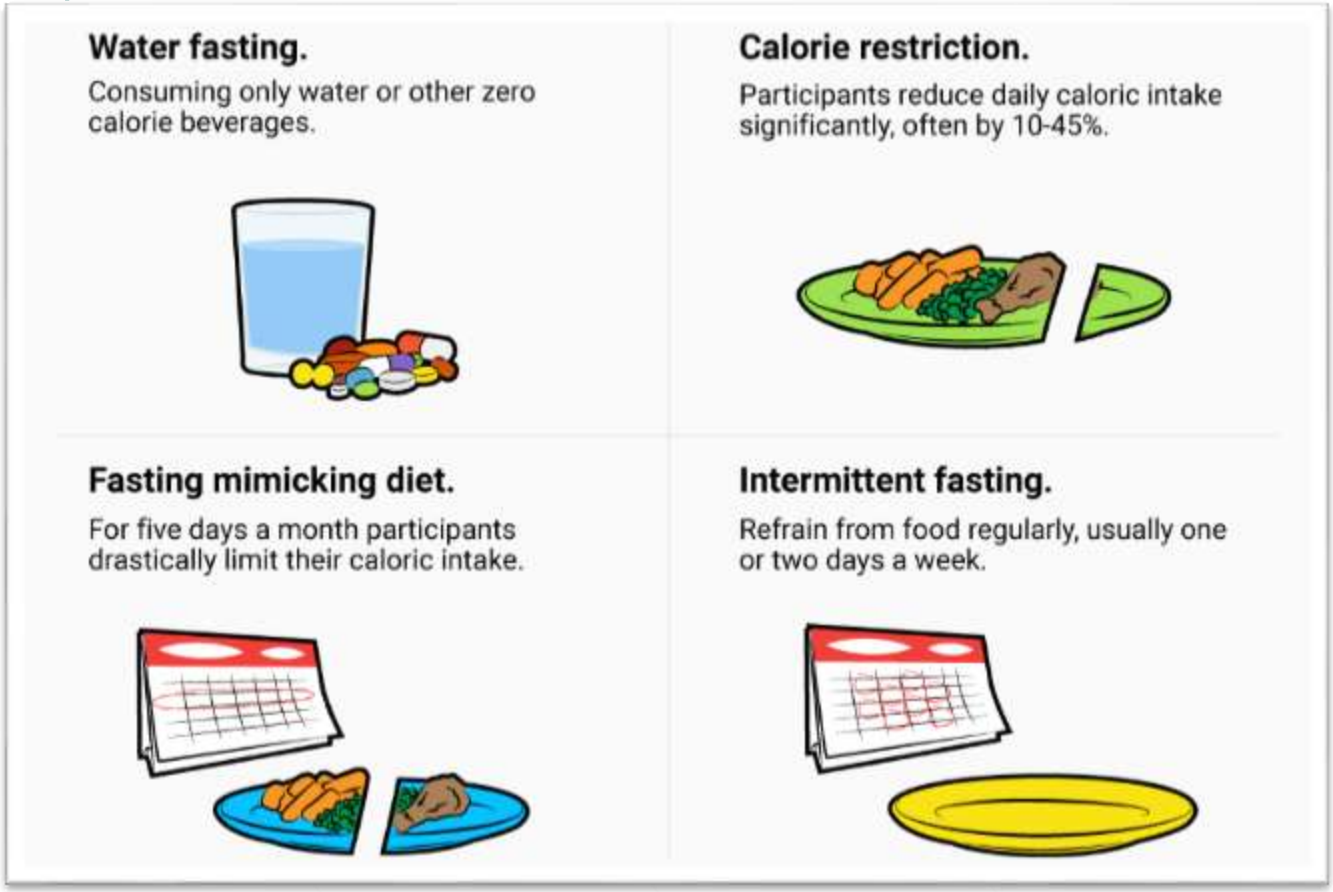


Longo V, Mattson P. Cell Metabolism, Volume 19 (Issue 2), 4 February 2014

INTERMITTENT FASTING: EFFECTS AT MULTIPLE LEVELS



DIFFERENT TYPE OF FASTING



Variety of regimens studied

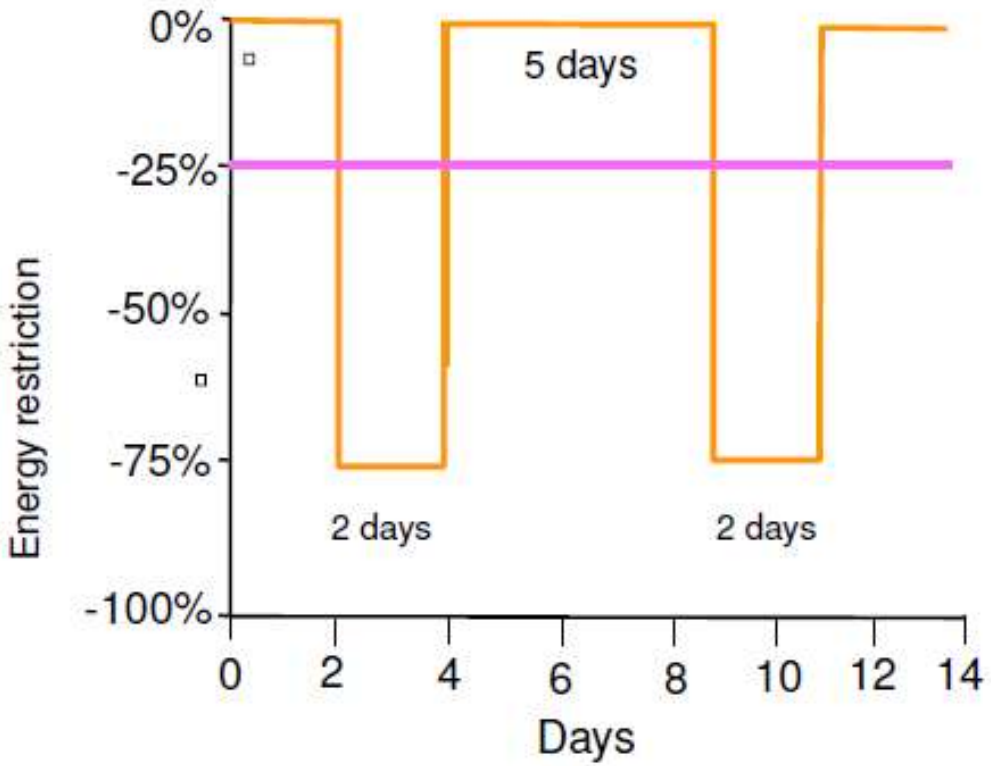
Intermitted fasting

- Alternate day fasting

Periodic prolonged fasting

- 3 weeks 50% restriction & 3 weeks ad lib
- Alternate weeks of 50% restriction & ad lib
- 5 days month for 3 months, 60% restriction
- 5:2 diet week

Intermittent energy restriction
5:2 diet



Overall 25% energy restriction

Daily energy restriction : 25% restriction 7 days / week

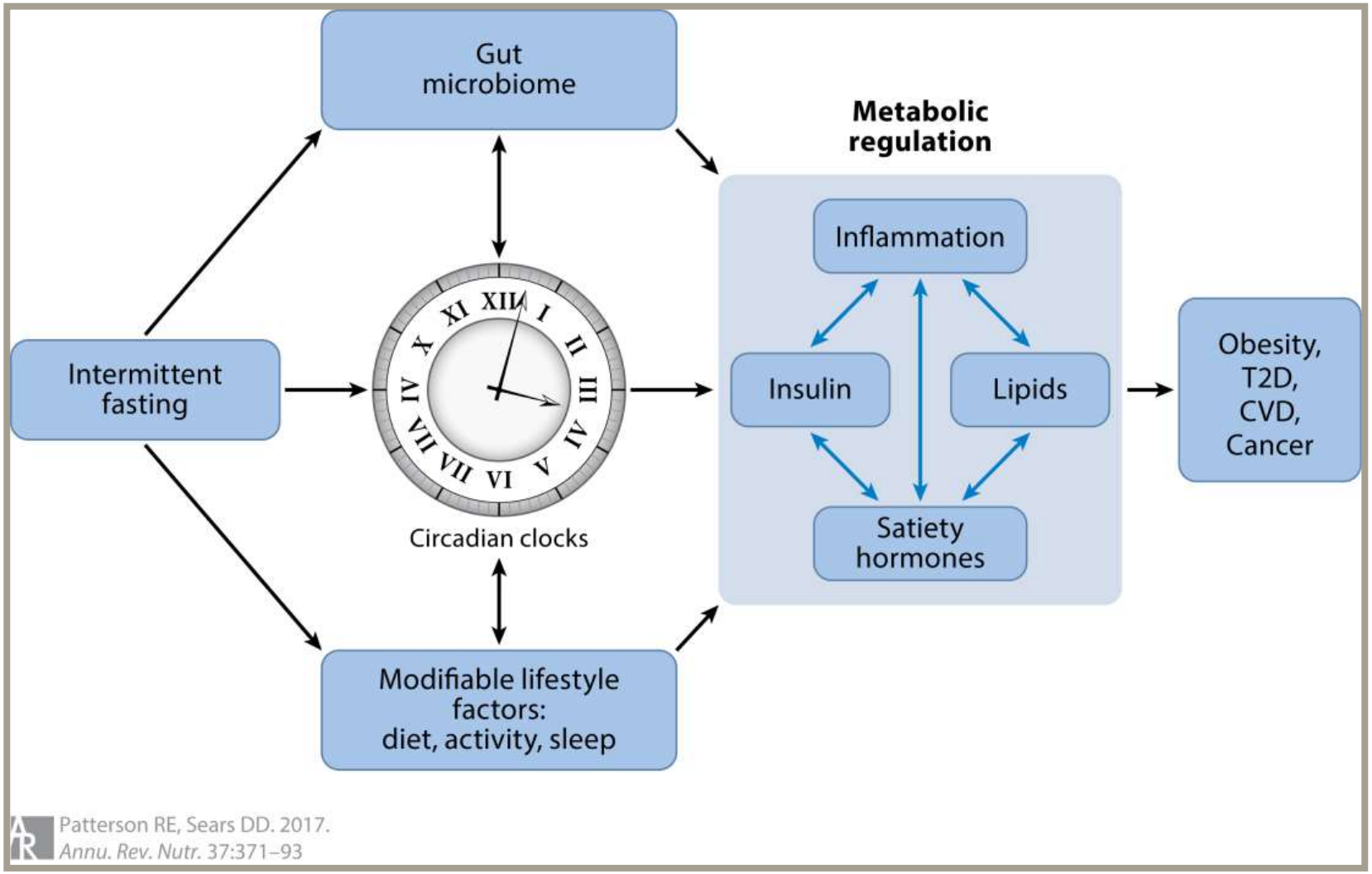
Intermittent energy restriction 75% restriction 2 days/ week

PATTERNS OF DAILY AND WEEKLY FOOD CONSUMPTION

A. 3 meals and snacks
B. 3 meals consumed during the day
C. 2 meals no breakfast
D. 3 small meals
E. Complete fast

	M	T	W	Th	F	S	Su
Common Diet	A	A	A	A	A	A	A
TRF	B	B	B	B	B	B	B
5:2 diet	D	D	B	B	B	B	B
Alternate day fast	A	E	A	E	A	E	A
Alternate day ER	A	D	A	D	A	D	A

POTENTIAL MECHANISMS LINKING INTERMITTENT FASTING WITH OBESITY,TYPE 2 DIABETES, CARDIOVASCULAR DISEASE AND CANCER



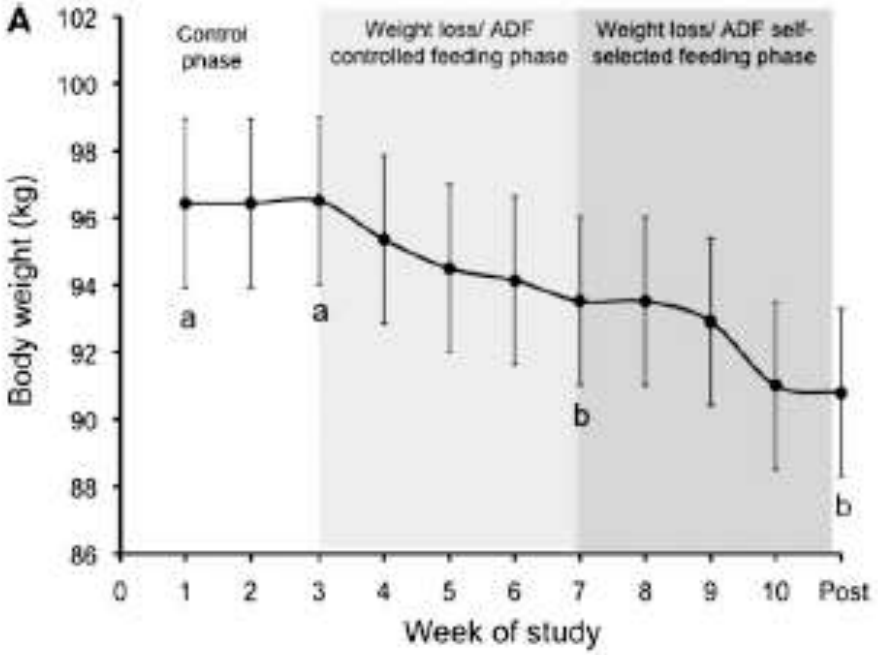
Annual Reviews Nutrition 2017

Short-term modified alternate-day fasting: a novel dietary strategy for weight loss and cardioprotection in obese adults[1–3]

Krista A Varady, Surabhi Bhutani, Emily C Church, and Monica C Klempel

TABLE 1
Nutrient composition of fast day meals during the controlled food intake phase[1]

	Fast day 1	Fast day 2	Fast day 3
Foods			
Entree	Chicken fettuccini	Vegetarian pizza	Chicken enchilada
Fruit/vegetable	Carrot sticks	Apple	Orange
Snack	Cookie	Peanuts	Crackers
Nutrients			
Energy (kcal)	450	450	450
Total fat (g)[2]	13	11	12
Saturated fat (g)	5	4	5
Monounsaturated fat (g)	4	4	5
Polyunsaturated fat (g)	4	3	2
trans Fat (g)	0	0	0
Cholesterol (mg)	35	30	35
Protein (g)[3]	25	29	27
Carbohydrate (g)[4]	60	60	60
Fiber (g)	10	10	10



16 soggetti obesi BMI 33,8 kg/m² seguiti per 10 settimane 4 settimane ADF con consumo di kcal 25% del fabbisogno. Pasti consumati fra le 12 e le 14. Calo ponderale di 5,6 kg

No controlli

Am J Clin Nutr 2009.90:1138-43

Meal Timing During Alternate Day Fasting: Impact on Body Weight and Cardiovascular Disease Risk in Obese Adults

Kristin K. Hoddy, Cynthia M. Kroeger, John F. Trepanowski, Adrienne Barnosky, Surabhi Bhutani, and Krista A. Varady

TABLE 1 Nutrient composition of the provided fast day meals

	Fast day 1	Fast day 2	Fast day 3
Foods			
Entrée	Chicken enchilada	Lasagna w/meat sauce	Roasted turkey
Fruit/vegetable	Grapes	Carrot sticks	Grapes
Dessert/snack	Peanuts	Cookie	Crackers
Dairy	Yogurt	Yogurt	Yogurt
Nutrients[a]			
Energy (kcal)	500	500	500
Fat (g)	15 (27%)[b]	13 (24%)[b]	12 (22%)[b]
Saturated fat (g)	5	5	4
Monounsaturated fat (g)	6	5	4
Polyunsaturated fat (g)	4	3	4
Trans fat (g)	0	0	0
Cholesterol (mg)	32	36	33
Protein (g)	20 (16%)[b]	23 (18%)[b]	22 (17%)[b]
Carbohydrate (g)	72 (57%)[b]	73 (58%)[b]	78 (61%)[b]
Fiber (g)	11	11	11

3 gruppi di 20 soggetti ciascuno ADF lunch, ore 12-14, ADF dinner, ore 18-20 ADF small meals, 100 kcal 6-8, 300 kcal 12-14 e 100kcal 18-20. 8 settimane di intervento
BMI medio 35, 34, 34 kg/m²
Durata 8 settimane

Obesity 2014

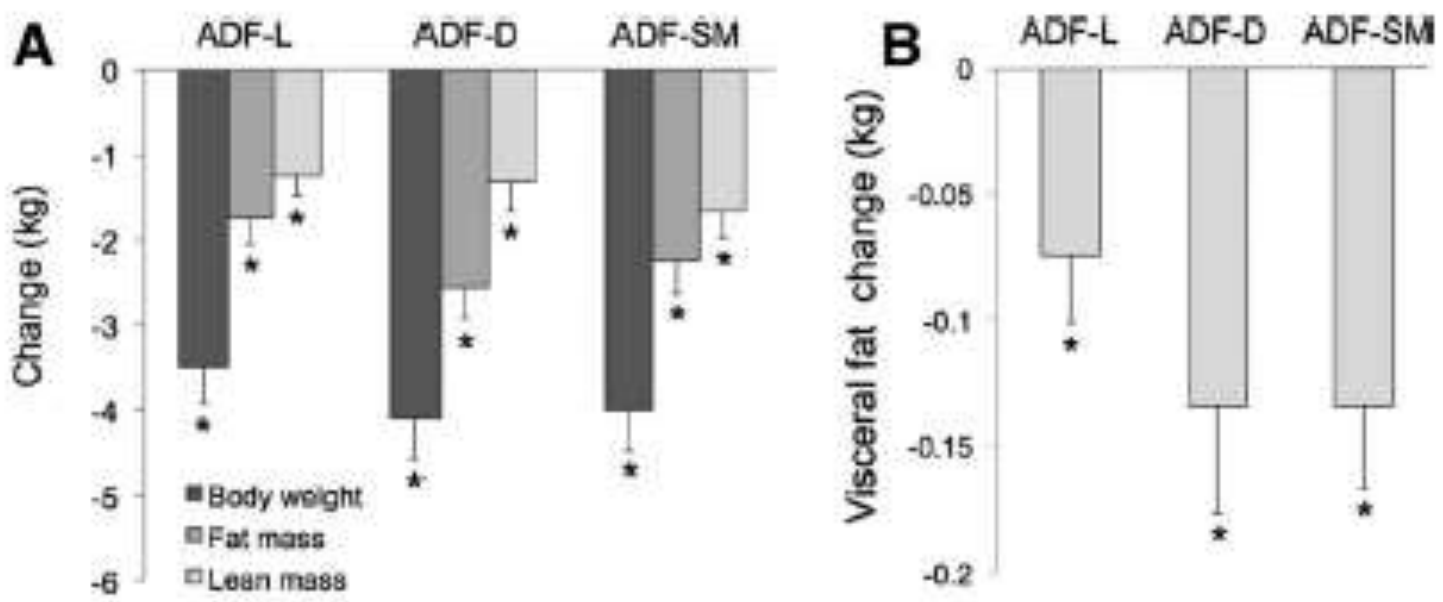
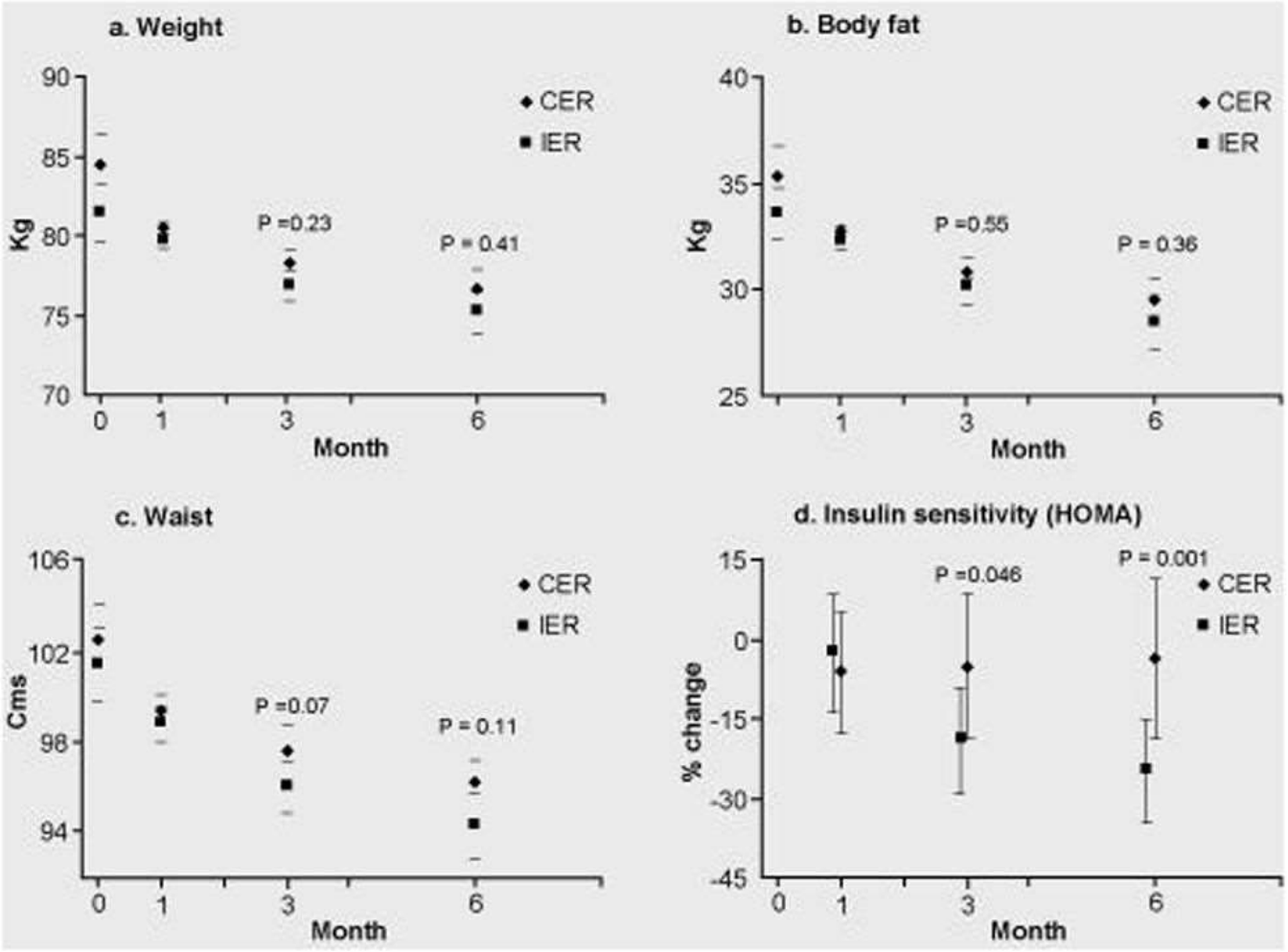


Figure 2 Changes in body weight and body composition during the weight loss period. (**A**) Absolute change in body weight, fat mass, and lean mass from weeks 3 to 10 in the ADF-L, ADF-D, and ADF-SM groups. (**B**) Absolute change in visceral fat mass from weeks 3 to 10 of the trial for each intervention group. Values reported as means ± SEM. *Week 3 value significantly ($P < 0.001$) different from week 10 values within group (paired *t*-test). No differences between groups for absolute change in body weight, fat mass, lean mass, or visceral fat mass (one-way ANOVA).

The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomised trial in young overweight women



42 IER vs 47 CR
Sesso F
BMI 30,5 e 30,7
Calo ponderale
6,4 vs 5,6 kg
IER=5:2
6 mesi

Conclusion—IER is as effective as CER in regards to weight loss, insulin sensitivity and other health biomarkers and may be offered as an alternative equivalent to CER for weight loss and reducing disease risk.

Int J Obes (Lond). 2011

From: **Effect of Alternate-Day Fasting on Weight Loss, Weight Maintenance, and Cardioprotection Among Metabolically Healthy Obese AdultsA Randomized Clinical Trial**

JAMA Intern Med. 2017;177(7):930-938. doi:10.1001/jamainternmed.2017.0936

Control 23
ADF 21
CR 25
Eta 44 anni
86/F 14/M

Calo peso
6 mesi
-6.8%
-6,8%
12 mesi
-6.0%
-5.3%

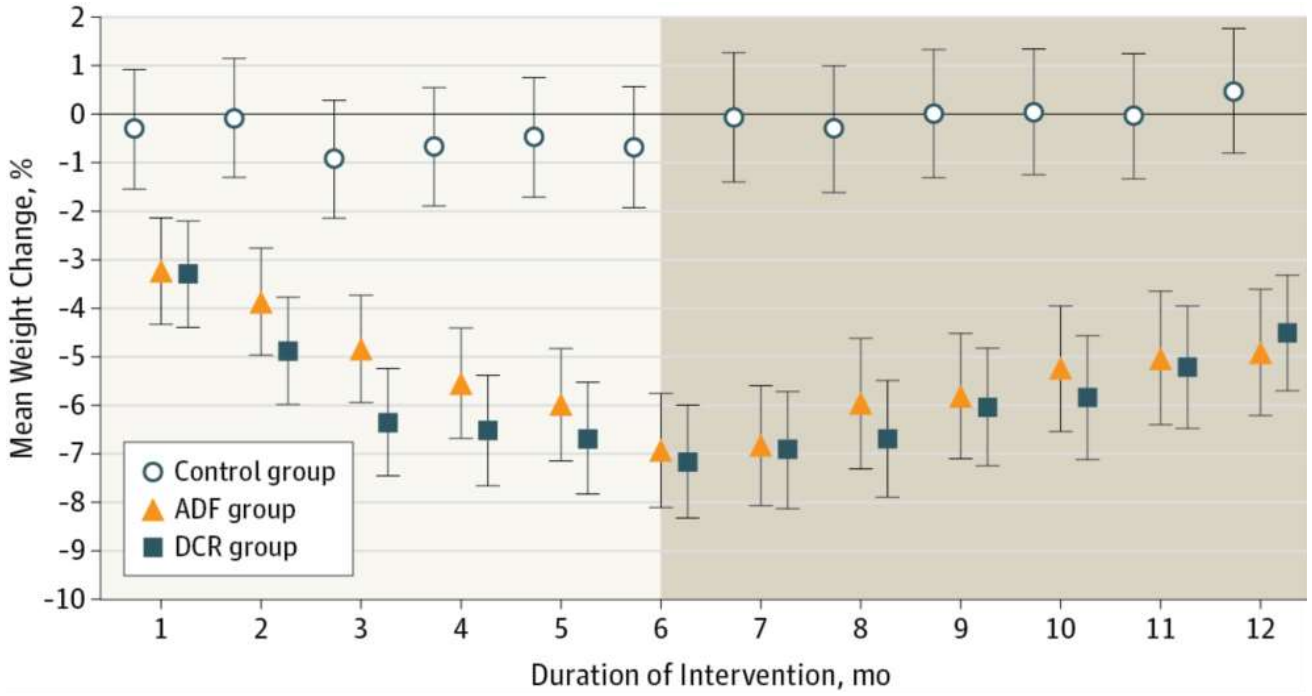
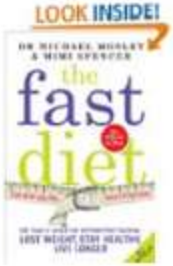
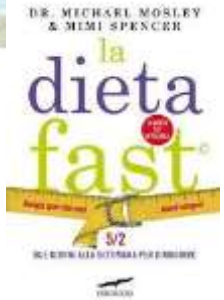
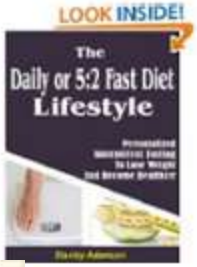


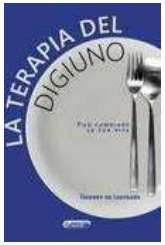
Figure Legend:

Weight Loss by Diet Group Relative to BaselineData were included for 100 participants; mean (SD) values were estimated using an intention-to-treat analysis with a linear mixed model. Error bars indicate 95% CIs for weight change from baseline by diet group at each time point (1-12 months). ADF indicates alternate-day fasting; DCR, daily calorie restriction.









In USA Jan 5 th 2014 ~ 130 books on fasting

COSA SAPPIAMO

- ✓Il calo ponderale si raggiunge attraverso un deficit calorico, più o meno pronunciato, con diete a diversa composizione nutrizionale (low carb, low fat etc) e a differente apporto calorico, **fondamentale è l'aderenza alla dieta.**
- ✓Un apporto nutrizionale completo in **vitamine e micronutrienti** è fondamentale per il raggiungimento del migliore risultato clinico
- ✓La dieta intermittente potrebbe essere un'alternativa alla dieta ipocalorica classica: **ulteriori evidenze cliniche sono necessarie**
- ✓**In soggetti sani** non vi è evidenza di alterazioni metaboliche in corso di un digiuno intermittente
- ✓In accordo con quanto si osserva in altri regimi ipocalorici, gli **outcome metabolici sono favorevoli**

COSA NON SAPPIAMO

- ✓Efficacia e sicurezza nel **lungo termine**
- ✓Quali intervalli siano maggiormente favorevoli sul calo ponderale, **quanto spesso** andrebbero attutati e **quanto a lungo**
- ✓Quale sia l'ottimale **apporto calorico** da attuare durante il regime
- ✓ Efficacia e **sicurezza in specifiche fasi della vita** (es. gravidanza, accrescimento) **o in soggetti con pat**ologie (diabete, grande obeso)
- ✓Impatto sullo stato della **massa muscolare** e sul **metabolismo basale**
- ✓Implicazioni in termini di **prevenzione** dell'obesità
- ✓Implicazioni cliniche **nei disturbi del comportamento alimentare**

Digiuno terapia, l'associazione italiana di Dietetica denuncia: "Pericolose per i pazienti con patologie gravi"

*"**Le terapie miracolistiche senza alcuna base scientifica** basate sul digiuno o sull'esclusione di determinate categorie di alimenti dalla dieta sono pericolose nei soggetti affetti da patologie gravi o malnutriti, nei bambini e negli anziani. Se adottate da soggetti sani possono indurre a stati carenziali e allo sviluppo di disturbi del comportamento alimentare."*

***Così l'Associazione italiana di Dietetica e Nutrizione Clinica ADI** prende posizione "**sull'ennesimo caso di cronaca legato alla somministrazione di terapie dietetiche scorrette prive di fondamento scientifico e di prescrizione medica" alla luce del caso perugino di una paziente sarda di 57 anni affetta da sclerosi multipla, che si è sottoposta a una terapia del digiuno.**»*

The NEW ENGLAND JOURNAL of MEDICINE

TO THE EDITOR: It is believed that low-carbohydrate diets work best in reducing weight when producing ketosis.[1] We report on a 51-year-old white woman who does not have diabetes but had ketoacidosis while consuming a "no-carbohydrate" diet. There was no family history of diabetes, and she was not currently taking any medications. While adhering to a regimen of carbohydrate restriction, she reached a stable weight of 59.1 kg, a decrease from 72.7 kg. After

Ketoacidosis during a Low-Carbohydrate Diet

Benign dietary ketosis resulting from restricting carbohydrates could, theoretically, cause ketoacidosis in persons with a predisposition to the condition. Carbohydrate-restricted, high-fat diets may have adverse metabolic sequelae when followed for protracted periods.

2006

FASTINGMIMICKDIET

CHE COS‘E’ PROLON®

ProLon® significa **digiunare mangiando**. ProLon® è un programma dietetico di 5 giorni che nutrendo l’organismo promuove nell’organismo tutti gli effetti benefici della dieta Mima Digiuno attraverso componenti alimentari totalmente vegetali.

Il box ProLon® è costituito da 5 piccoli boxes (uno per ogni giorno della dieta) che includono **componenti totalmente vegetali** come barrette energetiche, zuppe, una varietà di snacks, bevande e integratori.

Tutte le componenti sono state studiate e attentamente formulate al fine di nutrire accuratamente il tuo organismo e stimolare cambiamenti metabolici positivi.

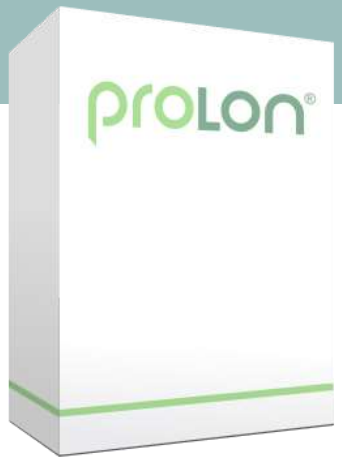
L"apporto calorico giornaliero di ProLon® è compresa **tra 770 e 1100 calorie** derivate da ingredienti sani che massimizzano il nutrimento.

La Bevanda energetica ProLon® contiene la polilisina, conservante naturale.

Ricerche di mercato hanno dimostrato che Prolon® presenta un buon sapore.

Praticità: Prolon e’ stato pensato e confezionato in modo da renderlo versatile e facile da preparare. Così facendo viene minimizzato l’impatto con lo stile di vita quotidiano.

NELL'AMBITO DELLA PIATTAFORMA **DIETA MIMA DIGIUNO™**
L-NUTRA STA SVILUPPANDO UNA SERIE DI **PROGRAMMI ALIMENTARI** CHE VERRANNO SOTTOPOSTI ALL'APPROVAZIONE DELLA **FOOD AND DRUG ADMINISTRATION AMERICANA (FDA) E DELLA EUROPEAN FOOD SAFETY AUTHORITY (EFSA)** PER LA VERIFICA DELLE **DICHIARAZIONI SULLA SALUTE RELATIVE ALLA PREVENZIONE, AL TRATTAMENTO DELLE PATOLOGIE CRONICHE, INCLUSE LE MALATTIE CARDIOVASCOLARI E AUTOIMMUNI, COME LA SINDROME METABOLICA, IL DIABETE MELLITO, IL CANCRO, LA MALATTIA DI ALZHEIMER E LA SCLEROSI MULTIPLA.**

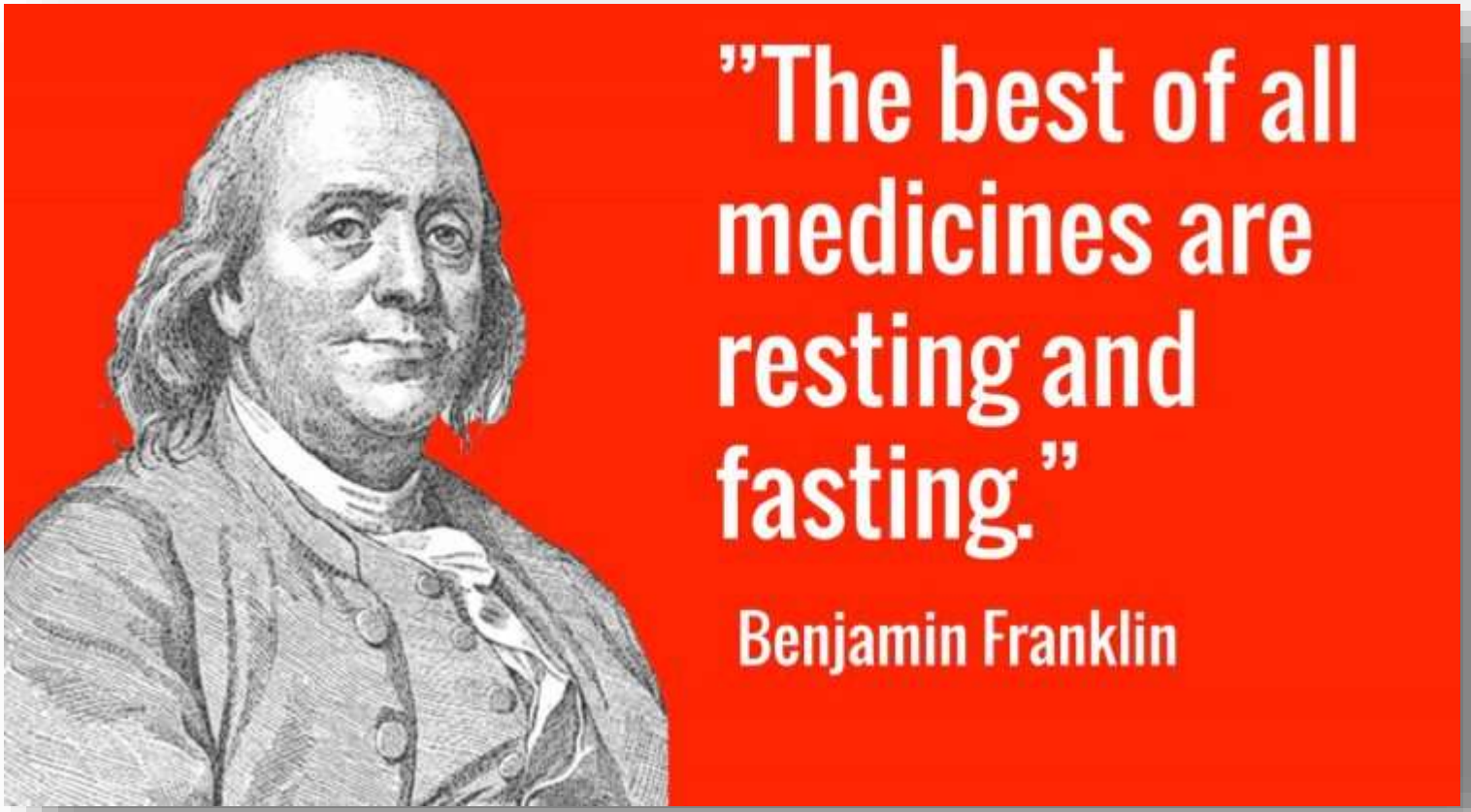


AREE POCO CHIARE AD OGGI

- **Quali dati clinici di efficacia in modelli di patologia umana?** I dati disponibili sono a livello preclinico
- **Quali dati clinici nel soggetto grande obeso?** Attualmente assenti
- **Quali outcome clinci sono maggiomente modificati da tale approccio?** Nessuna evidenza clinica

Consiglio di Amministrazione

- **Valter Longo, PhD** è fondatore di L-Nutra e Presidente del Comitato Scientifico. Il Dr. Longo ha vinto numerosi premi per la sua ricerca, tra cui premi dalla Associazione Alzheimer e dal National Institute on Aging, e ha raccolto oltre $6 milioni in sovvenzioni dal NIH e da fondazioni private negli ultimi 10 anni per la ricerca sull''invecchiamento, sul cancro e sulla malattia di Alzheimer.
- **Joseph Antoun, MD, MS, MPP** Presidente ad interim. è l'amministratore delegato della Health Systems Reform, una boutique di consulenza volta al miglioramento della salute pubblica attraverso riforme del sistema sanitario, rinforzando e potenziando il management dell'assistenza sanitaria
- **Chiara Tilesi** Membro del Consiglio (è una produttrice cinematografica italiana con una prospettiva alquanto filantropica. È la fondatrice della organizzazione di produzione cinematografica no-profit "We Do It Together", cui scopo è quello di finanziare e produrre film, documentari e altri format mediatici dedicati all'empowerment delle donne e delle minoranze etniche, raccontando le loro esperienze di vita.)
- **Brian Kennedy, PhD** è l'Amministratore delegato di The Buck Institute for Research on Aging, un'organizzazione no-profit, prima struttura di ricerca indipendente della nazione concentrata esclusivamente sul legame tra invecchiamento e malattie croniche
- **Vincenzo Maglione, PHAR, MD, MS, MBA** Membro del Consiglio Fondatore di Akademy Pharma. Prima di fondare Akademy Pharma, Mr. Maglione è stato Direttore Generale e Amministratore Delegato del gruppo Rottapharm/Madeus, con ruolo di responsabile per il settore marketing e vendite; fu Vice Direttore Generale per la Knoll Farmaceutici SpA, parte del Gruppo BASF



Niente di nuovo sotto il sole……
Ai posteri l'ardua sentenza…….

GRAZIE !

Int J Obes (Lond). 2015 May;39(5):727-33. doi: 10.1038/ijo.2014.214. Epub 2014 Dec 26.

Fasting for weight loss: an effective strategy or latest dieting trend?

Johnstone

With the increasing obesity epidemic comes the search for effective dietary approaches for calorie restriction and weight loss. Here I examine whether fasting is the latest 'fad diet' as portrayed in popular media and discuss fasting is the latest 'fad diet' as portrayed in popular media . Fasting has long been used under historical and experimental conditions and has recently been popularised by 'intermittent fasting' or 'modified fasting' regimes, in which a very low-calorie allowance is allowed, on alternate days (ADF) or 2 days a week (5:2 diet), where 'normal' eating is resumed on non-diet days. It is a simple concept, which makes it easy to follow with no difficult calorie counting every other day. This approach does seem to promote weight loss, but is linked to hunger, which can be a limiting factor for maintaining food restriction. The potential health benefits of fasting can be related to both the acute food restriction and chronic influence of weight loss; the long-term effect of chronic food restriction in humans is not yet clear, but may be a potentially interesting future dietary strategy for longevity, particularly given the overweight epidemic. One approach does not fit all in the quest to achieve body weight control, but this could be a dietary strategy for consideration. With the obesity epidemic comes the search for dietary strategies to (i) prevent weight gain, (ii) promote weight loss and (iii) prevent weight regain. With over half of the population of the United Kingdom and other developed countries being collectively overweight or obese, there is considerable pressure to achieve these goals, from both a public health and a clinical perspective. Certainly not one dietary approach

PNAS | November 25, 2014 | vol. 111 | no. 47 |

Fig. 2. A metabolic shift to ketogenesis that occurs with fasting bolsters neuronal bioenergetics. Liver glycogen stores are typically depleted within 10–12 h of fasting, which is followed by liberation of fatty acids from adipose tissue cells into the blood. The fatty acids are then transported into liver cells where they are oxidized to generate Acetyl-CoA. Acetyl-CoA is then converted to 3-hydroxy-3-methylgluaryl-CoA, which is in turn used to generate the ketones acetoacetate and β-hydroxybutyrate (β-OHB). The ketones are released into the blood and are transported into various tissues, including the brain, where they are taken up by neurons and used to produce acetyl-CoA. Acetyl-CoA enters the tricarboxylic acid (TCA) cycle to generate ATP.

Myths about 5:2 diets

1. 5: 2 diets: 500- 600 kcal for 2/days/ week & eat what you want 5 days/ week have not been researched !

1. You can eat what you want on non diet days and still lose weight and protect yourself against disease

2. You can just focus on calories and it does not matter what types of foods we eat

3. Intermittent diets are proven to have health benefits if you are a healthy weight

5. You need to take nutritional supplements

Fig. S4. Nutritional information of the FMD.

SOUPS

Vegetable Soup Mix

INGREDIENTS: Rice Flour, Dried Onion, Inulin (Chicory Fiber), Dried Tomato, Dried Carrot, Salt, Dried Red Pepper, Dried Leek, Potato Starch, Olive Oil, Freeze Dried Basil, Spinach Powder, Dried Parsley, Natural Flavor

Nutrition Facts

Serving Size 1.2 oz (33g); (10 fl oz Prepared)
Servings Per Package 1

Amount Per Serving		
Calories	100	
Calories from Fat 20		
		% Daily Value*
Total Fat	2 g	3%
Saturated Fat	1 g	5%
Trans Fat	0 g	
Cholesterol	0 mg	
Sodium	650 mg	27%
Total Carbohydrate	19 g	6%
Dietary Fiber	5 g	20%
Sugars	5 g	
Proteins	2 g	
Vitamin A (RAE)		45%
Vitamin C		45%
Calcium		4%
Iron		6%

* Percent Daily Values are based on a 2,000 calorie diet.

SOUPS

Mushroom Soup Mix

INGREDIENTS: Rice Flour, Carrot Powder, Dried Onion, Champignon Mushroom Powder, Inulin (Chicory Fiber), Dried Champignon Mushroom, Salt, Yeast Extract, Potato Starch, Olive Oil, Dried Parsley, Natural Flavor

Nutrition Facts

Serving Size 1.2 oz (33g); (10 fl oz Prepared)
Servings Per Package 1

Amount Per Serving		
Calories	100	
Calories from Fat 20		
		% Daily Value*
Total Fat	2 g	3%
Saturated Fat	1 g	5%
Trans Fat	0 g	
Cholesterol	0 mg	
Sodium	910 mg	38%
Total Carbohydrate	18 g	6%
Dietary Fiber	4 g	16%
Sugars	9 g	
Proteins	3 g	
Vitamin A (RAE)		90%
Vitamin C		4%
Calcium		2%
Iron		2%

* Percent Daily Values are based on a 2,000 calorie diet.

SOUPS

Tomato Soup Mix

INGREDIENTS: Rice Flour, Dried Tomato Powder, Dried Onion, Inulin (Chicory Fiber), Potato Starch, Dried Tomato Pieces, Olive Oil, Salt, Yeast Extract, Dried Basil, Dried Parsley, Natural Flavor

Nutrition Facts

Serving Size 1.2 oz (33g); (10 fl oz Prepared)
Servings Per Package 1

Amount Per Serving		
Calories 110		
Calories from Fat 10		
		% Daily Value*
Total Fat	1g	1%
Saturated Fat	0g	0%
Trans Fat	0g	
Cholesterol	0mg	
Sodium	800mg	33%
Total Carbohydrate	25g	8%
Dietary Fiber	6g	24%
Sugars	6g	
Proteins	3g	
Vitamin A (RAE)		0%
Vitamin C		6%
Calcium		10%
Iron		10%

* Percent Daily Values are based on a 2,000 calorie diet.

Energy Drink Mix

INGREDIENTS: Purified Water, Natural Vegetable Glycerin, Polylysine (Natural Preservative).

Nutrition Facts

Serving Size 0.6 fl oz (17mL)
Servings Per Package 4

Amount Per Serving	
Calories 20	
	% Daily Values*
Total Fat 0g	0%
Sodium 0g	0%
Total Carbohydrate 5g	2%
Proteins 0g	

Not a significant source of fat, cholesterol, fiber, sugars, vitamin A, vitamin C, calcium and iron.
*Percent Daily Values (DV) are based on a 2,000 calorie diet.

Algal Oil

INGREDIENTS: Gelatin, Glycerin, Purified Water, Turmeric (Color), Annatto Extract (Color)

Nutrition Facts

Serving Size 1 Softgel

Amount Per Serving	
Calories 6	
Calories from Fat 5	
	% Daily Values*
Total Fat 0.5g	< 1%
Sodium 0g	0%
Total Carbohydrate 0g	0%
Proteins 0g	
DHA Omega-3 (from Algal Oil) 200 mg**	

*Percent Daily Values (DV) are based on a 2,000 calorie diet.
**Daily value not established.

NR-1
Vegetable Powder with Vitamins and Minerals Supplements

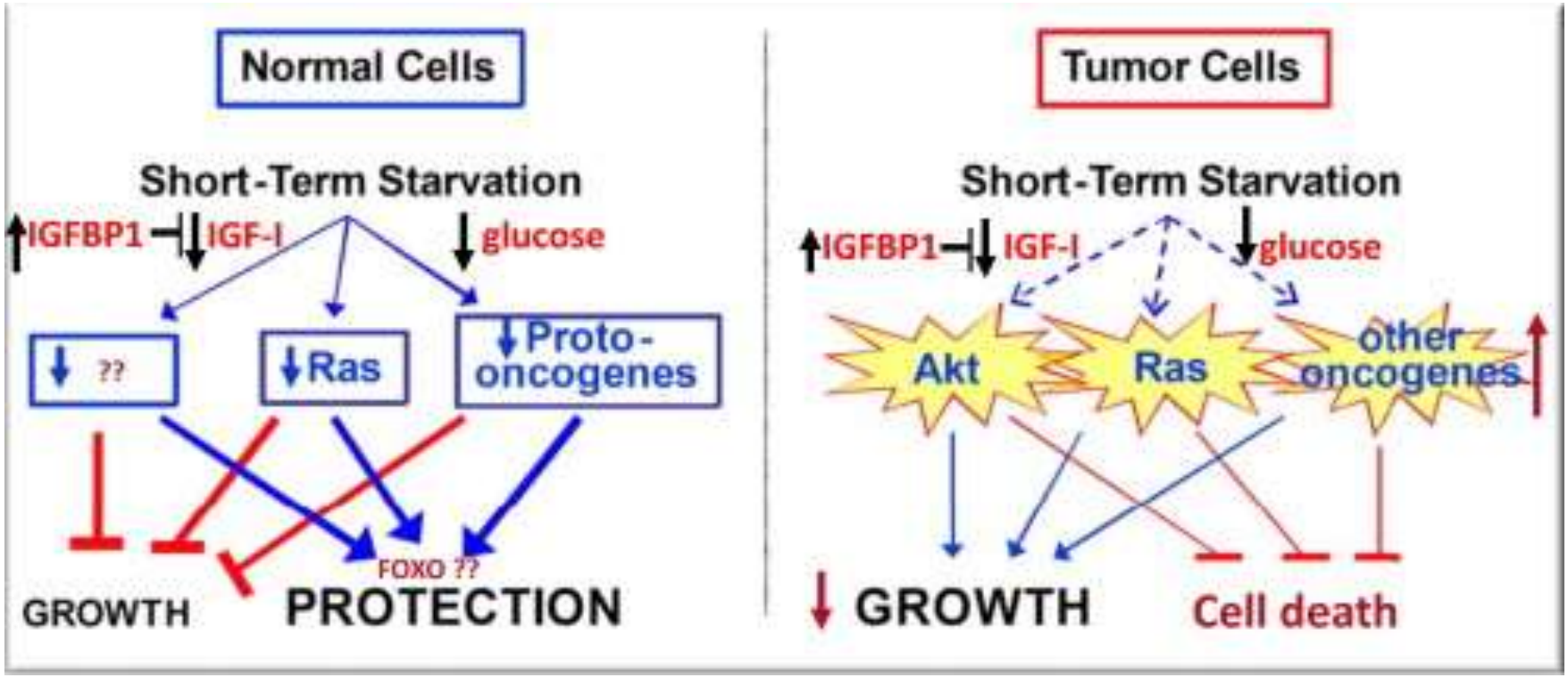
OTHER INGREDIENTS: Stearic Acid, Microcrystalline Cellulose, Dicalcium Phosphate, Croscarmellose Sodium, Magnesium Stearate, Silicone Dioxide, Food-grade Shellac

Nutrition Facts
Serving Size 1 Tablet
Servings Per Container: 2

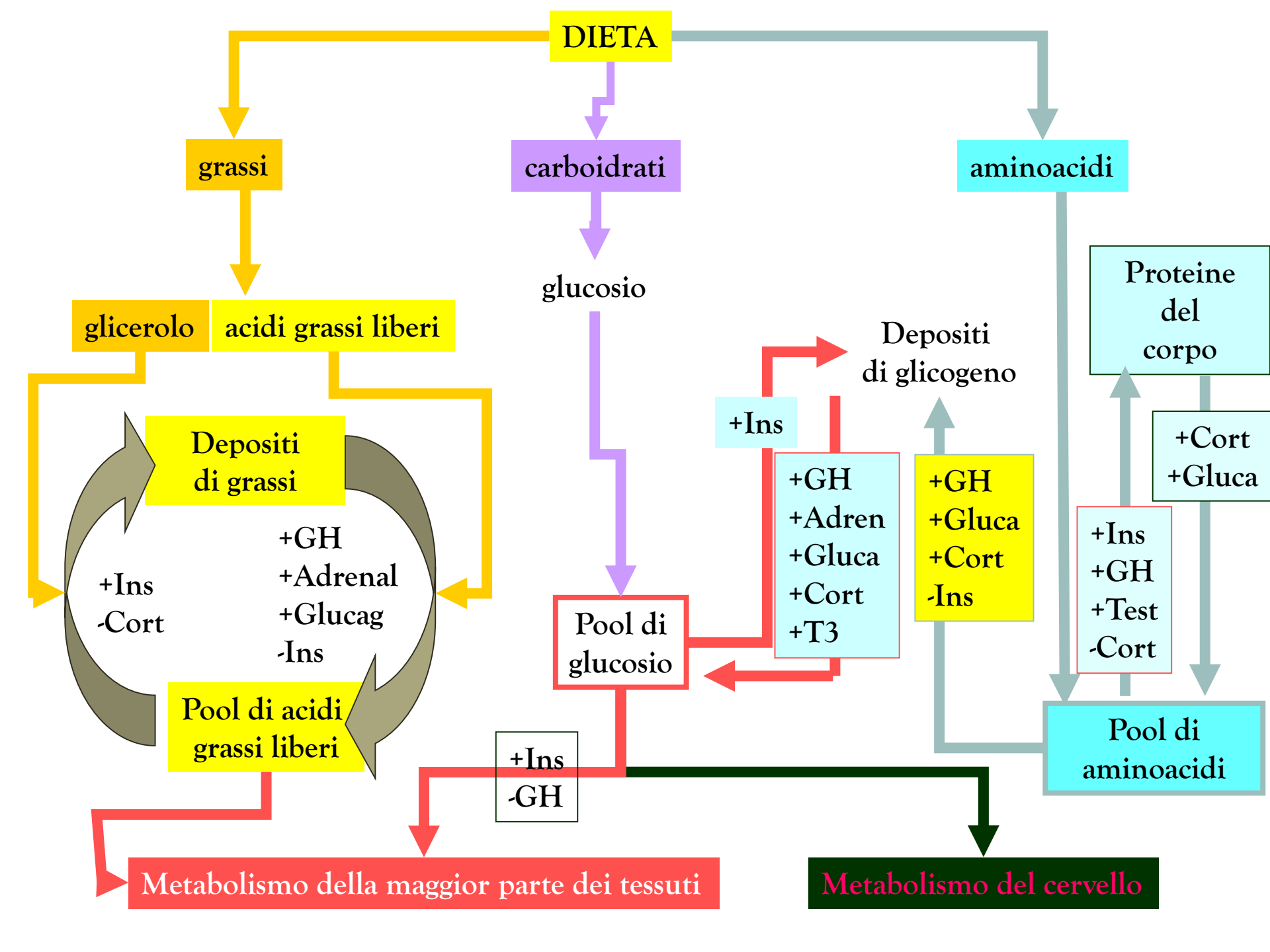
Amount per Serving		% Daily Value*
Vitamin A (as Beta Carotene)	1,250 IU	25%
Vitamin C (Ascorbic Acid)	15 mg	25%
Vitamin D (as Cholecalciferol)	100 IU	25%
Vitamin E (as DL-Alpha Tocopherol Acetate)	7.5 IU	25%
Vitamin K (as Phytonadione)	20 mcg	25%
Thiamine (as Thiamine Mononitrate)	0.37 mg	25%
Riboflavin	0.42 mg	25%
Niacin (as Niacinamide)	5 mg	25%
Vitamin B6 (as Pyridoxine HCl)	0.5 mg	25%
Folic Acid	100 mcg	25%
Vitamin B12 (as Cyanocobalamin)	1.5 mcg	25%
Biotin	15 mcg	5%
Pantothenic Acid (as Calcium-D-Pantothenate)	2.5 mg	25%
Calcium (as Calcium Carbonate and Tribasic Calcium Phosphate)	100 mg	10%
Iron (as Ferrous Fumarate)	4.5 mg	25%
Phosphorous (as Tribasic Calcium Phosphate)	10 mg	1%
Iodine (as Potassium Iodine)	37.5 mcg	25%
Magnesium (as Magnesium Oxide)	26 mg	7%
Zinc (Zinc Oxide)	3.75 mg	25%
Selenium (as Sodium Selenate)	7.5 mcg	11%
Copper (as Cupric Sulfate)	0.25 mg	13%
Manganese (as Manganese Sulfate)	0.5 mg	25%
Chromium (as Chromium Picolinate)	17.4 mcg	15%
Molybdenum (as Sodium Molybdate)	18.75 mcg	25%
L-Nutra Power Blend (Beet Root, Spinach Leaf, Tomato Fruit, Carrot Root, Collard Leaf, Kale Leaf)	600 mg	**

* Percent Daily Values are based on a 2,000 calorie diet.
** Daily Values not established.

Differential Stress Resistance and Sensitization in Aging, Disease Prevention, and Cancer Treatment

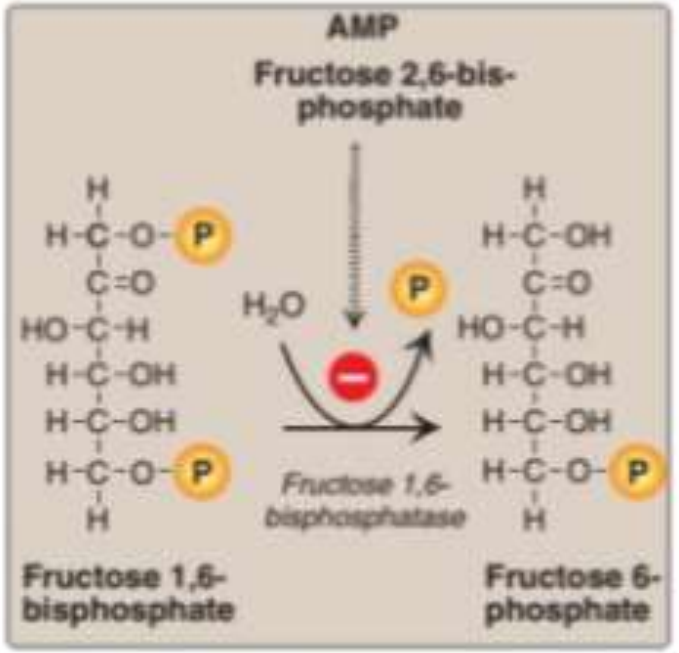


Longo V, Mattson P. Cell Metabolism, Volume 19 (Issue 2), 4 February 2014, Pages 181-192

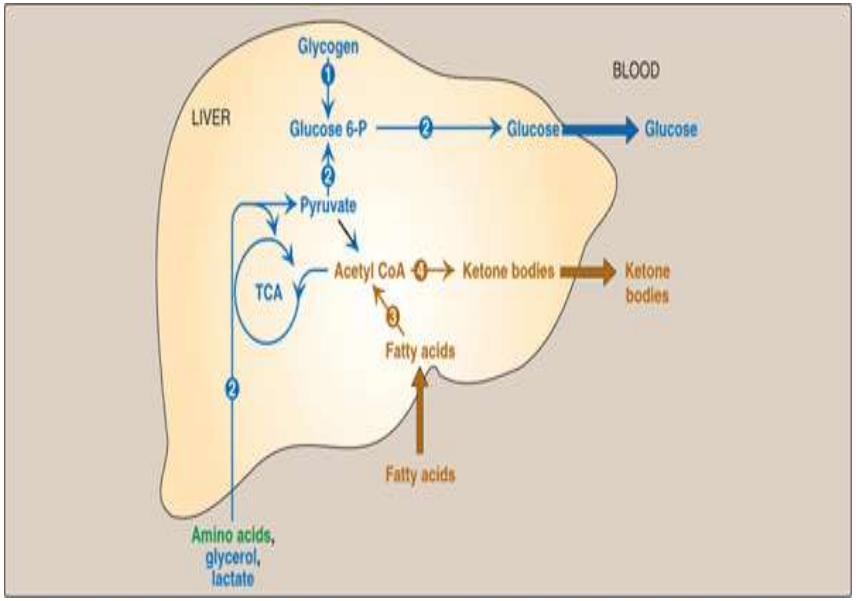

DIETA
grassi
carboidrati
aminoacidi
glicerolo
acidi grassi liberi
glucosio
Proteine del corpo
Depositi di grassi
+GH
+Adrenal
+Glucag
-Ins
+Ins
-Cort
Depositi di glicogeno
+Ins
+GH
+Adren
+Gluca
+Cort
+T3
+GH
+Gluca
+Cort
-Ins
+Cort
+Gluca
+Ins
+GH
+Test
-Cort
Pool di glucosio
Pool di acidi grassi liberi
+Ins
-GH
Pool di aminoacidi
Metabolismo della maggior parte dei tessuti
Metabolismo del cervello

INCREASED NEUGLOGENESIS

- Gluconeogenesis is favored by
  - Activation of **"fructose 1,6-bisphosphatase"** due to drop in its inhibitor **"fructose 2,6-bisphosphate"**
  - Induction of **"phosphoenolpyruvate (PEP) carboxykinase"** by glucagon.

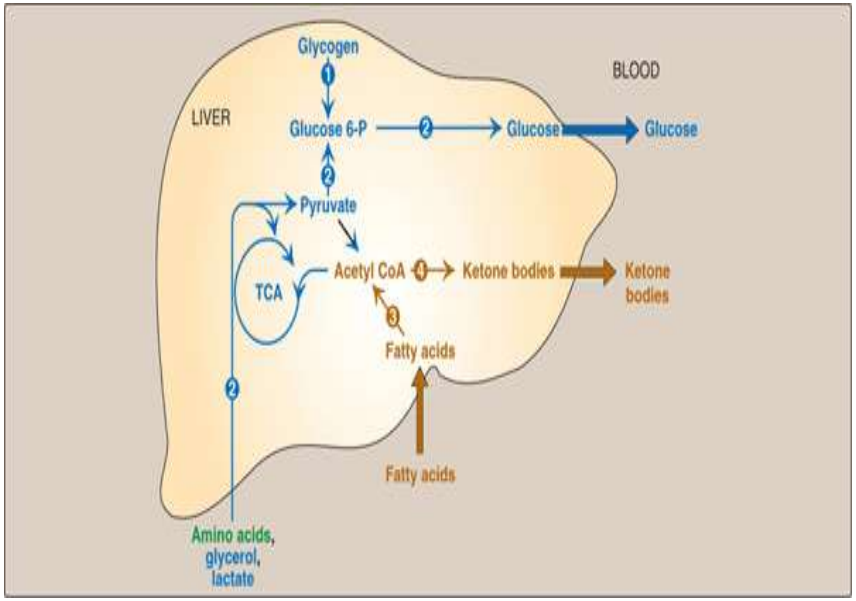


INCREASED GLYCOGEN DEGRADATION



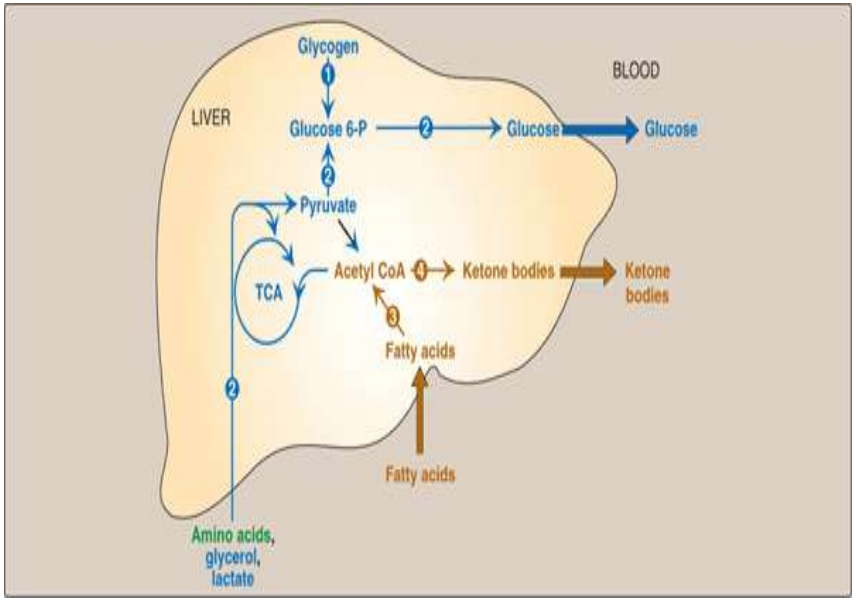
- During the brief absorptive period, glucose from the diet is the major source of blood glucose.
- Several hours after the meal, blood glucose levels have declined sufficiently to cause increased secretion of glucagon and decreased release of insulin.
- The increased glucagon to insulin ratio causes a rapid mobilization of liver glycogen stores (which contain about 80 g of glycogen in the well-fed state).
- Hepatic glycogenolysis is a transient response to early fasting.

INCREASED GLUCONEOGENESIS



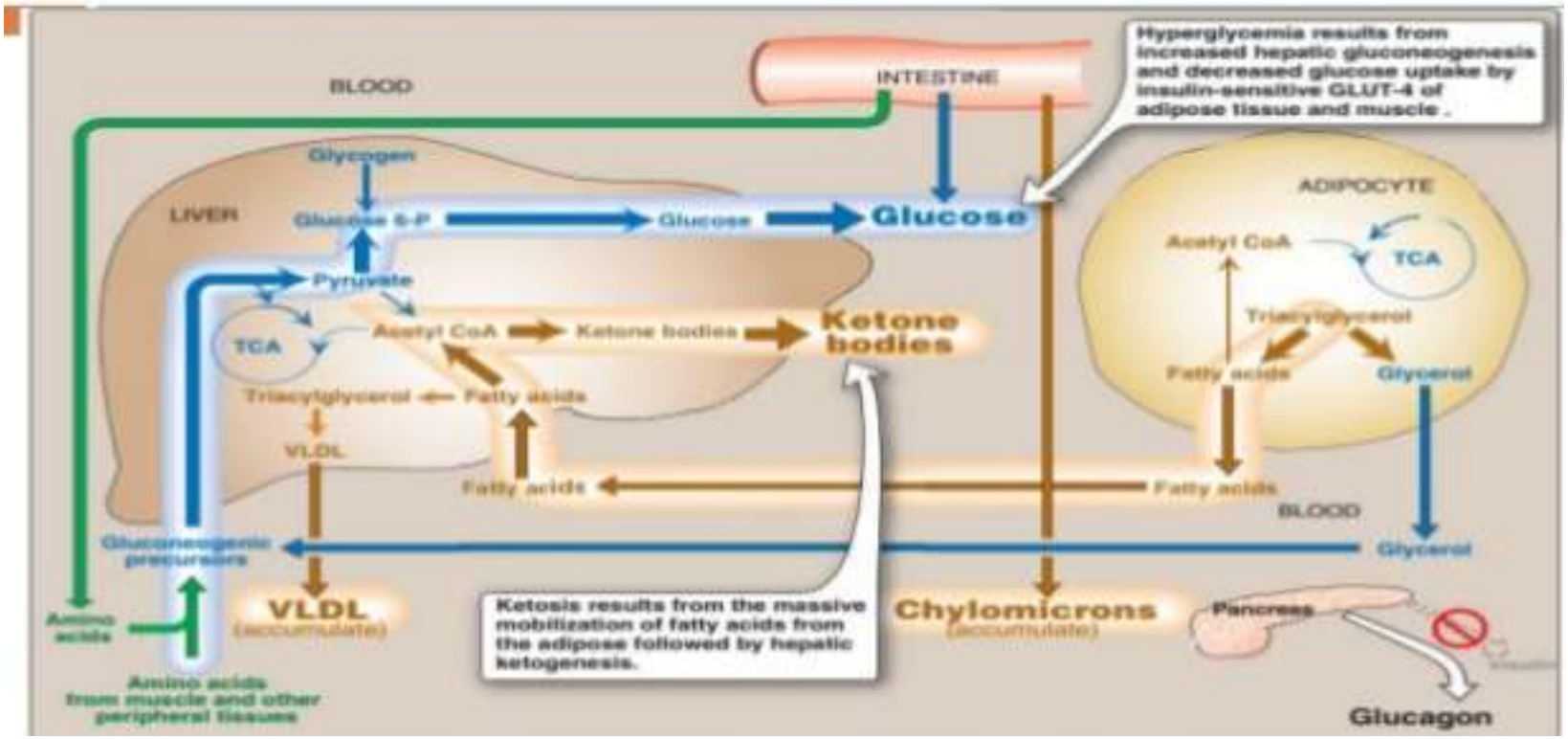
The synthesis of glucose and its subsequent release into the circulation are vital hepatic functions during fasting ②.

INCREASED GLUCONEOGENESIS



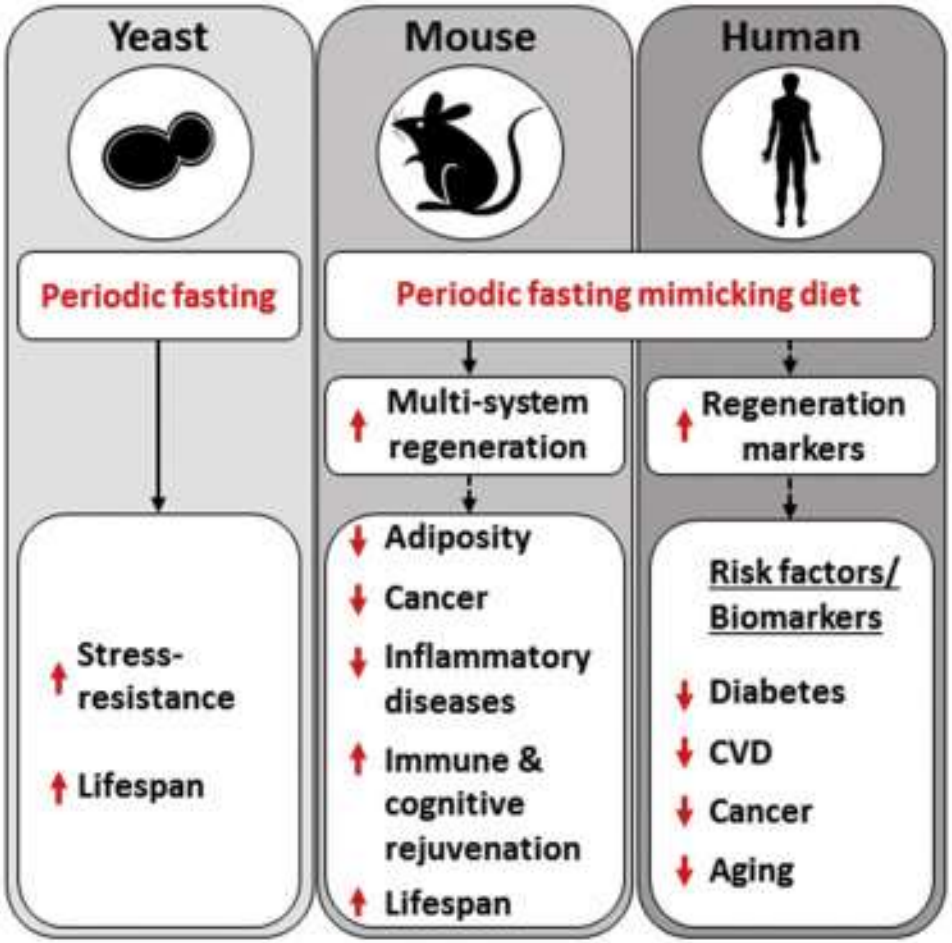
- Gluconeogenesis, favored by activation of fructose 1,6-bisphosphatase (due to a drop in its inhibitor, fructose 2,6-bisphosphate) and
- by induction of phosphoenolpyruvate (PEP) carboxykinase by glucagon.

SYNETSIS OF KETONE BODIES



A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan

- FMD rejuvenates the immune system and reduces cancer incidence in C57BL/6 mice
- FMD promotes hippocampal neurogenesis and improves cognitive performance in mice
- FMD causes beneficial changes in risk factors of age-related diseases in humans



Brandhorst S. et al. Cell Metabolism, Volume 22, 7 July 2015, Pages 86-99

Confronto delle variabili con dieta normale, dieta chetogena e chetoacidosi diabetica

	Dieta normale	Dieta chetogena	Ketoacidosi diabetica
Glicemia	80-100	65-80	>250
Insulina	moderata	bassa	assente
Glucagone	basso	elevato	elevato
Sintesi di ketoni g/die	Bassa	115-180	400
Ketonemia mmol/dl	0.1	4-10	20+
PH sangue	7.4	7.4	<7.3

EFFETTI COLLATERALI

- Disidratazione
- Nausea/vomito, diarrea, stipsi
- Cefalea, crampi muscolari
- Astenia
- Alitosi, rash-cutaneo
- Elevati livelli di colesterolo e trigliceridi ,ridotti livelli di colesterolo HDL
- Aumento transitorio dei livelli di ac. urico
- Ipoglicemia
- Carenze di Ca, di Mg, di Na e di vitamine

Sintomi e segni precoci

- Riduzione della densità ossea
- Nefrolitiasi
- Cardiomiopatia
- Deficit di ferro, anemia

Alterazioni pondero-staturali

Sintomi e segni tardivi

Necessarie Integrazioni minerali e vitaminiche

A LUNGO TERMINE MANTENERE LA PERDITA DI PESO:

Difficile per la riduzione nella spesa energetica indotta dal calo ponderale

Difficile per le modificazioni ormonali conseguenti il calo ponderale

Dipende soprattutto dal grado di aderenza alle prescrizioni nutrizionali più che dalla combinazione dei macronutrienti

Maggior aderenza se le prescrizioni nutrizionali considerano i gusti, le preferenze del paziente

Advances in Nutrition
AN INTERNATIONAL REVIEW JOURNAL

Could Intermittent Energy Restriction and Intermittent Fasting Reduce Rates of Cancer in Obese, Overweight, and Normal-Weight Subjects? A Summary of Evidence1,2

Michelle N Harvie* and Tony Howell
Genesis Prevention Centre, University Hospital South Manchester National Health Service Foundation Trust, Manchester, United Kingdom

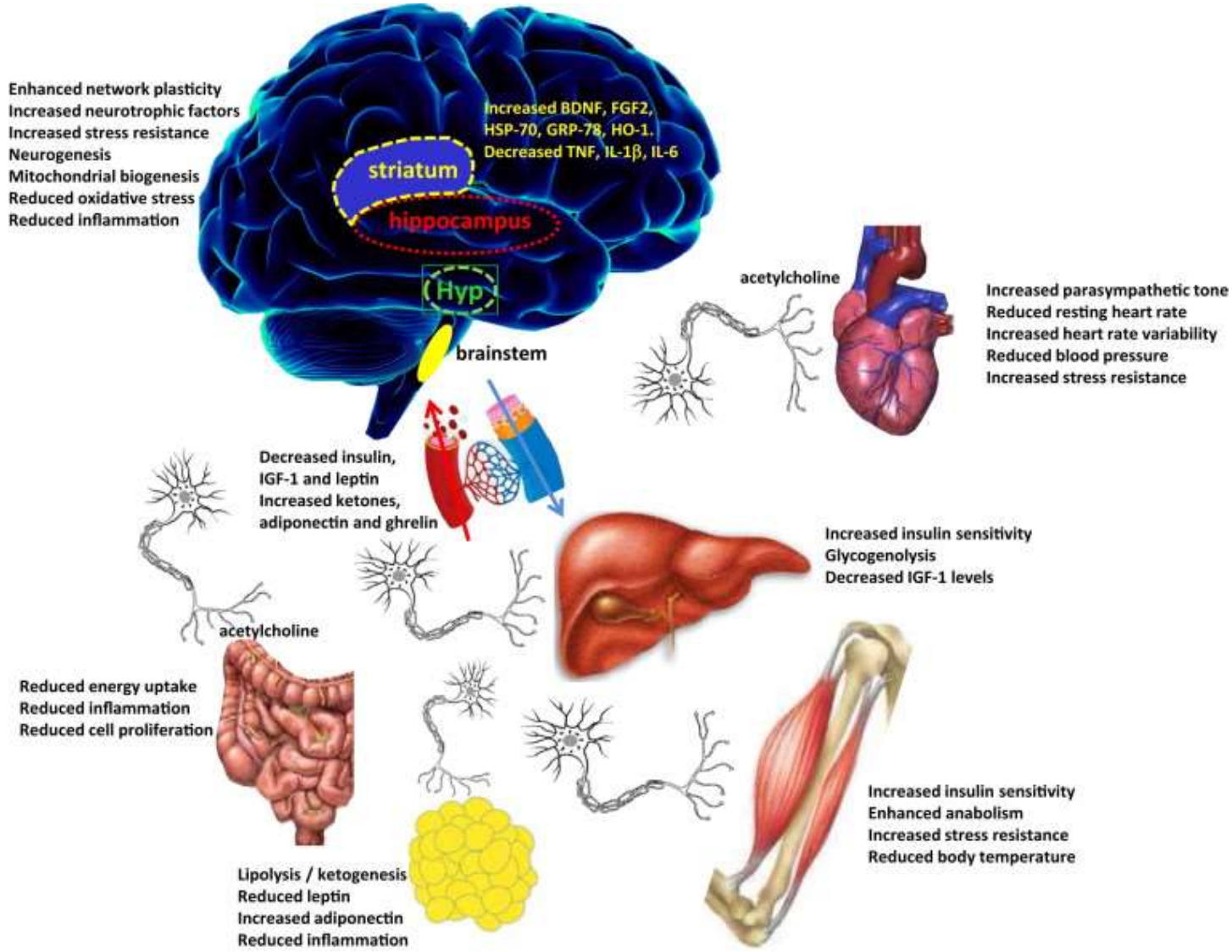
Compr Physiol. 2016 Mar 15;6(2):773-825. doi: 10.1002/cphy.c150013.

Integrative Physiology of Fasting.

Secor SM1, Carey HV

Extended bouts of fasting are ingrained in the ecology of many organisms, characterizing aspects of reproduction, development, hibernation, estivation, migration, and infrequent feeding habits. The challenge of long fasting episodes is the need to maintain physiological homeostasis while relying solely on endogenous resources. To meet that challenge, animals utilize an integrated repertoire of behavioral, physiological, and biochemical responses that reduce metabolic rates, maintain tissue structure and function, and thus enhance survival. We have synthesized in this review the integrative physiological, morphological, and biochemical responses, and their stages, that characterize natural fasting bouts. Underlying the capacity to survive extended fasts are behaviors and mechanisms that reduce metabolic expenditure and shift the dependency to lipid utilization. Hormonal regulation and immune capacity are altered by fasting; hormones that trigger digestion, elevate metabolism, and support immune performance become depressed, whereas hormones that enhance the utilization of endogenous substrates are elevated. The negative energy budget that accompanies fasting leads to the loss of body mass as fat stores are depleted and tissues undergo atrophy (i.e., loss of mass). Absolute rates of body mass loss scale allometrically among vertebrates. Tissues and organs vary in the degree of atrophy and downregulation of function, depending on the degree to which they are used during the fast. Fasting affects the population dynamics and activities of the gut microbiota, an interplay that impacts the host's fasting biology. Fasting-induced gene expression programs underlie the broad spectrum of integrated physiological mechanisms responsible for an animal's

Pivotal Roles of the Nervous and Endocrine Systems as Mediators of Adaptive Responses of Major Organ Systems to Intermittent Fasting



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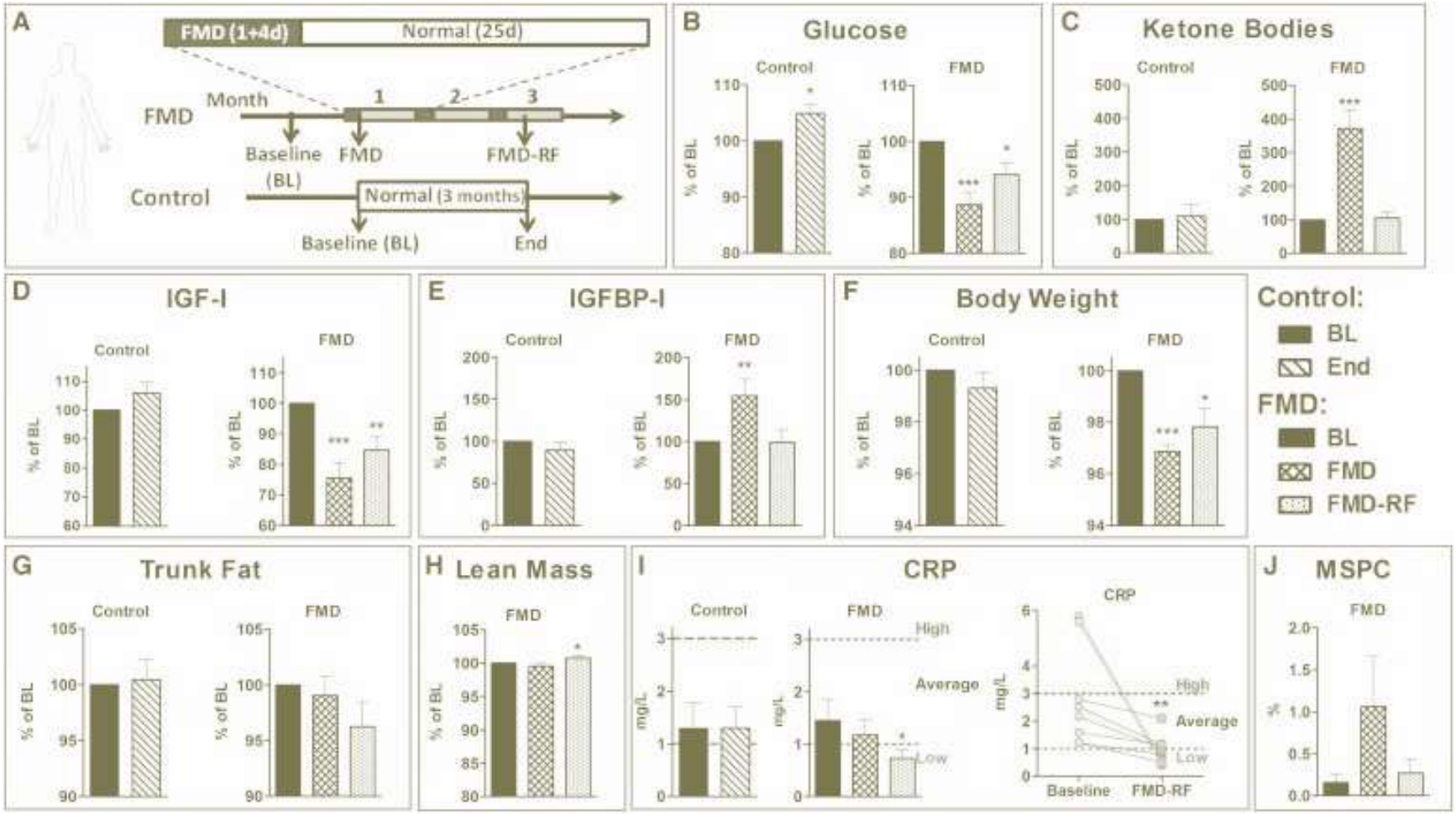
Effects of a Human-Adapted FMD Regimen in a Pilot Clinical Trial



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INTERMITTENT FASTING REGIMENS HYPOTHESIZED TO IMPACT HEALTH OUTCOMES

Type of fast	Description
Complete alternate-day fasting	Involves alternating fasting days (no energy-containing foods or beverages consumed) with eating days (foods and beverages consumed ad libitum)
Modified fasting regimens	Allows consumption of 20–25% of energy needs on scheduled fasting days; the basis for the popular 5:2 diet, which involves severe energy restriction for 2 nonconsecutive days per week and ad libitum eating for the other 5 days
Time-restricted feeding	Allows ad libitum energy intake within specific time frames, inducing regular, extended fasting intervals; studies of <3 meals per day are indirect examinations of a prolonged daily or nightly fasting period
Religious fasting	Variety of fasting regimens undertaken for religious or spiritual purposes
Ramadan fasting	A fast from sunrise to sunset during the holy month of Ramadan; the most common dietary practice is to consume one large meal after sunset and one lighter meal before dawn. Thus, the feast and fast periods of Ramadan are approximately 12 hours in length
Other religious fasts	Members of the Church of Jesus Christ of Latter-Day Saints routinely abstain from food and drink for extended periods of time. Some Seventh-day Adventists consume their last of two daily meals in the afternoon, resulting in an extended nighttime fasting interval that may be biologically important

A Randomized Pilot Study Comparing Zero-Calorie Alternate-Day Fasting to Daily Caloric Restriction in Adults with Obesity

Victoria A. Catenacci[1,2], Zhaoxing Pan[3], Danielle Ostendorf[2,4], Sarah Brannon[5], Wendolyn S. Gozansky[6], Mark P. Mattson[7,8], Bronwen Martin[9], Paul S. MacLean[1,2], Edward L. Melanson[1,10], and William Troy Donahoo[1,6]

Objective: To evaluate the safety and tolerability of alternate-day fasting (ADF) and to compare changes in weight, body composition, lipids, and insulin sensitivity index (Si) with those produced by a standard weight loss diet, moderate daily caloric restriction (CR).

Methods: Adults with obesity (BMI $\geq$30 kg/m^2, age 18-55) were randomized to either zero-calorie ADF ($n = 14$) or CR (−400 kcal/day, $n = 12$) for 8 weeks. Outcomes were measured at the end of the 8-week intervention and after 24 weeks of unsupervised follow-up.

Results: No adverse effects were attributed to ADF, and 93% completed the 8-week ADF protocol. At 8 weeks, ADF achieved a 376 kcal/day greater energy deficit; however, there were no significant between-group differences in change in weight (mean ± SE; ADF −8.2 ± 0.9 kg, CR −7.1 ± 1.0 kg), body composition, lipids, or Si. After 24 weeks of unsupervised follow-up, there were no significant differences in weight regain; however, changes from baseline in % fat mass and lean mass were more favorable in ADF.

Conclusions: ADF is a safe and tolerable approach to weight loss. ADF produced similar changes in weight, body composition, lipids, and Si at 8 weeks and did not appear to increase risk for weight regain 24 weeks after completing the intervention.

Obesity (2016) **24**, 1874–1883. doi:10.1002/oby.21581

Can a Diet That Mimics Fasting Turn Back the Clock?

Jennifer Abbasi