Mahidol University
Faculty of Medicine
Siriraj Hospital

SIPS539 : Advanced Endocrine and Reproductive Physiology

Master of Science Program in Medical Physiology (International Program)

“Obesity”

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Outline

- Obesity
- Energy balance
- Adipose tissue
- Weight-loss diet regimens
- Principle of Weight Management
- Weight regain
- Diet break or Cheat days
- Weight loss maintenance

Energy Balance

Energy Intake

Food intake

Appetite regulation

- Hypothalamus
  - Orexigenic (NPY&AGRP) neurons
  - Anorexigenic (POMC&CART) neurons
- Brainstem
- Reward system
- Periphery
  - Vagal signal
  - Leptin, insulin
  - Gut hormones

Positive energy balance

Obesity

- Prevalence
- Related diseases
- Adipose tissue & adipokines

Energy Expenditure

- Basal metabolic rate (BMR)
- Thermic effect of food
- Non-exercise activity thermogenesis (NEAT)
- Exercise

https://vectortoons.com/wp-content/uploads/2014/05/fat-people-collection-002.jpg

Obesity

http://cf067b.medialib.glogster.com/media/17/1766da671072324f3486b3785f97f2c5feed1e115e135f859505bac63a8b2def/really-fat-man-clip-art.jpg

What is Obesity?

Obesity

WHO:
“Abnormal or excessive fat accumulation that presents a risk to health”

Obesity: World Health Organization (WHO) Available from: https://www.who.int/health-topics/obesity#tab=tab_1

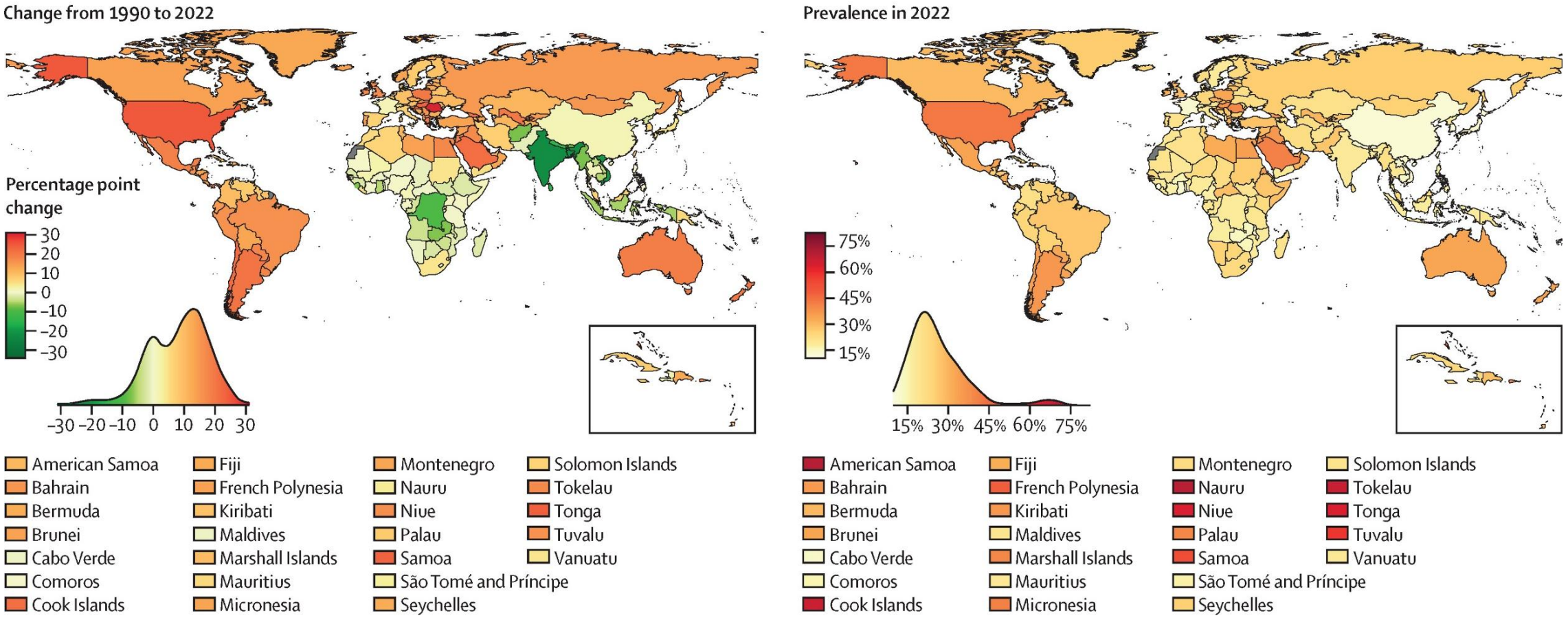
Prevalence of Obesity

- Globally from 1975 to 2016
  - ↑Prevalence of overweight or obese children and adolescents aged 5–19 years > four-fold from 4% to 18%

- In 2016,
  - Adults ≥ 18 years
    - >1.9 billion (39%) → overweight
    - >650 million (13%) → obese
  - Children ≤ 5 years
    - 39 million → overweight or obese
  - Children and adolescents, 5-19 years
    - >340 million → overweight or obese

Obesity: World Health Organization (WHO); 2020 [updated 9 July 2021.
Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

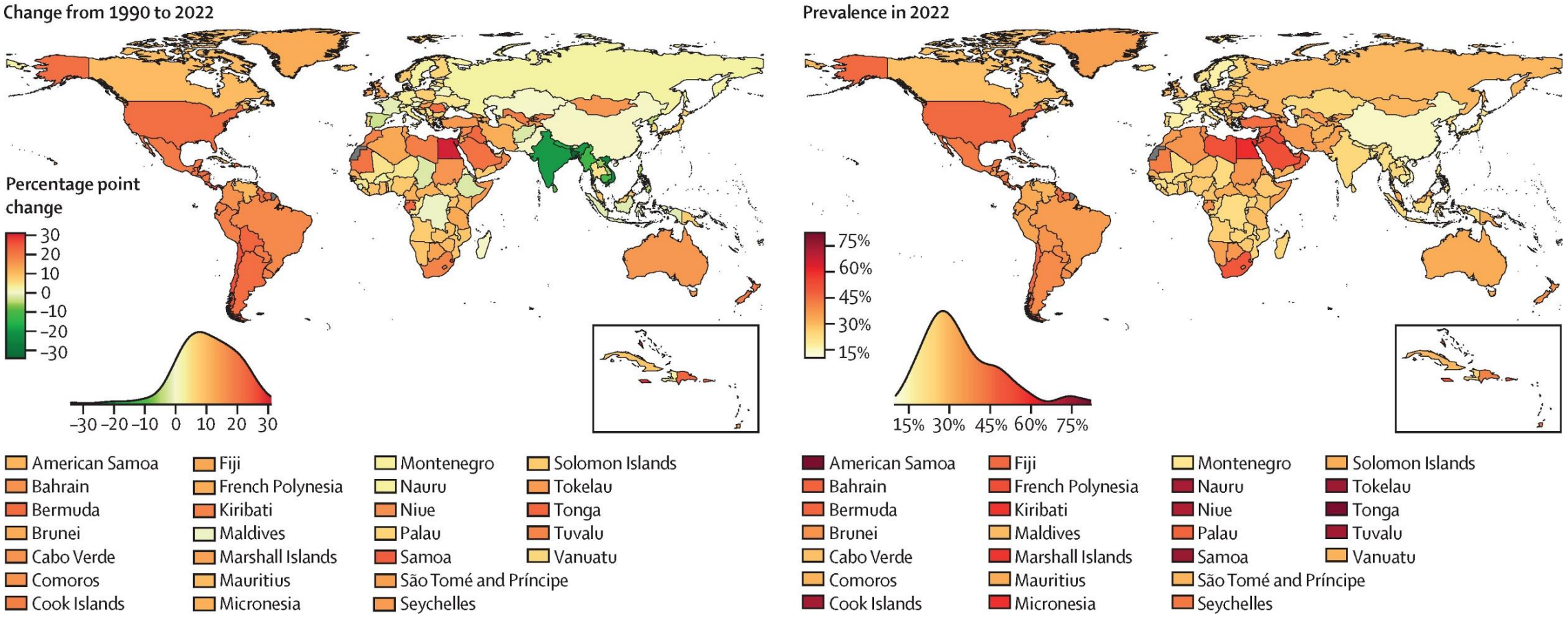
Men



Age-standardized combined prevalence of underweight and obesity by country, for adults (age ≥20 years)

Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population representative studies with 222 million children, adolescents, and adults. Lancet (London, England). 2024;403(104301):1027-1050.

Women



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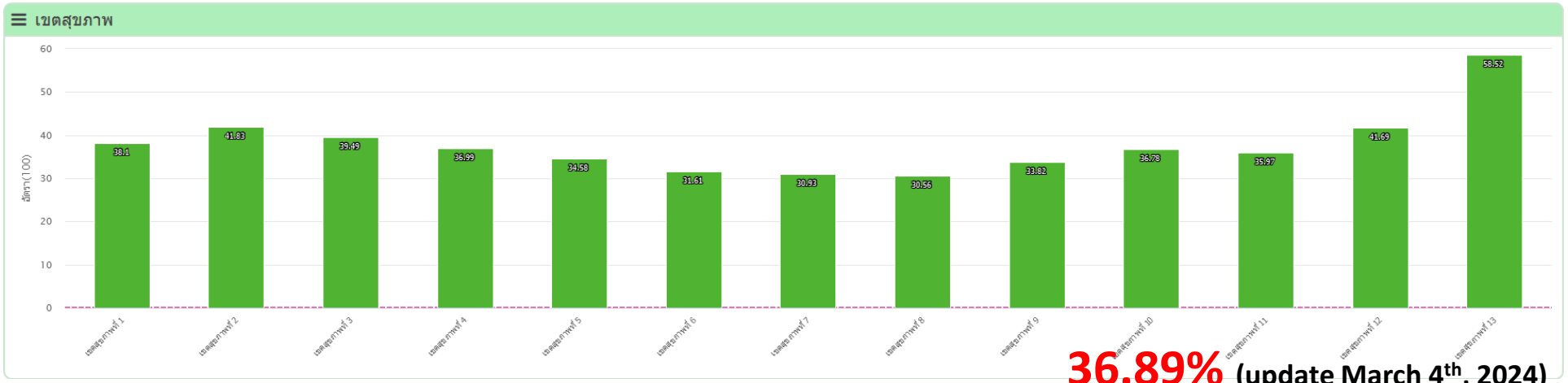
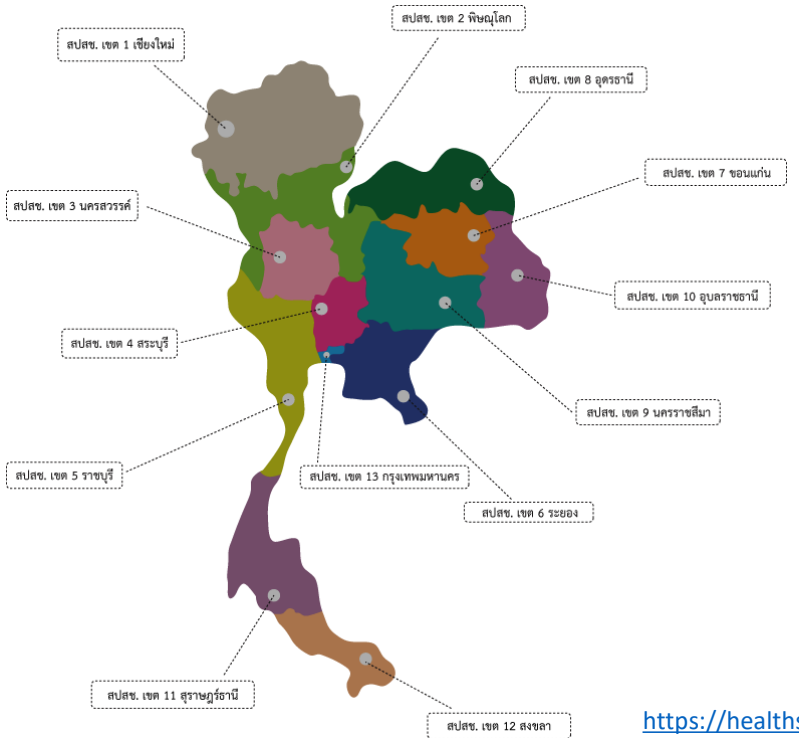
ความชุกของภาวะอ้วน (BMI ≥25 กก/ม^2 และหรือภาวะอ้วนลงพุง (รอบเอว ชาย ≥90 ซม. หญิง ≥80 ซม.)



36.89% **(update March 4th, 2024)**

https://hdcservice.moph.go.th/hdc/reports/report.php?source=kpi/kpi.php&cat_id=46522b5bd1e06d24a5bd81917257a93c&id=a75e43f7e044704ec9a993266d3f6704#



https://healthserv.net/1330

Available Metabolic Fuels in a Normal-Weight 70 kg Man and in an Obese 140 kg Man at the Beginning of a Fast

TABLE 23–5 Available Metabolic Fuels in a Normal-Weight 70 kg Man and in an Obese 140 kg Man at the Beginning of a Fast

Type of fuel	Weight (kg)	Caloric equivalent (thousands of kcal (kJ))	Estimated survival (months)*
Normal-weight, 70 kg man			
Triacylglycerols (adipose tissue)	15	141 (589)	
Proteins (mainly muscle)	6	24 (100)	
Glycogen (muscle, liver)	0.225	0.90 (3.8)	
Circulating fuels (glucose, fatty acids, triacylglycerols, etc.)	0.023	0.10 (0.42)	
Total		166 (694)	3
Obese, 140 kg man			
Triacylglycerols (adipose tissue)	80	752 (3,140)	
Proteins (mainly muscle)	8	32 (134)	
Glycogen (muscle, liver)	0.23	0.92 (3.8)	
Circulating fuels	0.025	0.11 (0.46)	
Total		785 (3,280)	14

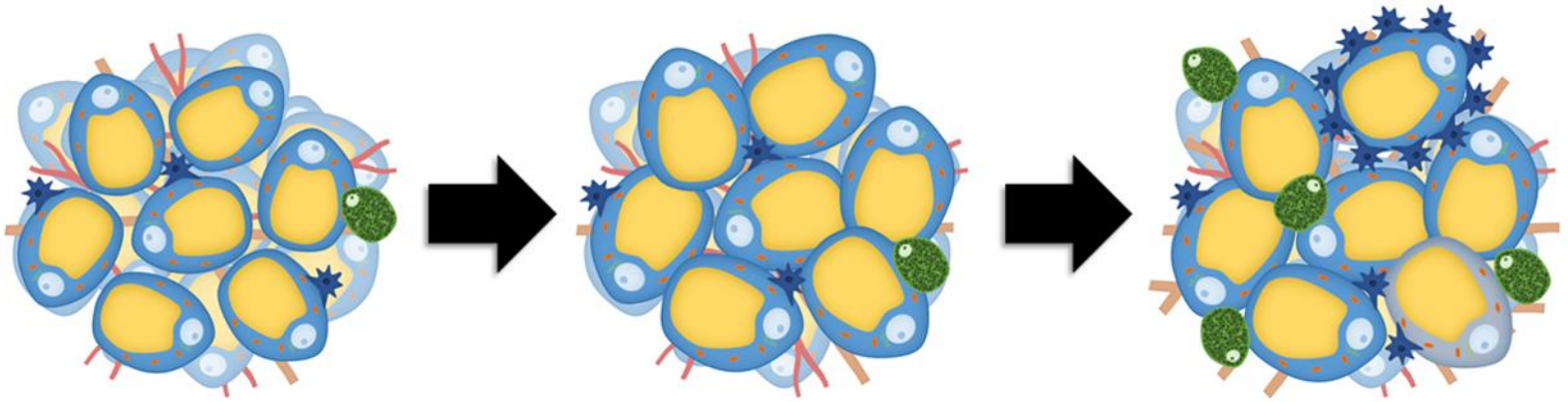
*Survival time is calculated on the assumption of a basal energy expenditure of 1,800 kcal/day.

Table 23-5
Lehninger Principles of Biochemistry, Fifth Edition

Lehnigner Principles of biochemistry

TAGs stored in the adipose tissue of a normal-weight adult could provide enough fuel to maintain a basal rate of metabolism for 3 months.
A very obese adult has enough stored fuel to endure a fast of more than a year.

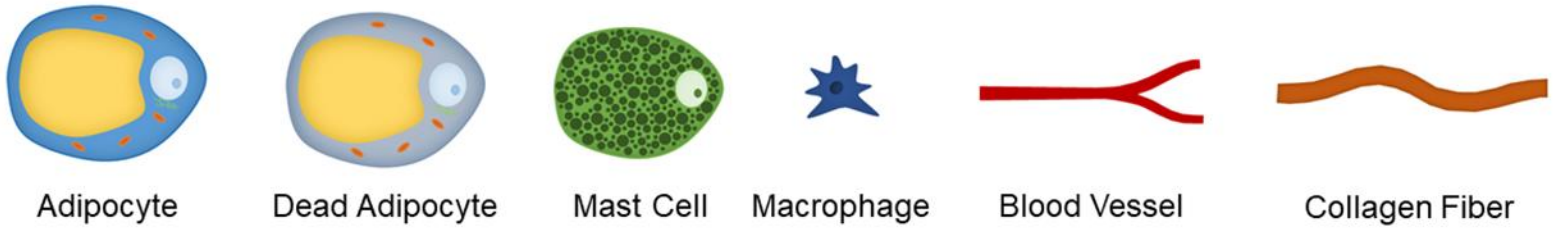
Obesity: Chronic inflammatory state



Healthy Adipose Tissue
Macrophage and mast cells are present in low numbers and blood vessels are near all cells.

Obese Adipose Tissue
Adipocytes enlarge during obesity creating acute hypoxia. Enlarged adipocytes begin producing proinflammatory chemokines.

Fibrotic Adipose Tissue
If hypoxia is not relieved, macrophage and mast cells are attracted to the area, adipocytes undergo cell death, and excess ECM proteins are produced.



Proinflammatory chemokines: tumor necrosis factor-alpha (TNFα), inducible nitric oxide synthase (iNOS), interleukin 6 (IL-6), interleukin 8 (IL-8), C-reactive protein, transforming growth factor beta 1 (TGFβ1), soluble intercellular adhesion molecule (ICAM), and monocyte chemoattractant protein 1 (MCP-1)

DeBari, M.K.; Abbott, R.D. Adipose Tissue Fibrosis: Mechanisms, Models, and Importance. *Int. J. Mol. Sci.* **2020**, *21*, 6030. https://doi.org/10.3390/ijms21176030

EXERCISE PHYSIOLOGY
Seventh Edition
NUTRITION, ENERGY, AND HUMAN PERFORMANCE

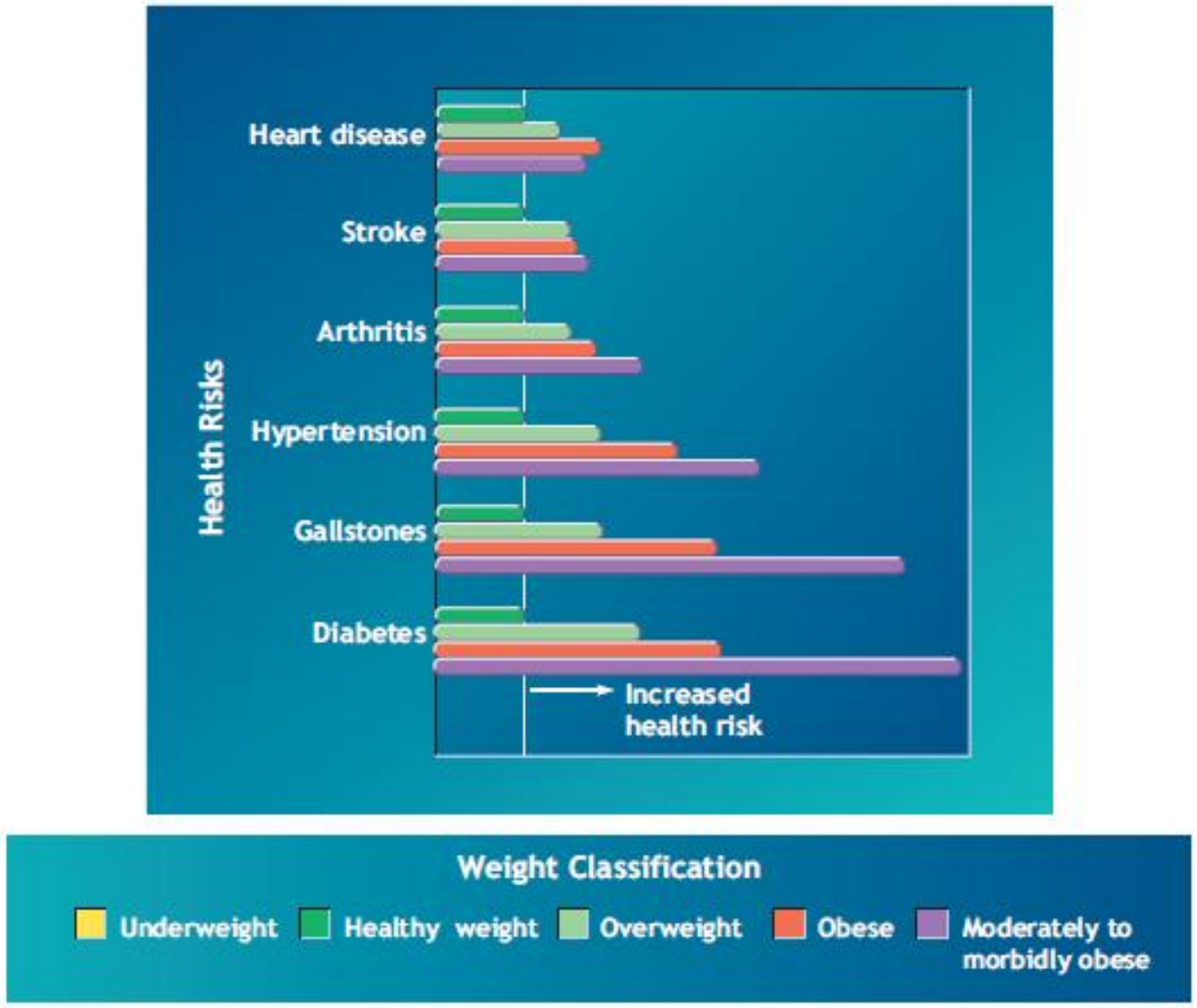


Figure 28.2 • Body mass index (BMI), weight classifications, and associated health risks.

How to Classify Obesity?

Classification of Obesity

Category	Caucasian BMI (Kg/m^2)	Asian BMI (Kg/m^2)
Underweight	<18.5	<18.5
Normal weight	18.5-24.9	18.5-22.9
Overweight	25-29.9	23-24.9
Obese	≥30.0	≥25
Obese class I	30.00 - 34.9	25.0-29.9
Obese class II	35.00 - 39.9	≥30.0
Obese class III	≥40.00	Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies, 2004, Jitnarin N et al 2011

WHO 2016, The Asia-pacific perspective: Redefining obesity and its treatment, 2000

Classification of Obesity

Asian compared to western people

- ↑% Body fat for the same age and sex and BMI
- ↑Risk factors for type 2 DM and cardiovascular diseases in the same BMI

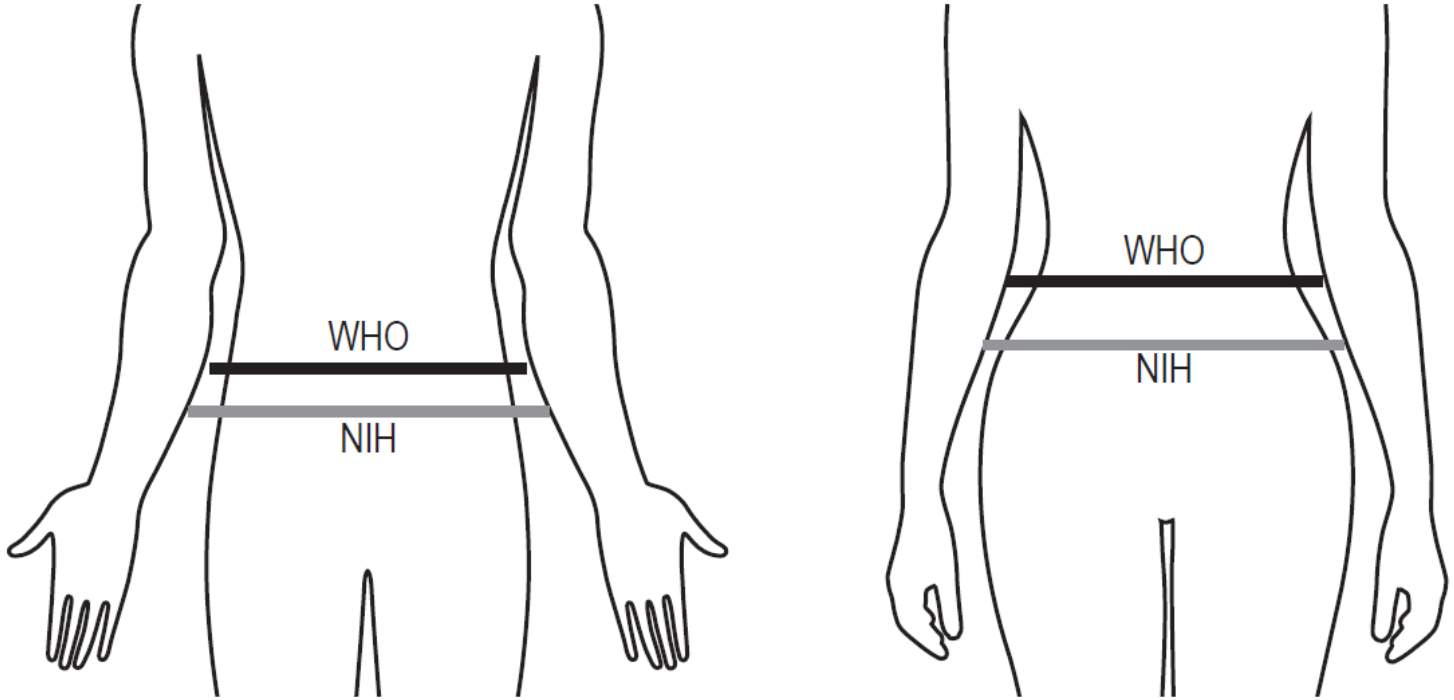
WHO 2016, The Asia-pacific perspective: Redefining obesity and its treatment, 2000

Anthropometric data

- Waist circumference and waist to hip ratio
  - Highly associated with
    - Abdominal or central obesity
    - ↑Risk of metabolic syndrome, cardiovascular diseases, chronic diseases
  - Better indicator of obesity related diseases > BMI

Waist circumference

Waist circumference measurement sites for men and women based on World Health Organization (WHO) and National Institutes of Health (NIH) protocols



Note: Following the WHO protocol, the measure is taken midway between the highest point of the iliac crest and the bottom of the ribcage. Following the NIH protocol, the measure is taken at the highest point of the iliac crest.

Patry-Parisien J, Shields M, Bryan S. Comparison of waist circumference using the World Health Organization and National Institutes of Health protocols. Health reports. 2012;23(3):53-60.

Adiposity measurements

- **Skinfold thickness**
  - Relative “fatness” or
  - To assess the size of specific subcutaneous fat depots

Biceps skinfold
(front side middle upperarm)

http://www.copdplatform.com/index.php?pg=home--ffmi-and-mamc-skinfold-measurement

Triceps skinfold
(back side middle upperarm)

https://nutritionalassessment.mumc.nl/en/skinfold-measurements

Subscapular skinfold
(under the lowest point of the shoulder blade)

http://www.copdplatform.com/index.php?pg=home--ffmi-and-mamc-skinfold-measurement

Suprailiac skinfold
(above the upper bone of the hip)

https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcSmJy6N4R8MG8WpbEyt0lMTESVhs3ZosHfe5x6osYpaes54bfvV

Adiposity measurements

- Bioelectrical Impedance Analysis (BIA)
  - Commonly used method for estimating body composition, in particular body fat and muscle mass
  - A weak electric current flows through the body and the voltage is measured in order to calculate impedance (resistance) of the body.
  - In recent years, BIA is more reliable and more acceptable way of measuring body composition.
- Dual energy X-ray absorptiometry (DXA)
  - Measures bone mineral mass, FM, and FFM
- Magnetic resonance imaging (MRI)
  - Estimates the volume rather than the mass of adipose tissue
- DXA and MRI (not BIA) - reference method in body composition analysis

Criteria for diagnosis of metabolic syndrome

3 out of 5

1. Waist circumference
   - ≥102 cm in male or ≥88 cm in female
   - Or ≥90 cm in male or ≥80 cm in female in Asians
2. Triglyceride ≥150 mg/dl
3. HDL-cholesterol
   - <40 mg/dl in male or <50 mg/dl in female
4. BP ≥130/85 mmHg
5. FBS ≥100 mg/dl or diabetes

Misra A et al. Waist circumference cutoff points and action levels for Asian Indians for identification of abdominal obesity. Int J Obes. [Multicenter Study Research Support, Non-U S Gov't Validation Studies]. 2006;30(1):106-11.

Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama. [Guideline Practice Guideline]. 2001;285(19):2486-97

Treatment for overweight and obesity in adult populations: a systematic review and meta-analysis, 2014

3 principal findings:

1. Every 1 kg of weight loss (people with impaired glucose tolerance)

- ↓16% Incidence of type 2 DM

2. Weight outcomes

- No significant difference between behavioral and pharmacologic
- Pharmacologic treatments >> potential adverse outcomes

3. Modest weight reduction

- Loss of ≥5% and ≥10% of baseline body weight
  - Clinically important effects
  - ↓38% Incidence of type 2 DM in prediabetic populations

(Peirson, L et al., 2014)

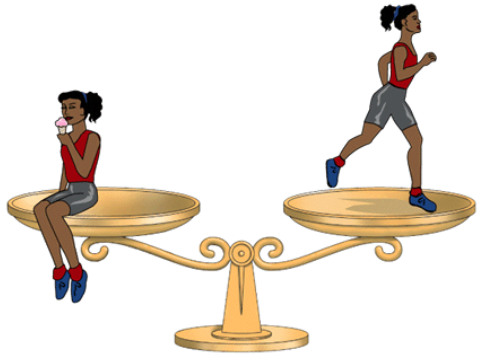
Diseases caused from obesity…

TREAT OBESITY

Case study

Case study

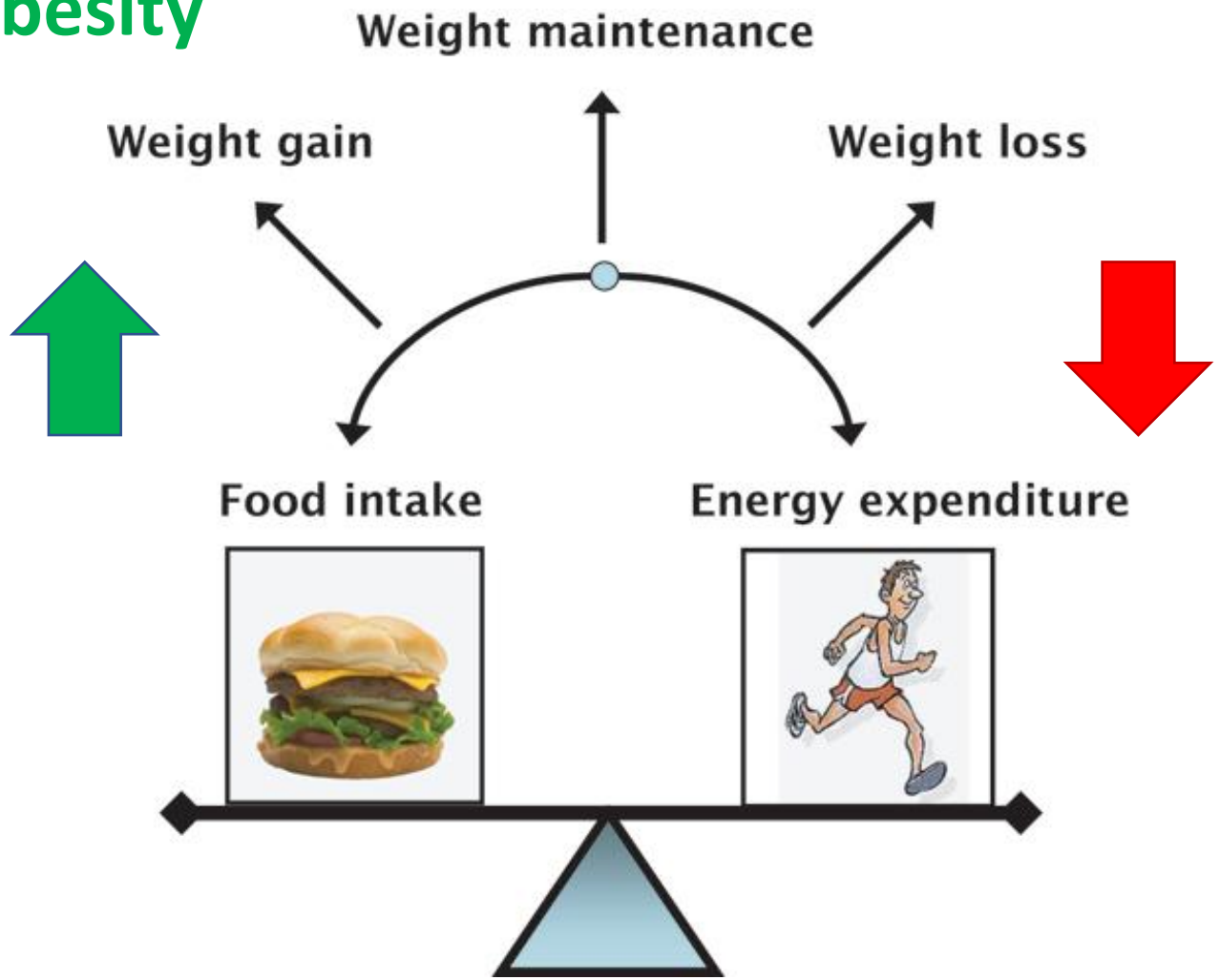
Energy balance



http://higheredbcs.wiley.com/legacy/college/smolin/047052474X/practice_quiz/smln2_ch07_pq_files/q35-1.png

Energy balance

Obesity



http://www.precisionnutrition.com/wordpress/wp-content/uploads/2009/04/energy-balance-continuum.jpg

Quiz

Diet vs. *Exercise*

Which one has more impact on weight loss?

1. Diet
2. Exercise

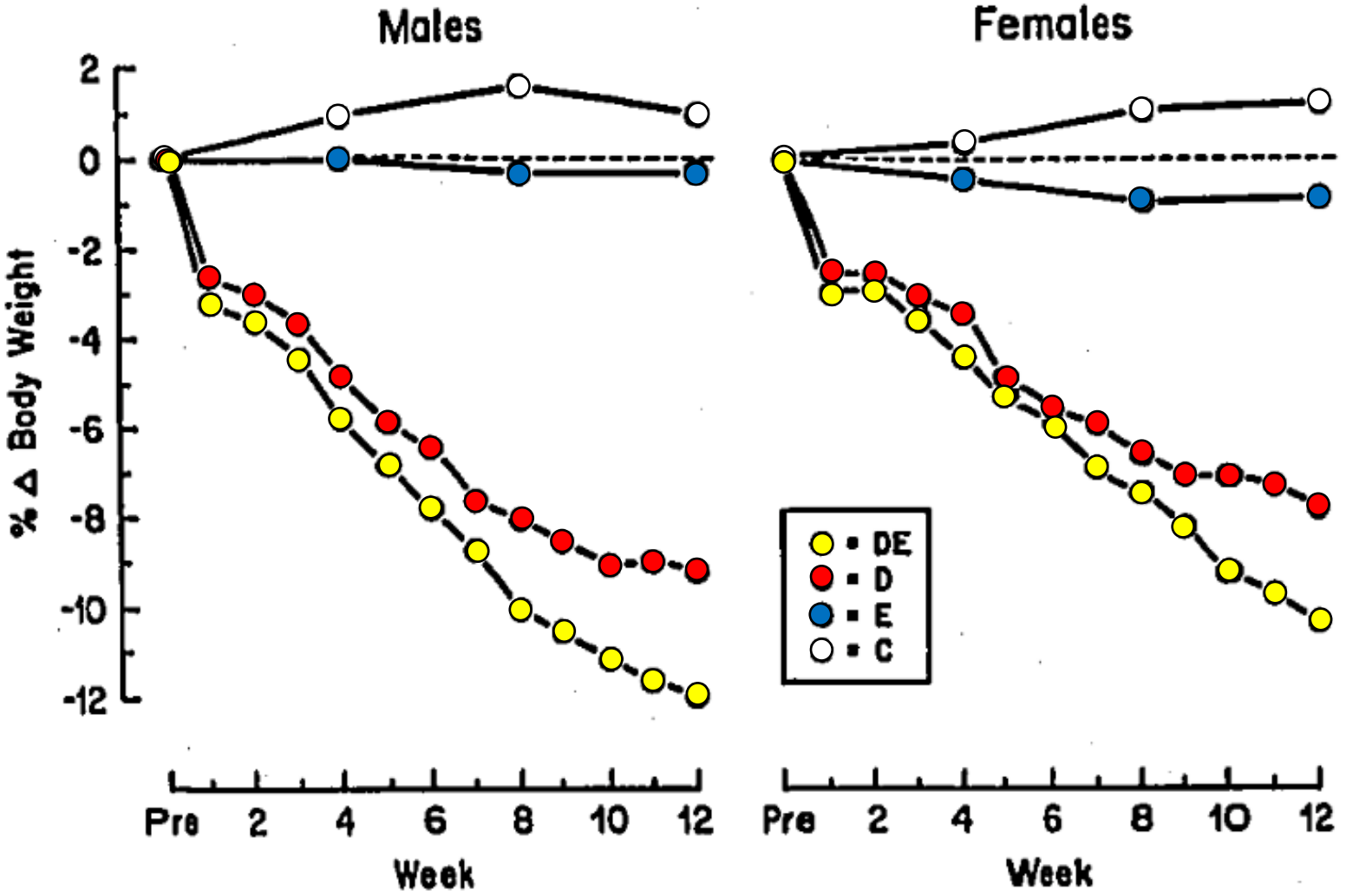


Figure 1—Percentage changes in body weight in males and females according to treatment effects of diet and exercise (DE), diet (D), exercise (E), and control (C).

Hagan RD et al. Sci Sports Exerc 1986;18:87–94

Quiz

What is the major factor determining energy expenditure?

1. BMR
2. Exercise
3. Thermic effects of food
4. Non-exercise activity thermogenesis (NEAT)

Energy output

Energy output

= Basal metabolic rate (BMR) 60-70%

+ Spontaneous physical activities (PA) 20-30%

+ Thermogenesis (Harrison's Principles of Internal Medicine, 18th e)

= BMR 70% + Active PA 5-10%

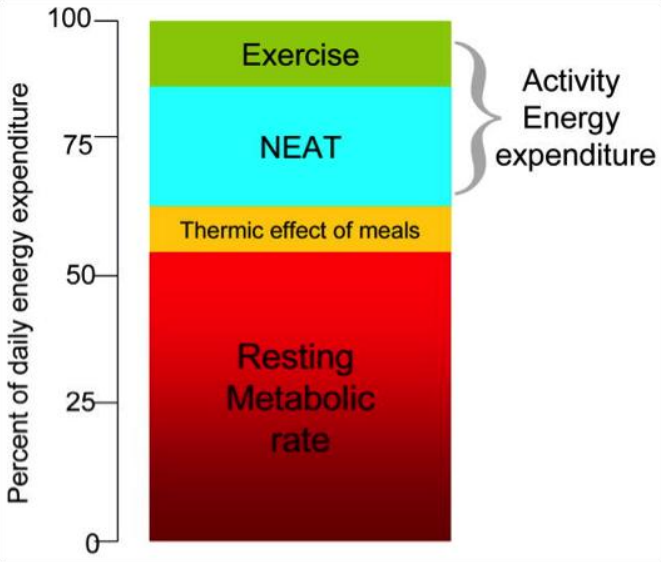
+ The energy cost of metabolizing and storing food

+ Adaptive thermogenesis

= External work (PA) + internal heat production (BMR + Diet induced thermogenesis - DIT)

± stored energy (Human physiology, 7th e, 2010)

Energy output



http://4.bp.blogspot.com/-obEju6EGjzo/T6FmPh8cgoI/AAAAAAAAExA/euaH3NKQBss/s1600/NEAT_graph.png

- **Exercise** (การออกกำลังกาย) ~ **5-15%**
  - Continuous activity at an intensity which ↑oxygen consumption or heart rate to an appropriate training level

C J Caspersen et al. , Public Health Rep., 1985,
Petrella RJ et al. Diabetes Care., 2005

- **Non-exercise activity thermogenesis, NEAT** (กิจกรรมทางกาย) ~ **15-25%**
  - Energy expenditure due to physical activities other than active sports-like exercise and resistance training
  - The main determinant of variability in total daily energy expenditure

- **Thermic effect of meals** ~ **10-15%**
  - The consumption, digestion, metabolism, and storage of food

- **Resting metabolic rate** ~ **60%**
  - Energy expenditure at rest

James A. Levine, Nutrition Reviews, 2004

Basal metabolic rate (BMR)

- Amount of energy expended while at rest
- Vital activities (respiration, pumping of blood around the body, maintenance of body temperature, brain function, etc.)
- In a neutrally temperate environment
- Post-absorptive state (inactive digestive system ~ 12 hours fasting)
- BMR/body surface area (Cal/m^2/hr)
- Closely related to resting metabolic rate (RMR)

Factors determining BMR

1. Genetics
2. Gender: Male (↑muscle mass, ↓fat) > Female
3. Age: ↓ ~ 2 %/decade after 20 years
4. Weight: the heavier weight, the higher BMR
5. Height: the taller, the higher BMR
6. Body Surface Area: the greater BSA, the higher BMR
7. %Body Fat: the lower % body fat, the higher BMR
8. Fasting: starvation, serious abrupt calorie-reduction, restrictive low-calorie weight loss diets

   → dramatically ↓BMR by up to 30 %

Fasting in humans

- The first 36-60 hours
  - ↑BMR
  - ↑NE and GH production
- Afterwards (72 or more)
  - ↓BMR
  - ↓NE and GH production

Factors determining BMR

9. Body Temperature: ↑0.5°C body T → ↑BMR ~ 7 %
10. External temperature:

    Cold T → ↑BMR

    Short exposure to hot T → Little effect on BMR (compensated by ↑heat loss)

    Prolonged exposure to heat → ↑BMR
11. Hormones: Thyroxin → ↑BMR
12. Exercise: ↑BMR (↑muscle mass)
13. Diets

Quiz

Which nutrient generates the highest thermic effect of food (TEF)?

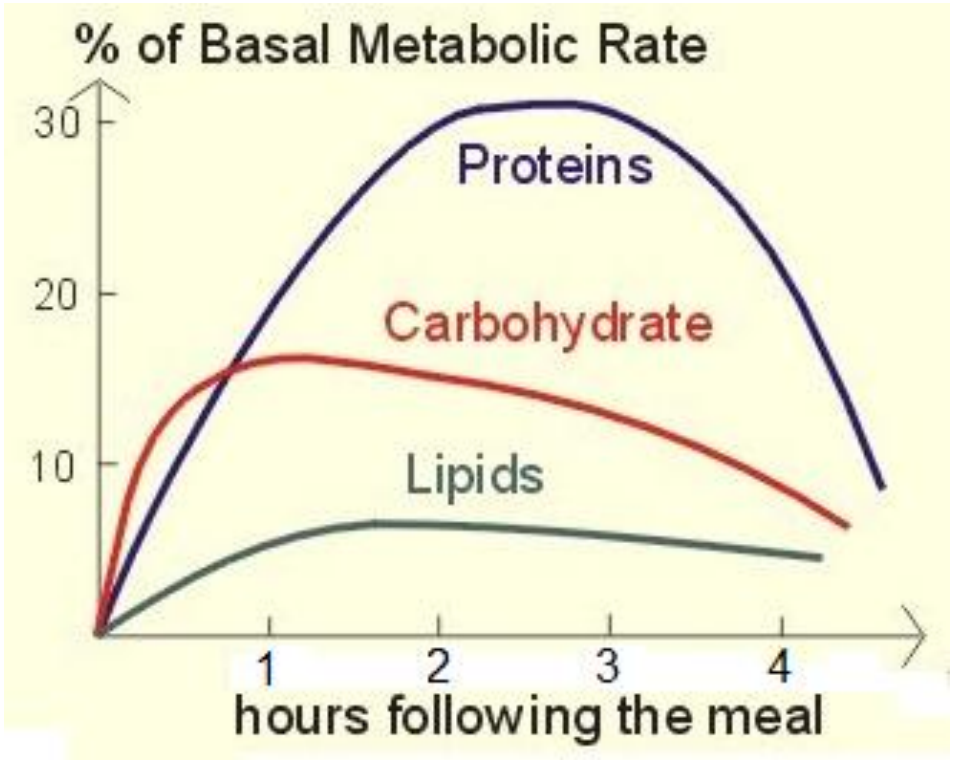
1. CHO
2. Lipid
3. Protein
4. Vitamins
5. Minerals

Basal metabolic rate

Thermic effects of nutrient are 0-3% for fat,

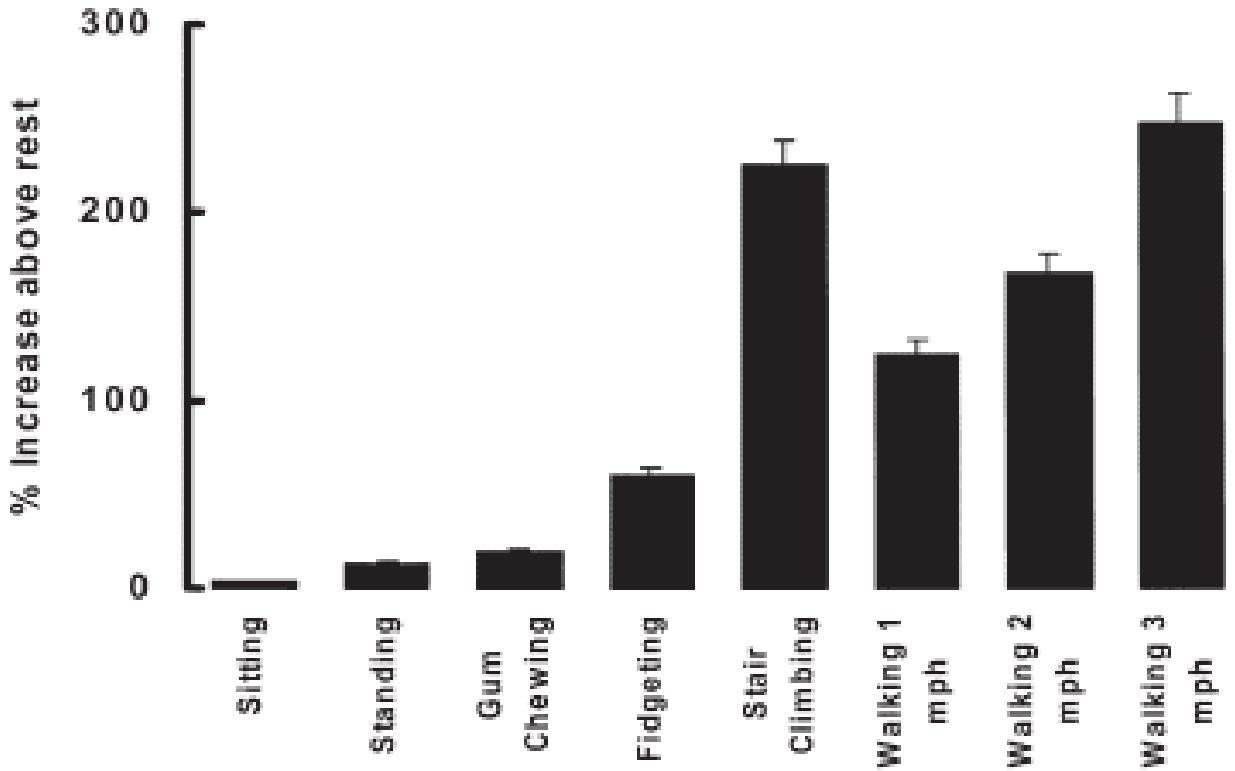
5-10% for carbohydrates and 20-30% for proteins.

Tappy L. Thermic effect of food and sympathetic nervous system activity in humans. Reproduction Nutrition Development. 1996;36(4):391–397.



http://upload.wikimedia.org/wikipedia/commons/8/81/Postprandial_thermogenesis.png

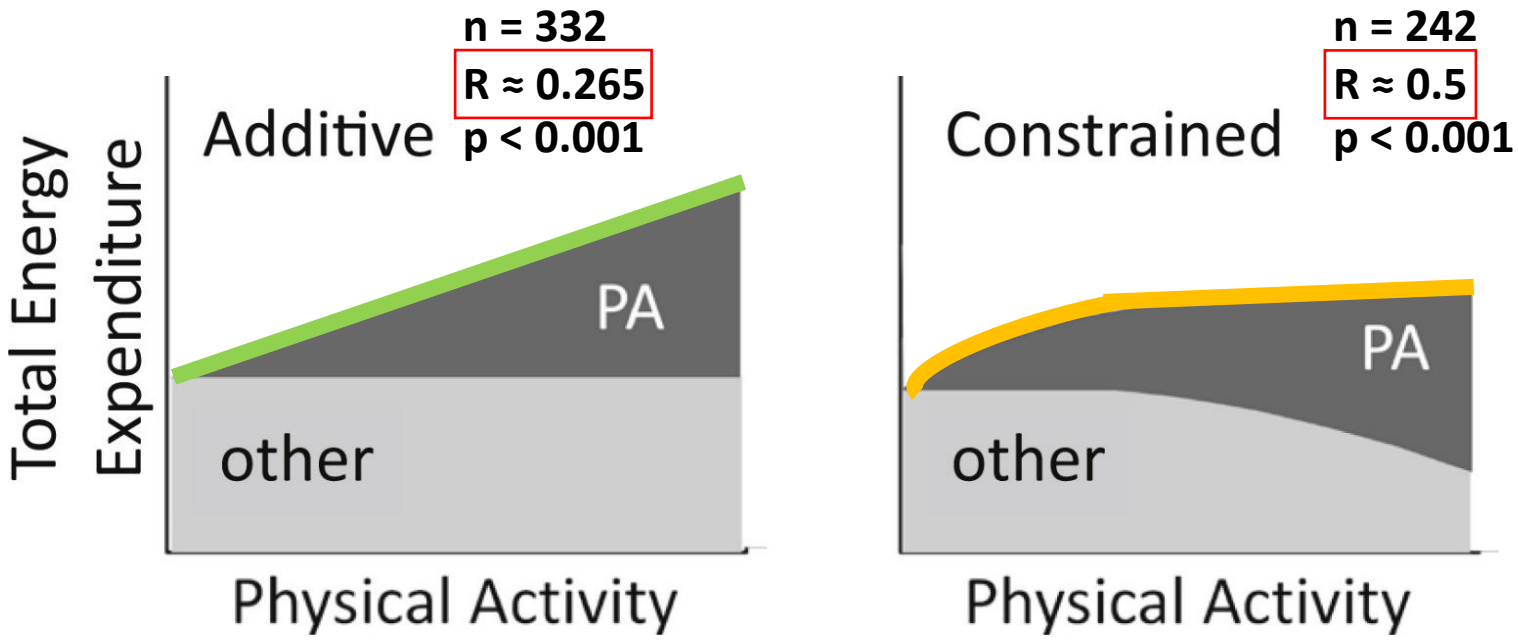
Non-exercise activity thermogenesis (NEAT)



1 mph (miles per hour) = 0.44704 m/s

James A. Levine, Nutrition Reviews, 2004

Long term effect of exercise on total energy expenditure

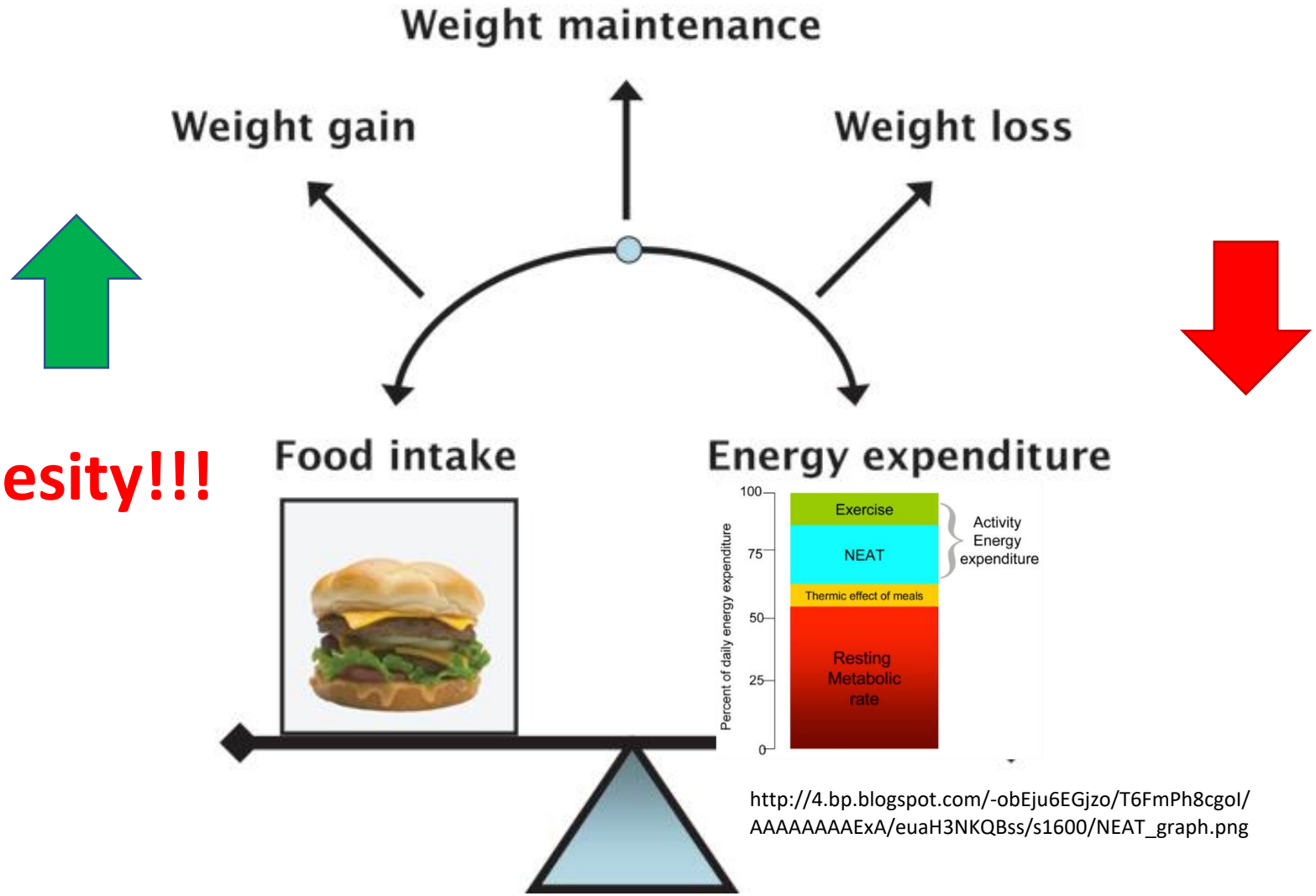


Pontzer H et al., Curr Biol., 2016

PA = physical activity energy expenditure,
TEE = total energy expenditure

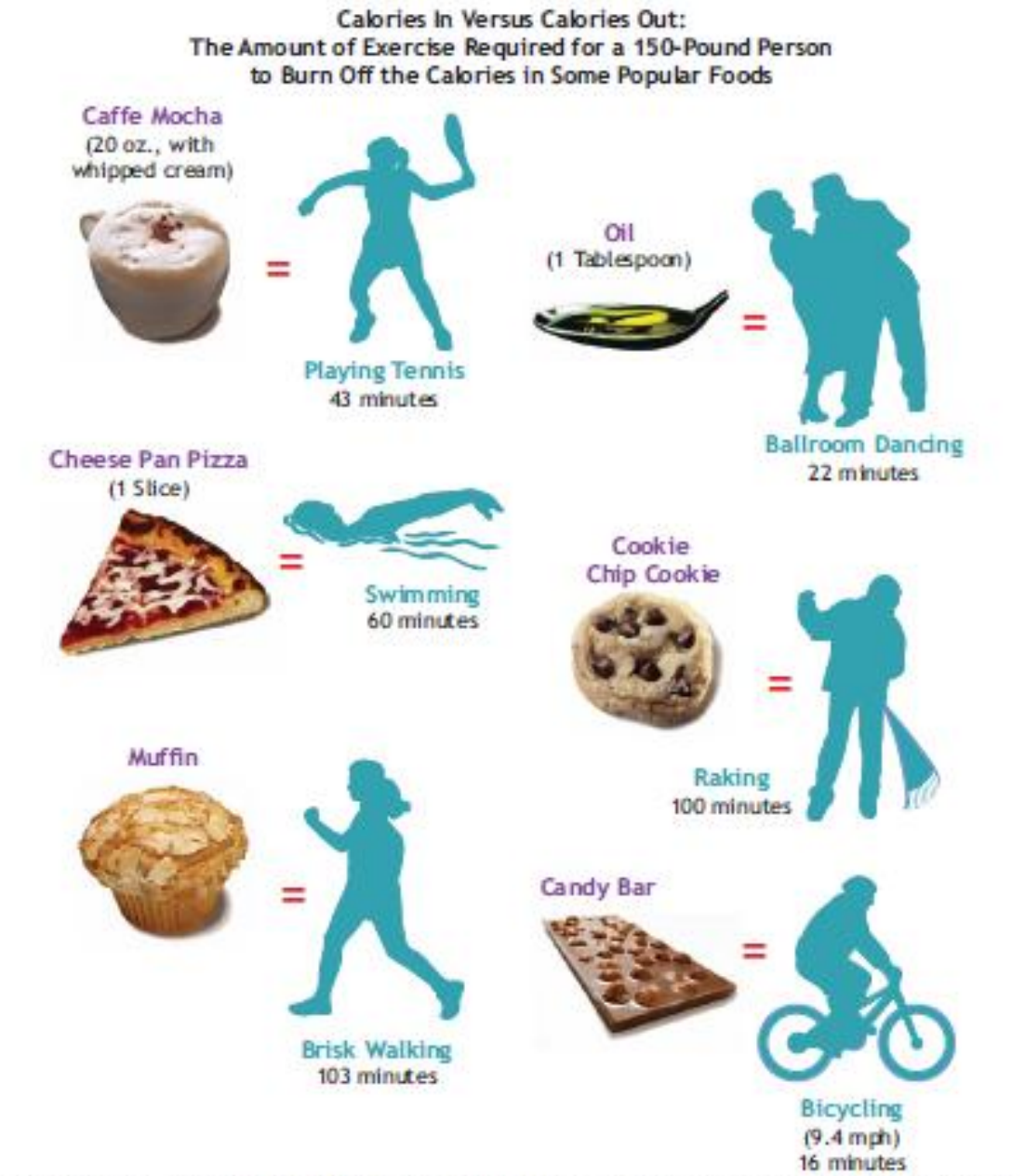
- ↓BMR at week 40
- Behavior change
  - Sitting instead of standing
  - Less fidgeting

Energy balance



http://4.bp.blogspot.com/-obEju6EGjzo/T6FmPh8cgoI/AAAAAAAAExA/euaH3NKQBss/s1600/NEAT_graph.png

http://www.precisionnutrition.com/wordpress/wp-content/uploads/2009/04/energy-balance-continuum.jpg



Calories in versus calories out: the amount of exercise required for a 150-pound person to burn off the calories in some popular foods.

- Exercise alone cannot effectively reduce body weight
  - A relatively slow elimination of energy due to its relatively low rate of energy expenditure
  - Take a long time to exercise or engage in physical activity to produce the same amount of energy as the food ingested
- Many people do not assess or are unable to assess the energy of the food eaten and/or the energy used in exercise correctly.

Appetite regulation

http://www.picgifs.com/clip-art/activities/eating/clip-art-eating-577214.jpg

http://www.bestfoodfacts.org/images/thought/4313895320_e68c831828.jpg

Appetite, Food intake, and Feeding Behavior

- Appetite
  - Sensations of hunger and fullness or the desire to eat food or the state of willingness to accept food primarily for its pleasurable or rewarding properties
- Food intake
  - The amount of food consumed
- Appetite ≠ Food intake

[Kissileff et al., 1982]

Appetite, Food intake, and Feeding Behavior

- Appetite
  - Also regulated by short-term and long-term control systems
- Short-term control
  - The initiation and termination of meals
- Long-term control
  - Signals that reflect the status of energy stores, such as the fat-derived hormone, leptin, provide information to the central nervous system (CNS) for further regulation of feeding behaviour to promote energy homeostasis

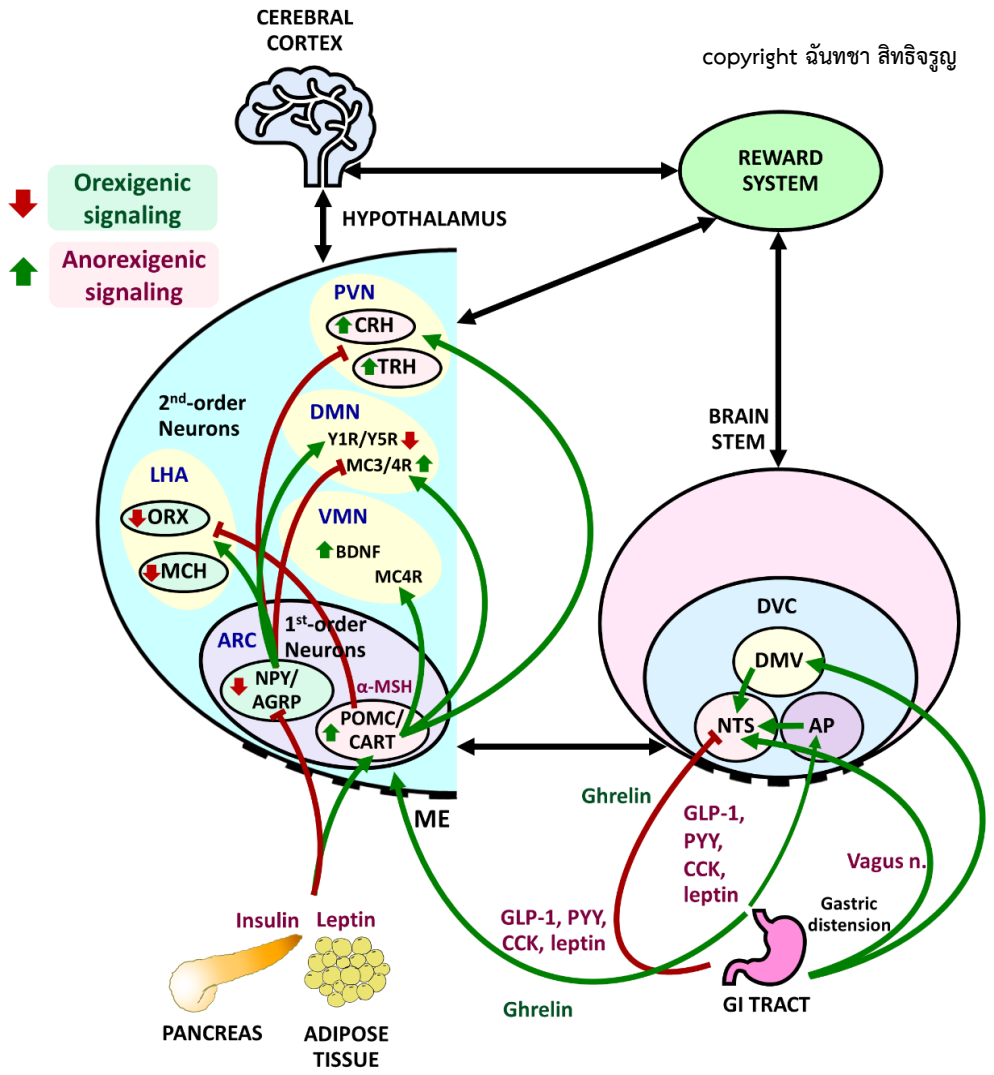
[Spiegelman et al., 2001].

[Ahima et al., 2000b]

Homeostatic system & Hedonic system

Homeostatic system

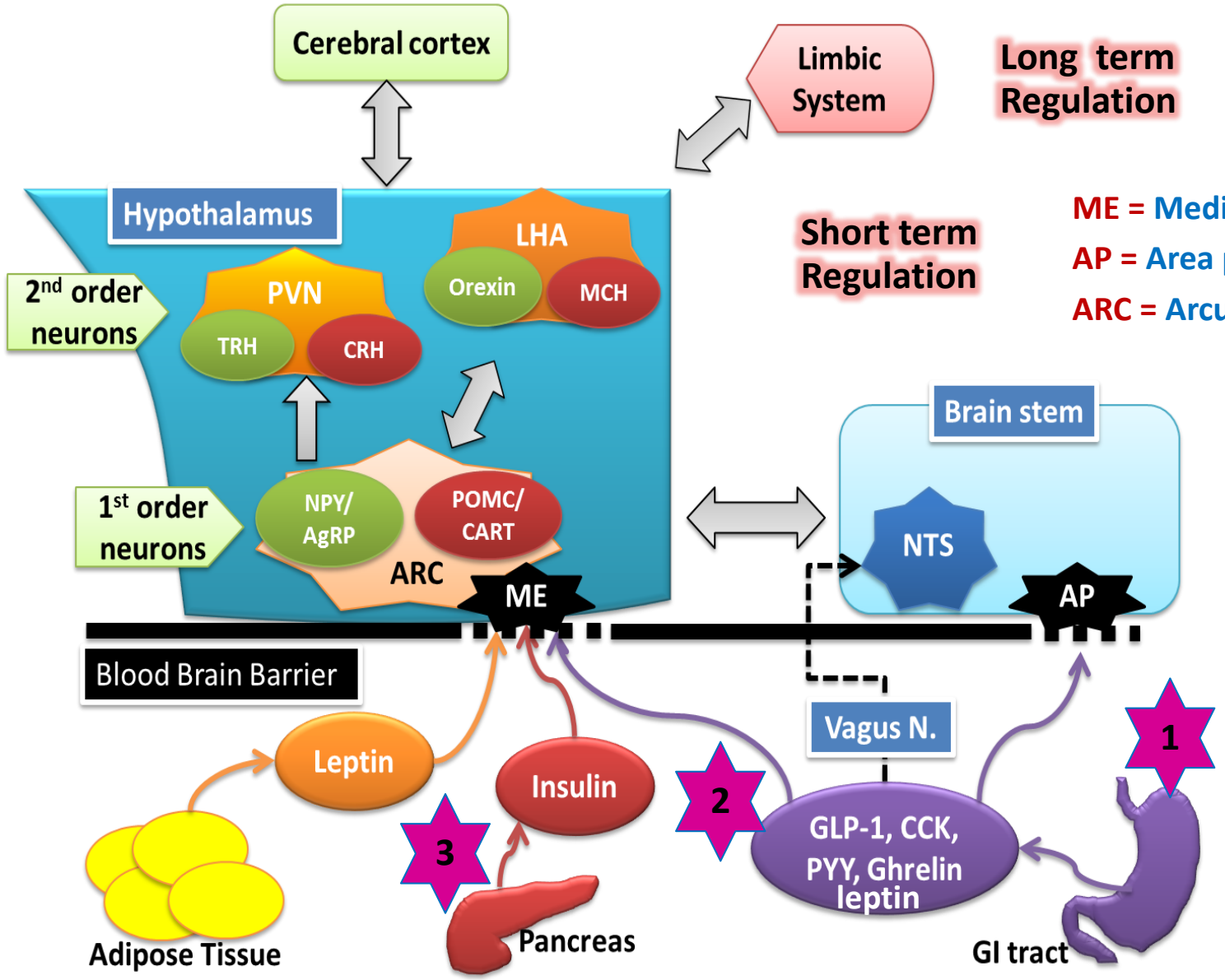
- The physiological system that maintains energy balance by regulating hunger and satiety based on signals from the body, such as hormones and nutrients.



Hedonic system

- The brain's reward system that influences appetite and food intake based on the pleasurable sensations associated with eating, responding to sensory cues and promoting the desire for certain foods.

Appetite Control



Adapted from Endocr J 57(5): 359-372

Appetite Control

We have appetite regulation to maintain neutral energy balance.

Why are we still obese?

Why Obesity?

- Appetite regulation disturbance
  - An abundance of convenient, highly palatable, energy-dense, inexpensive food
  - Popularity of buffet
  - Sweet, dessert
  - Medias
  - Social values
  - Strong stimuli e.g. visual, olfactory
- High set point
- Leptin resistance
- Low leptin per fat volume-relative leptin deficiency
- Low NEAT (Non-exercise activity thermogenesis)

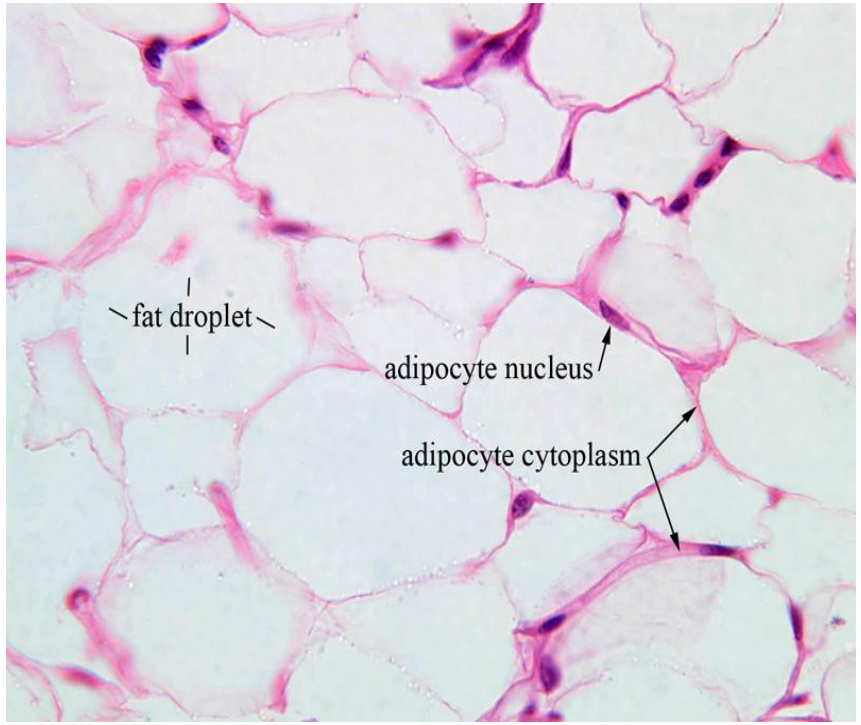
http://omicsonline.org/blog/wp-content/uploads/2012/03/obesity-risk-factors.jpg

Why Obesity?

- High energy extraction from food (energy > heat)
- Lean → ↑UCP-1 (heat instead of fat)
- Development of an excessive number of fat cells as a result of overfeeding → ready to refill
- Emotional disturbances in which overeating replaces other gratifications
- Stress, chronic stress → ↑peripheral NPY → ↑deposition of visceral fat
- Too little sleep (↓leptin, ↑ghrelin in sleep deprived people)
- Sedentary lifestyle

http://www.sikhnet.com/files/news/2012/04-April/couch-potato.jpg

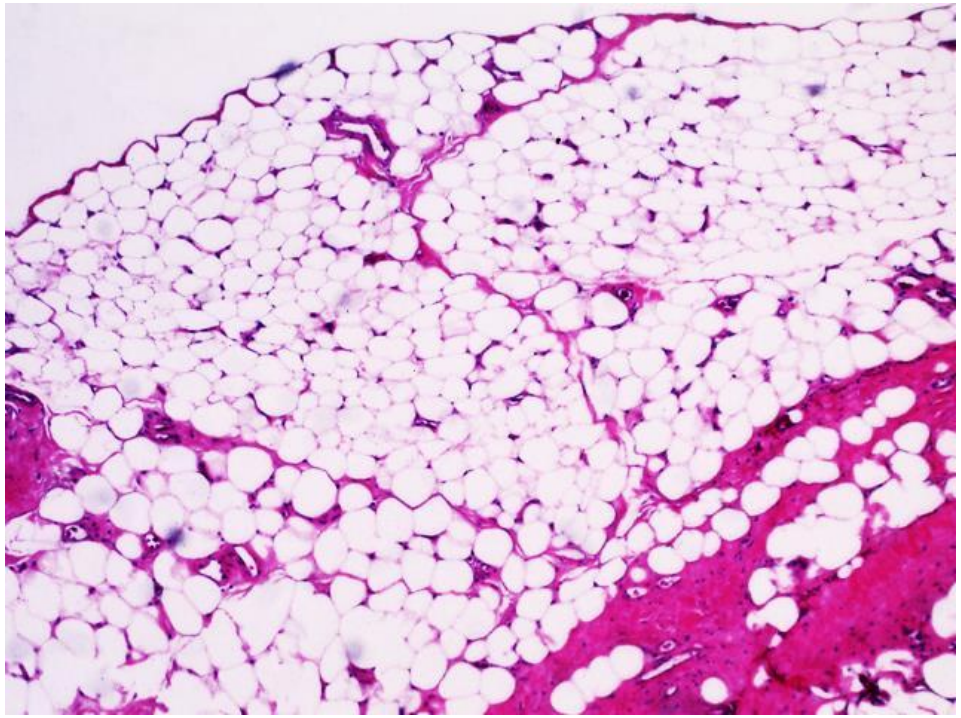
Adipose tissue



http://www.medicalhistology.us/twiki/pub/Main/ChapterTwoSlides/a73b_adipose_tissue_neck_40x_labeled.jpg

What are components of adipose tissue?

Adipose tissue



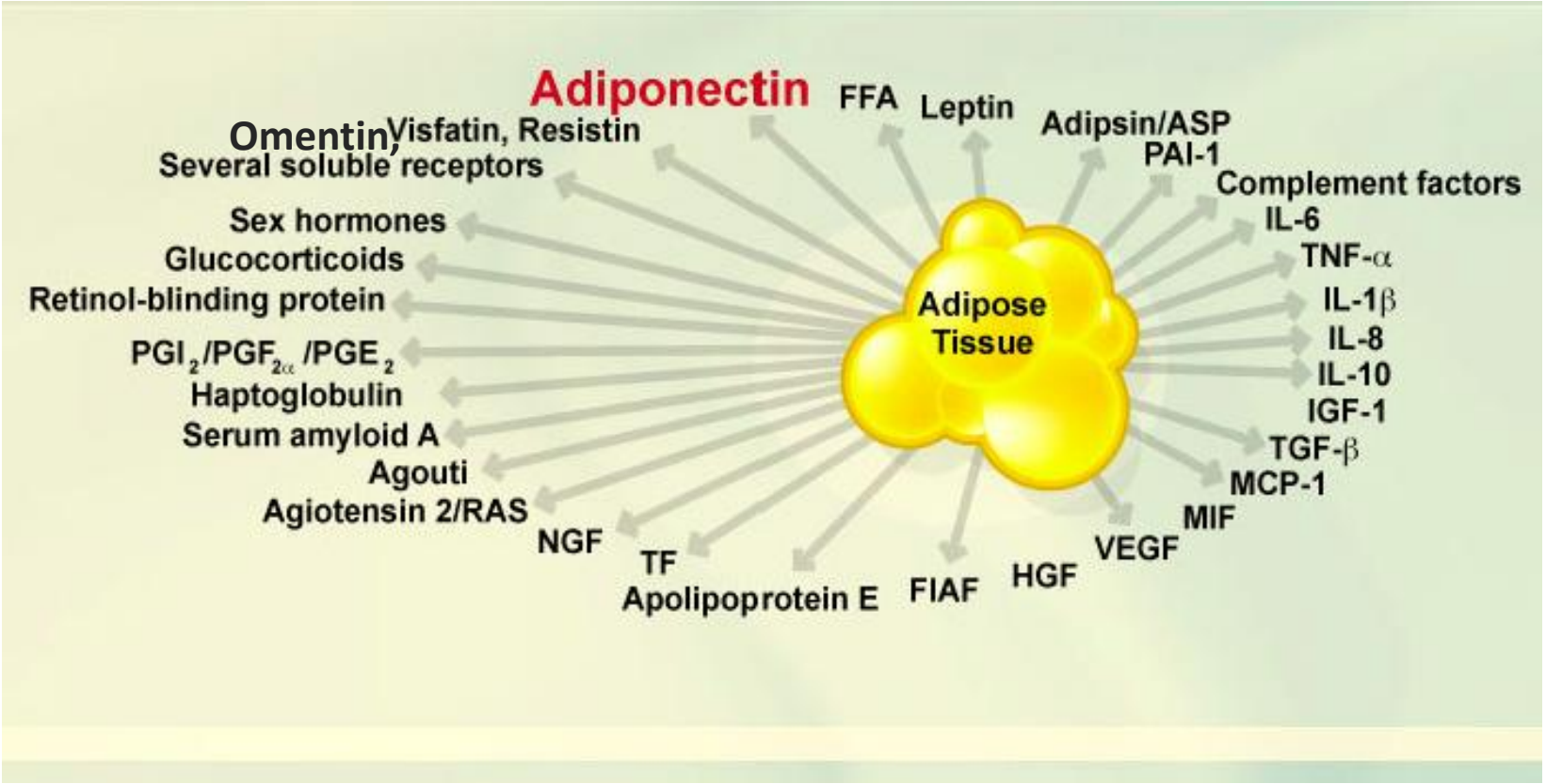
http://medpics.ucsd.edu/images/hist_640/CNT/hist_cnt_014_00.jpg

- Stores the excess consumed energy
- Active endocrine gland

  composed of the mature adipocytes, vascular endothelium cells, fibroblasts, and immune cells including M1 and M2 macrophages, T helper 2 cells, and T regulatory cells

Kahn CR, et al., The Journal of Clinical Investigation. 2019;129(10):3990-4000. Ahmad B, et al., Frontiers in Molecular Biosciences. 2020;7(76).

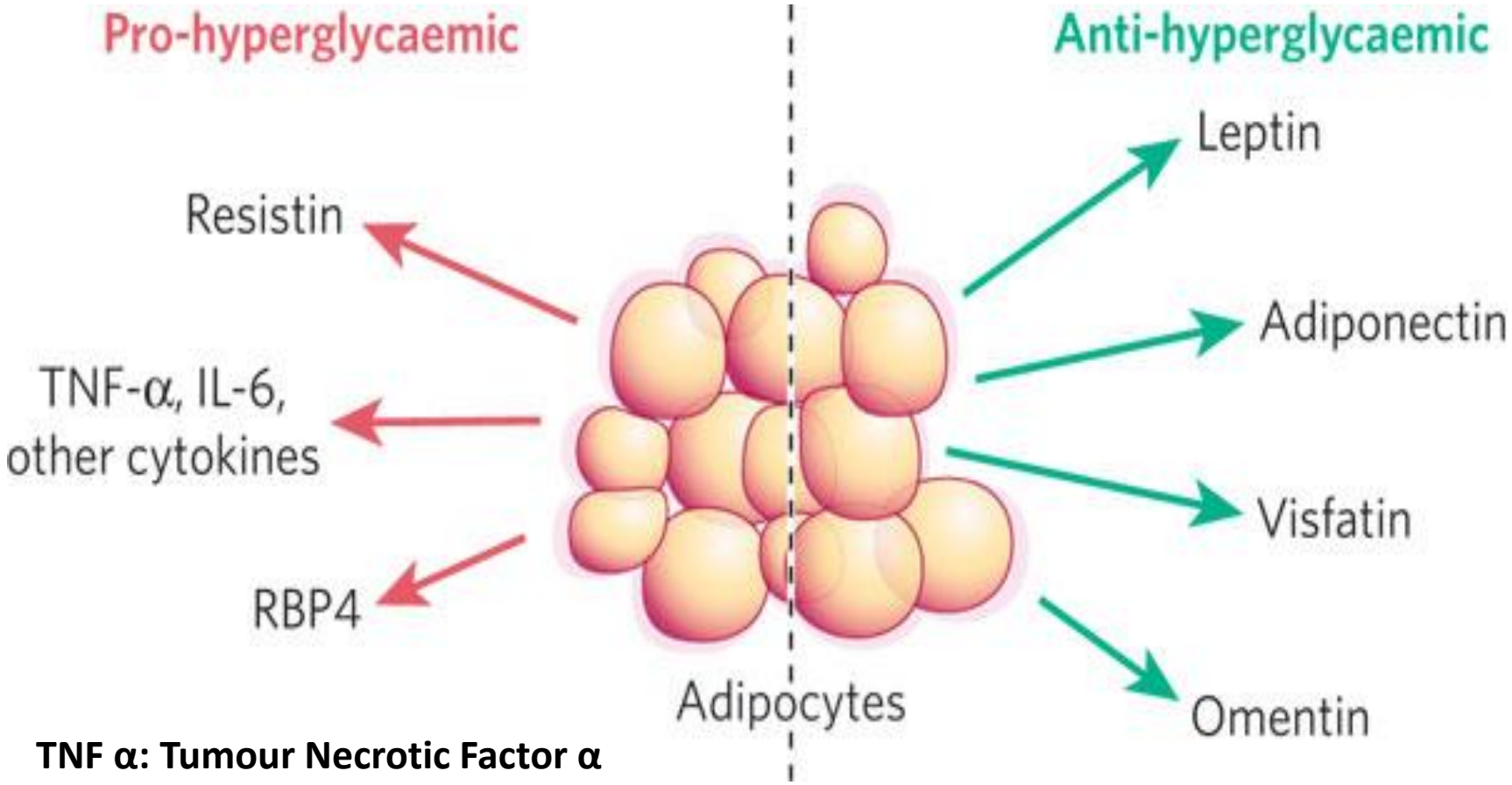
Adipokines



Guerre-Millo M et al., 2003

http://www.myhealthywaist.org/cmrejournal/articles/vol1/v1i1a4.php

Adipokines

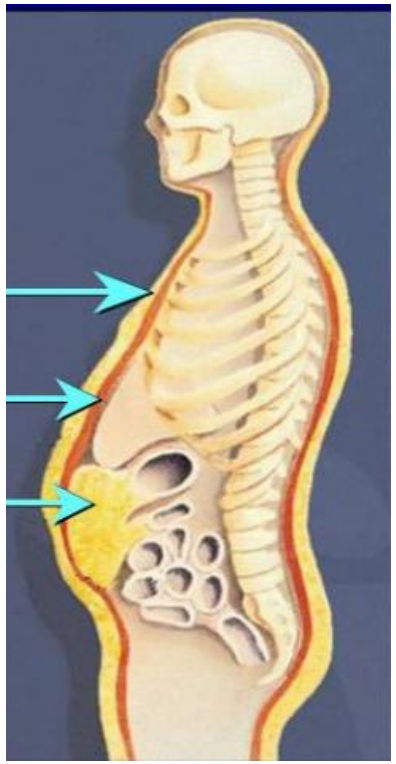


TNF α: Tumour Necrotic Factor α
IL 6: Interleukin 6
RBP4: Retinol Binding Protein 4

Evan D. Rosen et al., 2006

Adipose tissue

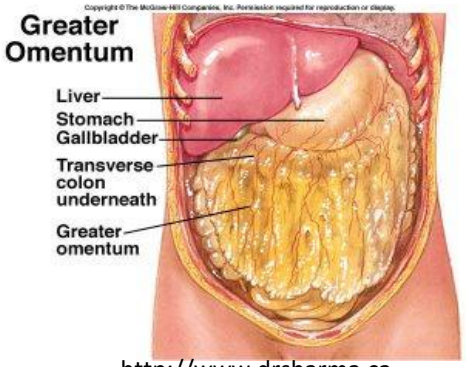
Subcutaneous adipose tissue



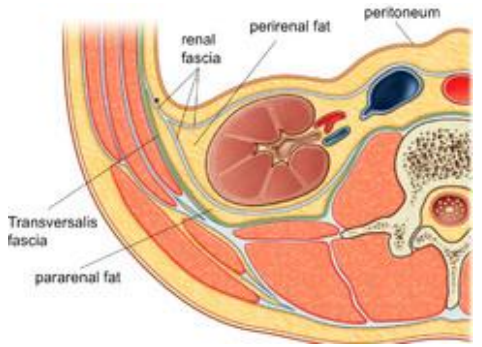
http://www.cadiresearch.org/topic/obesity/abdominal-obesity/abdominal-obesity-causes

- The hypodermis fat depot all over the body

Visceral adipose tissue



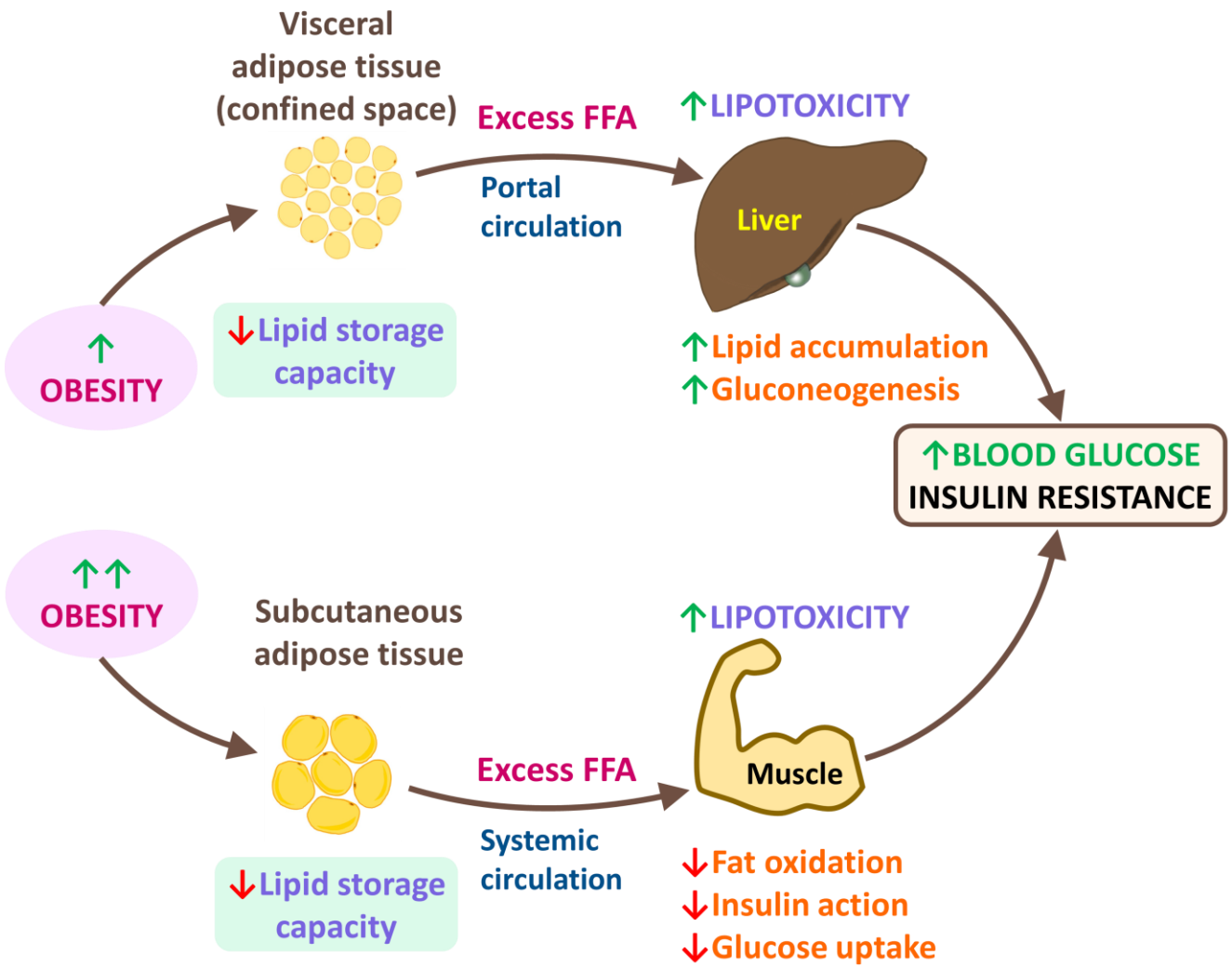
http://www.drsharma.ca



http://quizlet.com

- Fat tissue of
  - Mesenteric
  - Omental
  - Retroperitoneal
  - Perirenal
  - Pericardial
  - Perigonadal

Adipose tissue

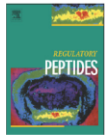


Regulatory Peptides 185 (2013) 65–72

Contents lists available at SciVerse ScienceDirect

Regulatory Peptides

journal homepage: www.elsevier.com/locate/regpep



Expressions of neuropeptide Y and Y1 receptor in subcutaneous and visceral fat tissues in normal weight and obese humans and their correlations with clinical parameters and peripheral metabolic factors

Chantacha Sitticharoon *, Saimai Chatree, Malika Churintaraphan

Department of Physiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

Peptides 62 (2014) 164–175

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Interactions between adiponectin, visfatin, and omentin in subcutaneous and visceral adipose tissues and serum, and correlations with clinical and peripheral metabolic factors

Chantacha Sitticharoon*, Nay Chi Nway, Saimai Chatree, Malika Churintaraphan, Peerada Boonpuan, Pailin Maikaew

Department of Physiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

Obesity Research & Clinical Practice (2016) 10, 256–263

ELSEVIER

ORIGINAL ARTICLE

Correlations between the expression of the insulin sensitizing hormones, *adiponectin*, *visfatin*, and *omentin*, and the appetite regulatory hormone, *neuropeptide Y* and its receptors in subcutaneous and visceral adipose tissues

Nay Chi Nway, Chantacha Sitticharoon*, Saimai Chatree, Pailin Maikaew

Department of Physiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

OriginalArticle

Expression of Y2R mRNA Expression in Subcutaneous and Visceral Adipose Tissues Compared between Normal Weight and Obese Female Subjects

Saimai Chatree, Malika Churintaraphan, Nay Chi Nway, Chantacha Sitticharoon, M.D.*

Department of Physiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Original Research

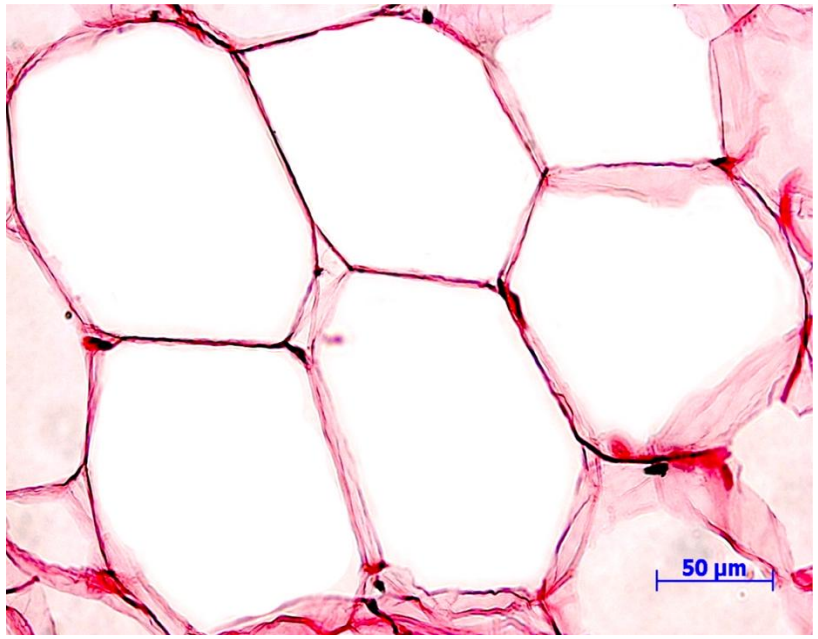
Adipose *Y5R* mRNA is higher in obese than non-obese humans and is correlated with obesity parameters

Saimai Chatree, Chantacha Sitticharoon, Pailin Maikaew, Panapat Uawithya and Supornpim Chearskul

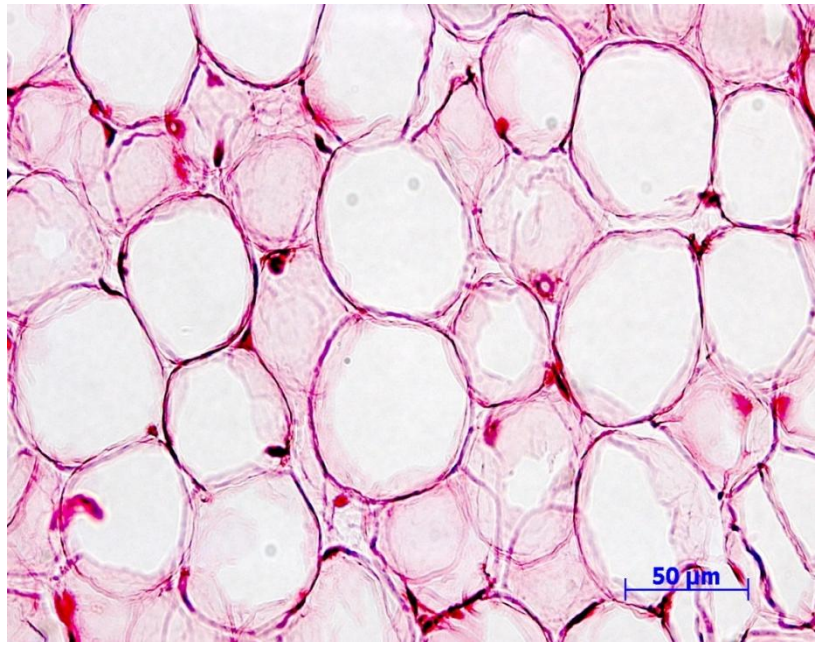
Department of Physiology, Department of Physiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, 10700, Thailand
Corresponding author: Chantacha Sitticharoon. Email: chantacha.sit@mahidol.ac.th

Experimental Biology and Medicine 2018; 243: 786–795. DOI: 10.1177/1535370218774889

Subcutaneous *vs.* Visceral adipose tissue



Subcutaneous



Visceral

Chatree S, **Sitticharoon C**, et al., Experimental Biology and Medicine. 2018;243(9):786-95.

Subcutaneous *vs.* Visceral adipose tissue

Correlation	R value	P value
waist circumference - Area of subcutaneous adipocytes	0.557	0.002**
waist circumference - Width of subcutaneous adipocytes	0.569	0.002**
waist circumference - Height of subcutaneous adipocytes	0.423	0.025*
waist circumference - Perimeter of subcutaneous adipocytes	0.570	0.002**
waist circumference - Area of visceral adipocytes	0.733	0.000***
waist circumference - Width of visceral adipocytes	0.679	0.000***
waist circumference - Height of visceral adipocytes	0.747	0.000***
waist circumference - Perimeter of visceral adipocytes	0.749	0.000***
hip circumference - Area of subcutaneous adipocytes	0.597	0.001**
hip circumference - Width of subcutaneous adipocytes	0.520	0.005**
hip circumference - Height of subcutaneous adipocytes	0.430	0.022**
hip circumference - Perimeter of subcutaneous adipocytes	0.612	0.001**
hip circumference - Area of visceral adipocytes	0.649	0.000***
hip circumference - Width of visceral adipocytes	0.649	0.000***
hip circumference - Height of visceral adipocytes	0.706	0.000***
hip circumference - Perimeter of visceral adipocytes	0.660	0.000***

Chatree S, **Sitticharoon C**, et al., Experimental Biology and Medicine. 2018;243(9):786-95.

Subcutaneous *vs.* Visceral adipose tissue

Correlation	R value	P value
Insulin - Area of visceral adipocytes	0.441	0.021*
Insulin - Width of visceral adipocytes	0.410	0.034*
Insulin - Height of visceral adipocytes	0.480	0.011*
Insulin - Perimeter of visceral adipocytes	0.443	0.021*
HOMA-IR - Area of visceral adipocytes	0.451	0.018*
HOMA-IR - Width of visceral adipocytes	0.405	0.036*
HOMA-IR - Height of visceral adipocytes	0.493	0.009**
HOMA-IR - Perimeter of visceral adipocytes	0.454	0.017*
QUICKI - Area of visceral adipocytes	-0.453	0.018*
QUICKI - Width of visceral adipocytes	-0.410	0.034*
QUICKI - Height of visceral adipocytes	-0.502	0.008*
QUICKI - Perimeter of visceral adipocytes	-0.457	0.017*

Nway NC, **Sitticharoon C**, et al., Obesity research & clinical practice. 2016;10(3):256-63

The fasting state

- ↓Blood glucose → ↓Insulin
- ↑Counter regulatory hormones (oppose the action of insulin) → ↑Blood sugar
  - Glucagon
  - Epinephrine
  - Norepinephrine
  - Cortisol
  - GH

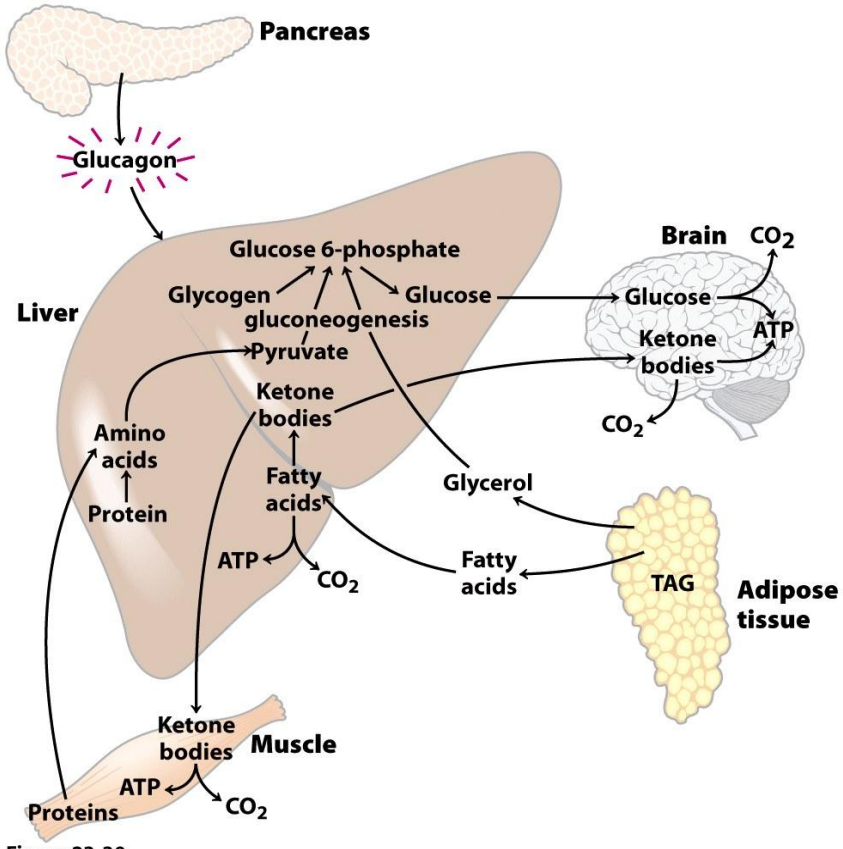


Figure 23-30
Lehninger Principles of Biochemistry, Fifth Edition

Lipolysis

- A breakdown of triglyceride accumulated in adipocytes into FFA and glycerol by hormone-sensitive lipase (HSL), a rate-limiting enzyme of fat catabolism

Zechner R et al. Lipolysis: pathway under construction.
Curr Opin Lipidol. [Research Support, Non-U S Gov't Review]. 2005

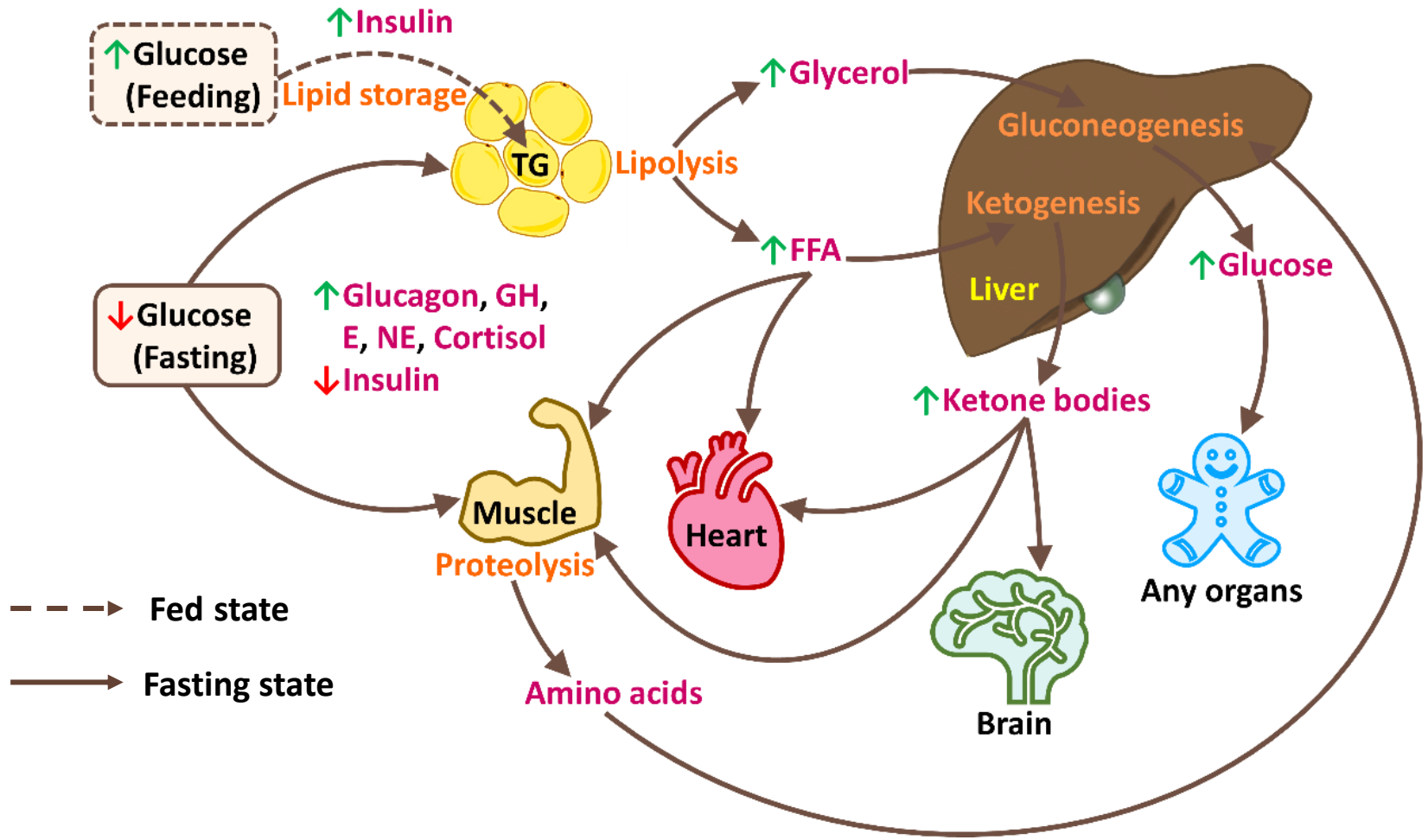
- The rate of lipolysis
  - Low in the subcutaneous femoral/gluteal region
  - Intermediate in the subcutaneous abdominal region
  - High in the visceral (i.e. omental) region

- The lipolytic beta 1 and beta 2 adrenoceptors, as well as the newly discovered beta 3, are most active in the visceral fat cells.

- The antilipolytic insulin receptors, alpha 2 adrenoceptors and adenosine receptors are most active in the subcutaneous fat cells.

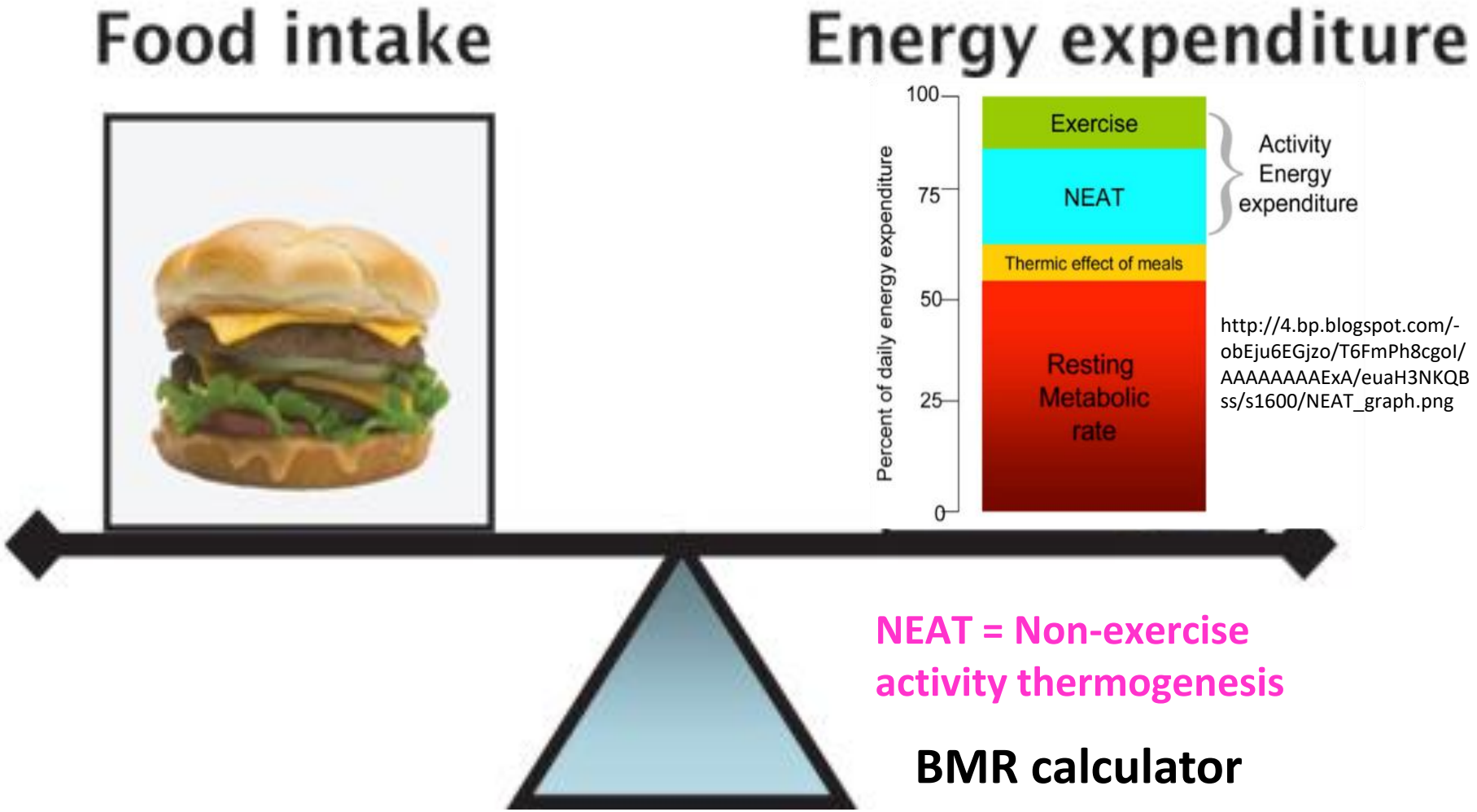
(Arner P. Differences in lipolysis between human subcutaneous and omental adipose tissues) Annals of medicine. 1995 Aug;27(4):435-8.

The fasting state



TG: triglyceride; FA: free fatty acid; GH: growth hormone; E: epinephrine; NE: norepinephrine

Energy balance



http://4.bp.blogspot.com/-obEju6EGjzo/T6FmPh8cgoI/AAAAAAAAExA/euaH3NKQBss/s1600/NEAT_graph.png

NEAT = Non-exercise activity thermogenesis

BMR calculator

http://www.precisionnutrition.com/wordpress/wp-content/uploads/2009/04/energy-balance-continuum.jpg

Weight-loss diet regimens

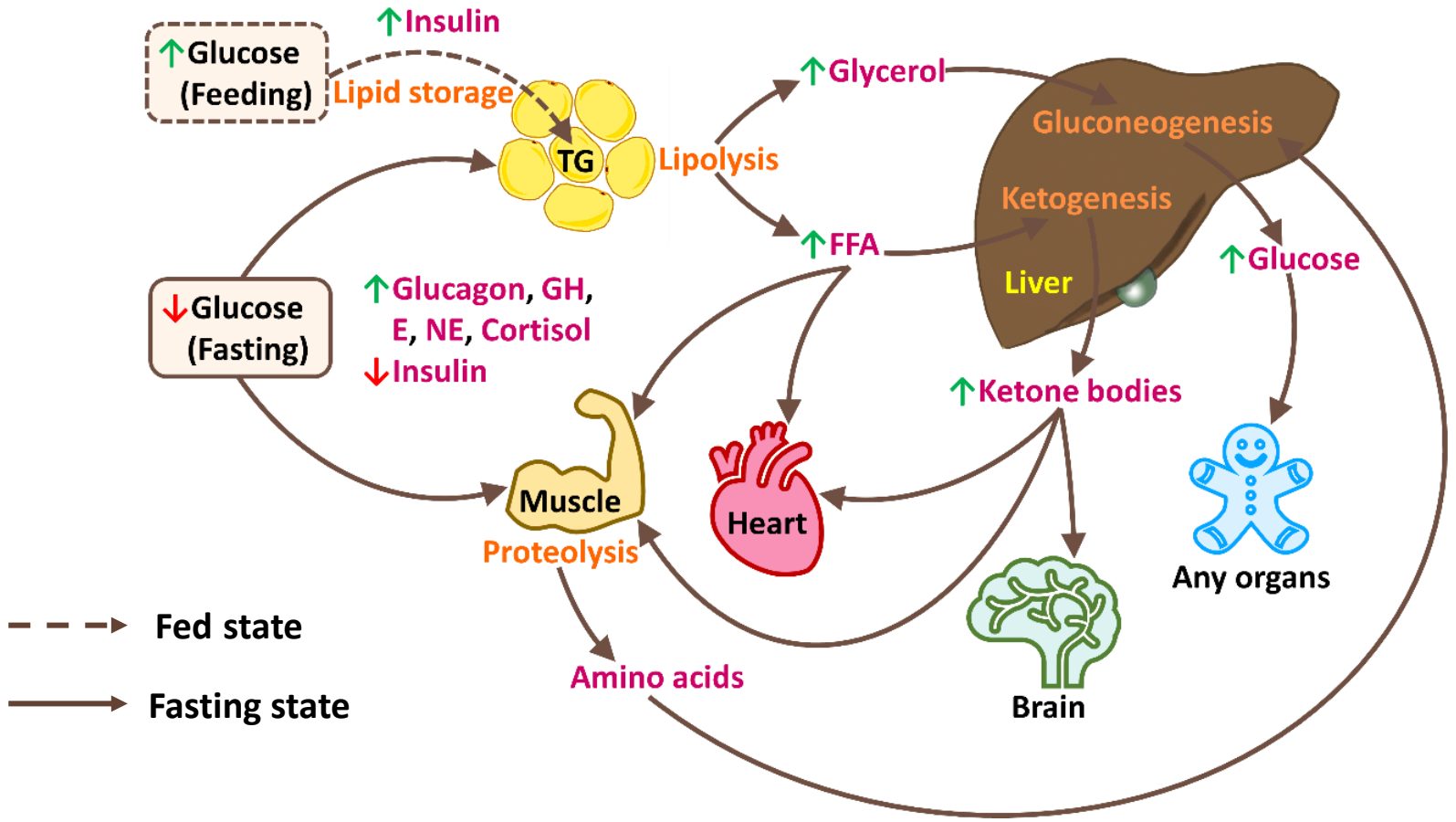
Weight loss diet regimens

1. General Recommendation (↓Carbohydrate, ↓Sugar, ↑Protein, ↓Fat, ↑Vegetable/Fiber, ↑Drinking water)
   - Metabolism boosting meals (High protein, Low fat, No carb with 1 day cheating/week)
   - Plate method
2. Calories reduction
3. Paleolithic diet
4. Mediterranean diet
5. "Eating breakfast like a king, lunch like a prince, and dinner like a pauper"
6. Intermittent fasting (including Time-restricted eating, TRF)
7. Ketogenic Diet

1. General Recommendation

- ↓Carbohydrate
- ↓Sugar
- ↓Fat
- ↑Protein
- ↑Vegetable/Fiber
- ↑Drinking water

↓Carbohydrate, ↓Sugar, ↓Fat, ↑Protein



- Carbohydrates & Protein 1 g → 4 calories
- Fat 1 g → 9 calories

TG: triglyceride; FA: free fatty acid; GH: growth hormone; E: epinephrine; NE: norepinephrine

Metabolism of fatty acids in the liver

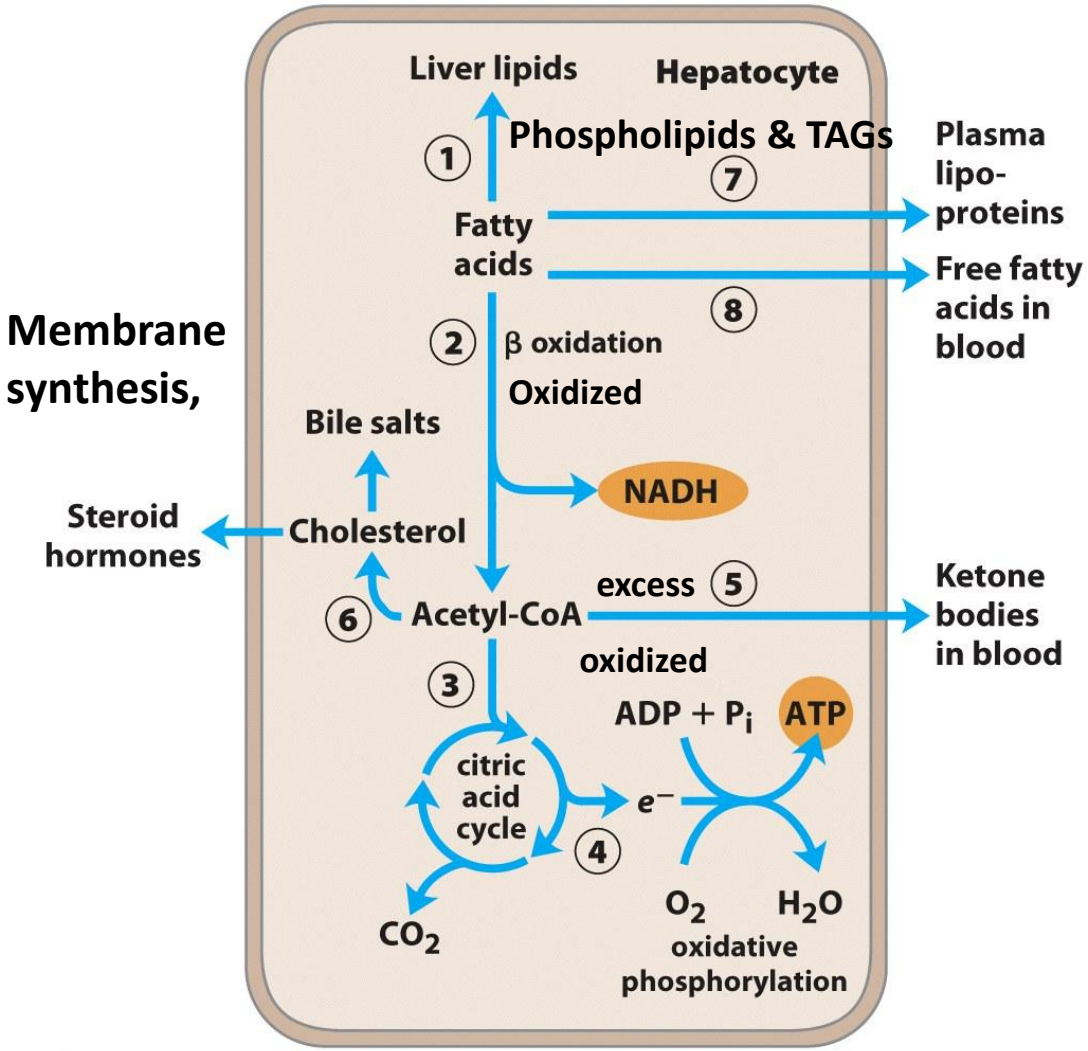


Figure 23-15
Lehninger Principles of Biochemistry, Fifth Edition

- Carry lipids to adipose tissue for storage of TAG.
- Bound to serum albumin and carried to the heart and skeletal m. which take up and oxidize FFA as a major fuel.

Acetoacetate,
β-hydroxybutyrate

- Fuel for the citric acid cycle for other tissues
- Supply energy for up to 1/3 → heart, 60-70% → brain, muscle

Hyperglycemic conditions

- Advanced glycation end products (AGEs)
  - Non-enzymatic modifications of proteins or lipids after exposure to sugars
  - Loss of protein function and impaired elasticity of tissues such as blood vessels, skin, and tendons
  - Acceleration of the aging process (the accumulation of glycated macromolecules, including proteins, is a hallmark of aging both in humans and experimental animals.
  - Triggering organ dysfunction and tissue aging

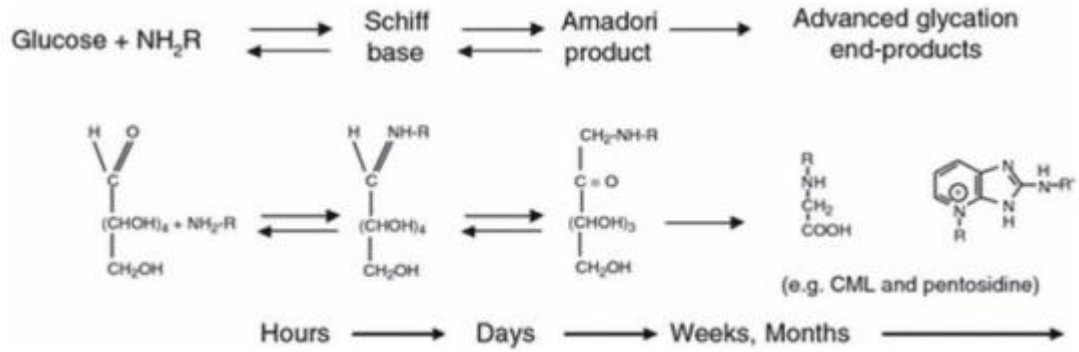


Illustration from Bohlender et al., 2005

- Glycation process → the formation of advanced glycation end-products (AGEs).

Dietary Protein

- Recommended Dietary Allowance of protein for a healthy adult with minimal physical activity → 0.8 g protein/kg body weight/day.
- To meet the functional needs such as promoting skeletal-muscle protein accretion and physical strength
  - Dietary intake of 1.0, 1.3, and 1.6 g protein per kg BW per day → minimal, moderate, and intense physical activity, respectively.
- Long-term consumption → 2 g protein/kg body weight/day is safe for healthy adults (1-2 g protein per kg BW per day)
- The tolerable upper limit → 3.5 g protein/kg body weight/day for well-adapted subjects.

Wu G. Dietary protein intake and human health. Food Funct. 2016 Mar;7(3):1251-65. doi: 10.1039/c5fo01530h. PMID: 26797090.

- Protein in food (g/100 g)
  - Chicken 32 g (1/3)
  - Beef 26 g (1/4)
  - Pork 24 g (1/4)
  - Fish 20 g (1/5)
  - Egg 12 g
  - Soy bean 34 g
  - Peanut 26 g (Protein 26.3%, Fat 49%)
  - green beans 20 g

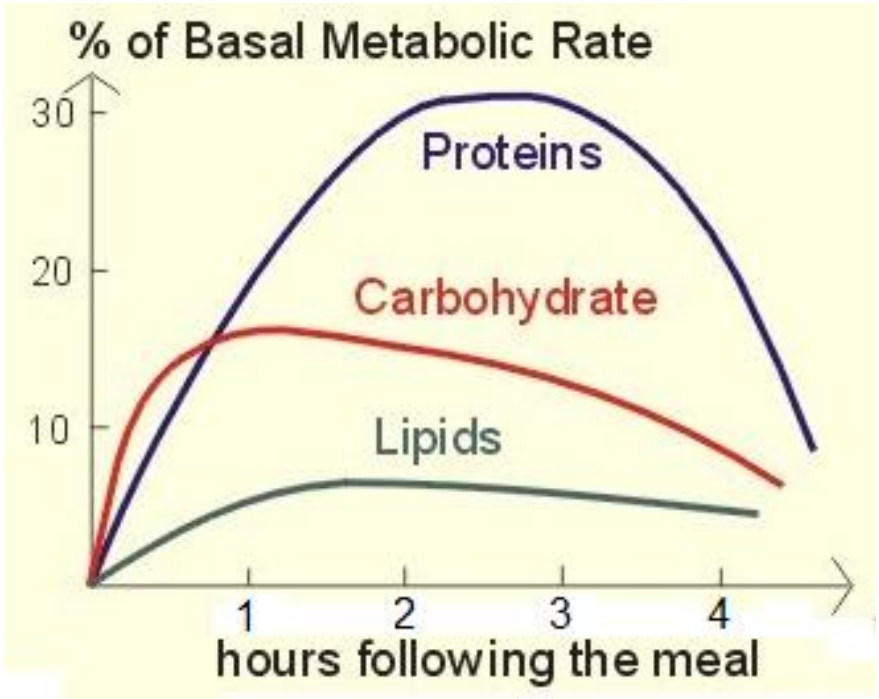
ปัญญ์ญใหญ่, น. (2017). อาหารและโภชนาการ (Food and Nutrition). บทที่ 3 โปรตีน.
Retrieved from http://www.facagri.cmru.ac.th/research/?p=subject_detail&subject_id=5

Basal metabolic rate

Thermic effects of nutrient		Energy expenditure	
Protein	20-30%	Amino acids	20-30%
Carbohydrate	5-10%	Glucose	5-10%
Fat	0-3%	fat	0-3%

Tappy L. Thermic effect of food and sympathetic nervous system activity in humans. Reproduction Nutrition Development. 1996;36(4):391–397.

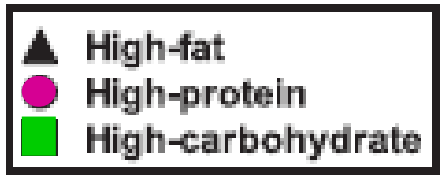
Jequier E. The influence of nutrient administration on energy expenditure in man. Clinical nutrition (Edinburgh, Scotland). 1986;5(4):181-6.



http://upload.wikimedia.org/wikipedia/commons/8/81/Postprandial_thermogenesis.png

Effects of macronutrient on appetite regulating hormones

Agatha A. et al. High protein intake stimulates postprandial GLP1 and PYY release, Obesity, 2013



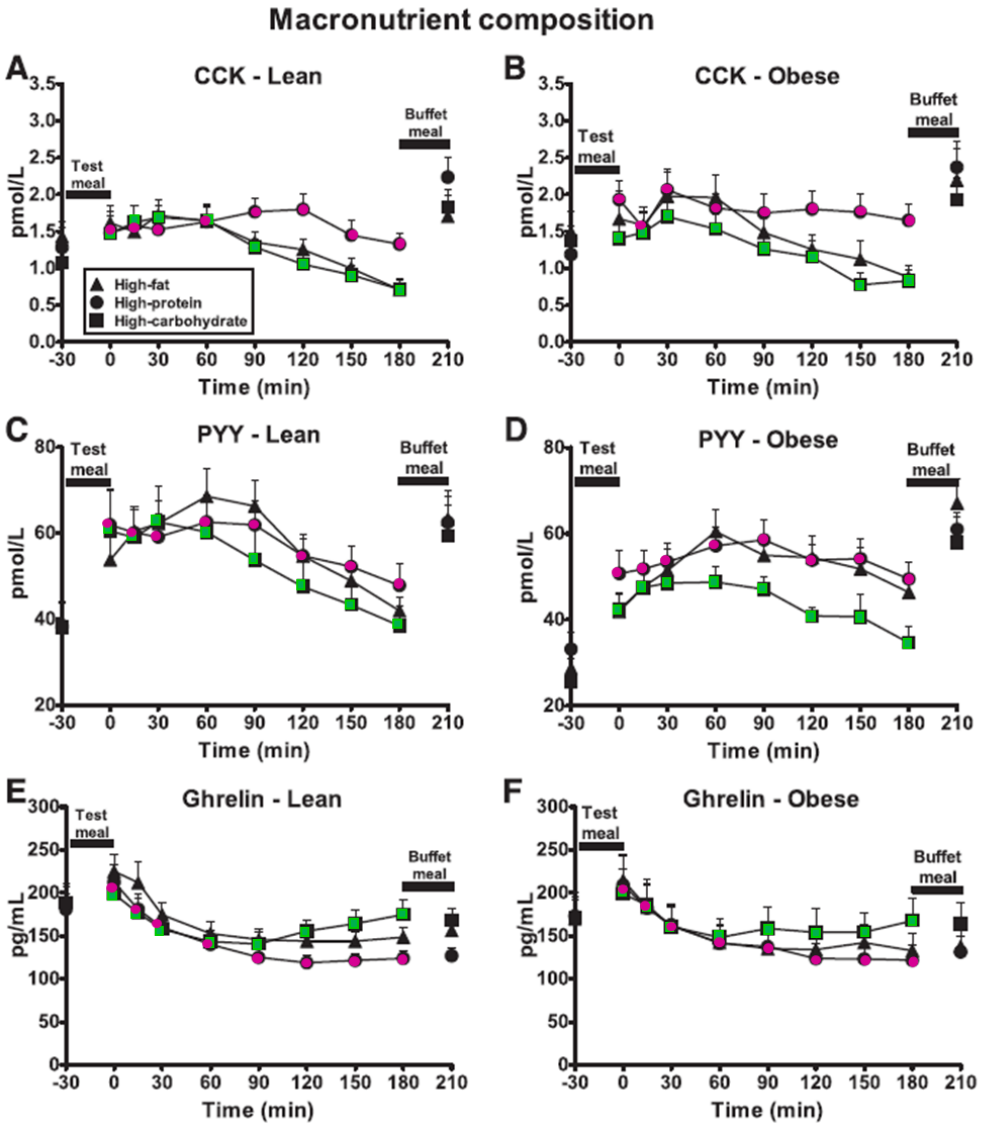


Fig. 2. Plasma concentrations (means ± SE) for cholecystokinin (CCK), peptide YY (PYY), and ghrelin in lean and obese subjects following ingestion of test meals varying in their macronutrient composition (i.e., high-fat, high-protein, high-carbohydrate). Repeated-measures ANOVAs, with treatment and time as factors, were used to determine statistical differences. Treatment-by-time interaction: $P < 0.05$ (*A*); treatment-by-time interaction: $P < 0.05$ (*B*); treatment-by-time interaction: $P < 0.01$ (*C*); treatment-by-time interaction: $P < 0.05$ (*D*); treatment-by-time interaction: $P < 0.01$ (*E*); treatment-by-time interaction: $P < 0.05$ (*F*). Data are absolute values, $n = 16$ lean and $n = 16$ obese subjects.

Effects of Low-CHO vs Low-Fat Diets on Weight Loss and Cardiovascular Risk Factors

- Systematic Reviews and Meta- and Pooled Analyses
- Randomized controlled trials for 6-24 months, mean energy intake ~ 2,000 Cal
- Low-CHO diet (4-45 %, mean 23% CHO) Vs. Low-fat diet (10-30 %, mean 26% fat)
  - ~↓Weight (−6.1 Vs. −5.0 kg)
  - ↓Waist circumference (−6.2 Vs. −6.0 cm)
  - Improved metabolic risk factors
    - >↓TG (−30.4 Vs. −17.1 mg/dL)

      ↑HDL (4.5 Vs. 1.6 mg/dL)
    - <↓Total cholesterol (−4.6 Vs. −10.1 mg/dL),

      ↓LDL (−2.1 vs.−6.0 mg/dL)
    - ~ SBP (−3.5 Vs. −3.0 mmHg), FBS (−10.4 Vs. −10.1 mg/dL)

Am J Epidemiol. 2012 Oct 1; 176(Suppl 7): S44–S54.

A High Protein, Low Carbohydrate Diet

- A high protein, low carbohydrate (20 g/day) or low fat (30%) diet for 13 weeks
  - >↓BMI-Z-score than low fat group
  - No serious adverse effects related to metabolic profiles, cardiac function, or subjective complaints

J Pediatr. 2010 Aug; 157(2): 252–258.

- A high protein, low carbohydrate diet
  - Improve satiety through their actions on measures of adiposity and gut peptides that influence appetite and caloric intake
  - Specific macronutrients such as low glycemic index carbohydrates and dietary protein → appetite, calorie intake, and metabolic parameters independent of weight loss
  - The long-term safety of low-carbohydrate, high-protein diets on cardiovascular disease risk remains undetermined.

Current Opinion in Gastroenterology: March 2008 - Volume 24 - Issue 2 - p 198-203

Increased vegetable/High Fiber

- ↑Gastric volume → gastric distension → satiety
- Vitamin and minerals

High-fiber vegetable diet compared with the starch-based and low-fat diets for 2 weeks

- ↓LDL (33%)
- ↑Fecal bile acid (1.13 ± 0.30 g/d)
- ↑Fecal bulk (906 ± 130 g/d)
- ↑Fecal short-chain fatty acid outputs (78 ± 13 mmol/d)
- ↑Urinary mevalonic acid excretion reflecting large fecal steroid losses

Metabolism, Volume 50, Issue 4, April 2001, Pages 494-503

Drinking water

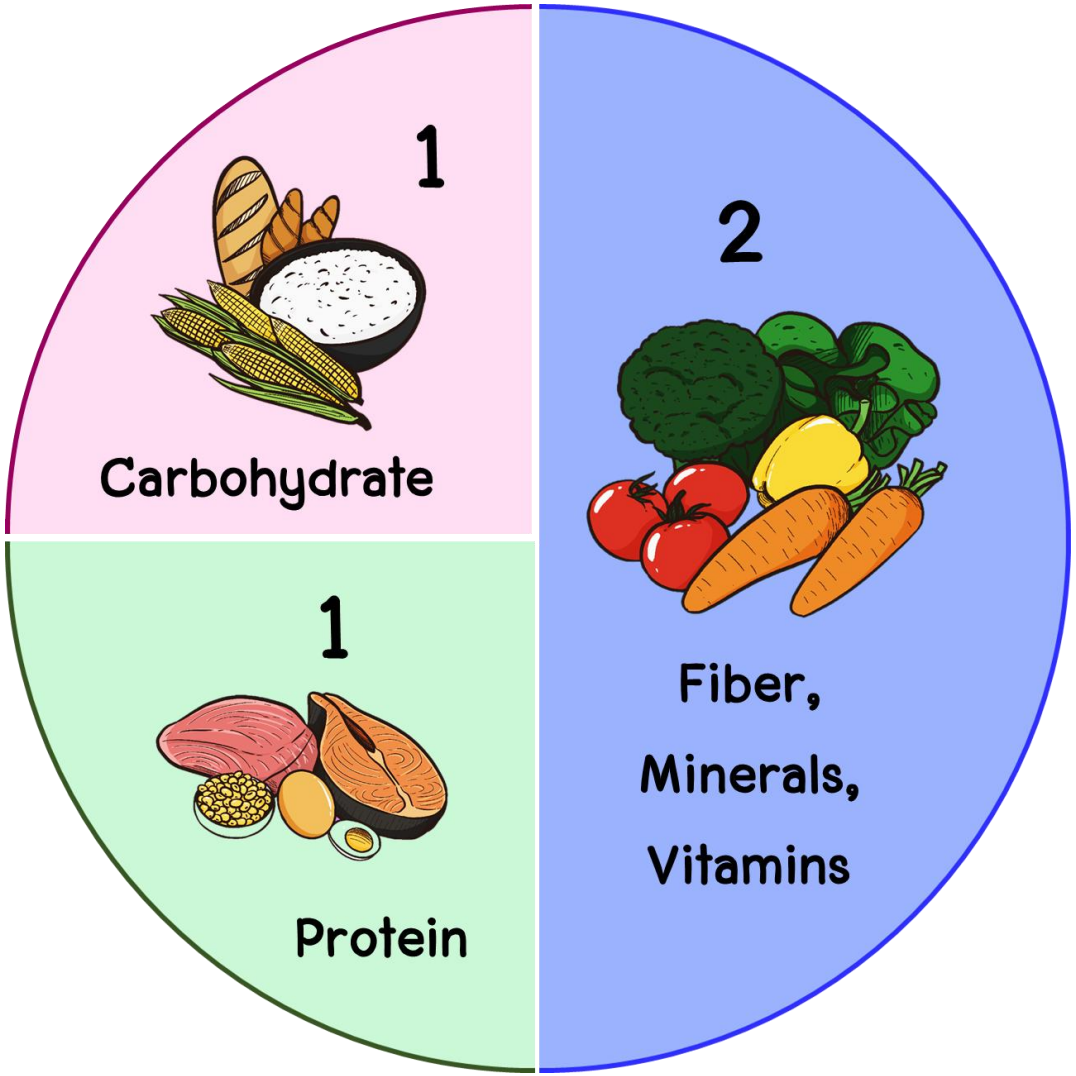
- Drinking 1.5 L of water, over and above the usual intake for 8 weeks
  - ↓Body weight (-1.44 kg)
  - ↓BMI (-0.5778 kg/m^2)
  - ↓Sum of skinfold thickness (-3.048 mm)
  - ↓The appetite score (- 2.207)

J Nat Sci Biol Med. 2014 Jul-Dec; 5(2): 340–344.

- Appetite suppressant
  - ↑Gastric volume → Gastric distension → ↑Satiety signal
- ↓Core body temperature
- ↑Activity of the SNS (↑NE levels and ↑Muscle SNS activity)
- ↑Thermogenesis
- ↑Resting energy expenditure by 30% within 10 min of drinking (peaked at 30-40 min) and sustained for over an hour
- Proper hydration (remove waste, metabolizing fat or CHO)

SNS = sympathetic nervous system, CHO = carbohydrate

Plate method



Reduce sweet, oily, and salty with the formula 6: 6: 1

Sugar	Oil	Salt
		
≤ 6 Teaspoon/day	≤ 6 Teaspoon/day	≤ 1 Teaspoon/day

1 Teaspoon = 5 g 1 Tablespoon = 15 g

Sugar

Be aware of the hidden sugar content

Honey Lemon Green Tea

Sugar 12 teaspoon

(48 g)

Soft drink

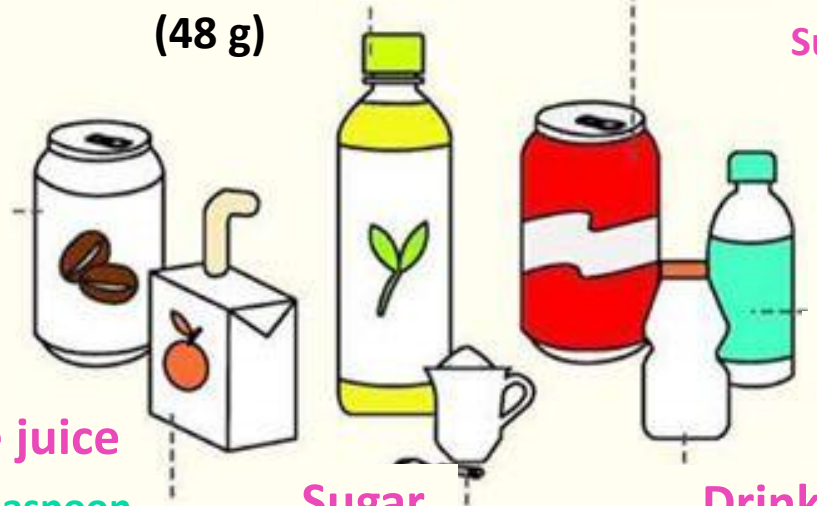
Sugar 8.7 teaspoon

(34.8 g)

Canned Coffee

Sugar 4.3 teaspoon

(17.2 g)



Energy drink

Sugar 7.5 teaspoon

(30 g)

25% orange juice

Sugar 11.2 teaspoon

(44.8 g)

Sugar

Sugar 1 teaspoon

(4 g)

Drinking Yoghurt

Sugar 4.4 teaspoon

(17.6 g)

Fat

Be aware of the hidden fat content

boiled egg
70
kcal

fried egg
160
kcal

omelet
250
kcal

Thai stir-fried noodles 1 dish
Oil 6 teaspoon

Fried mussel pancakes 1 dish
Oil 6 teaspoon

Chicken rice
1 dish
Oil 5 teaspoon

Fried chicken
1 piece
Oil 2.6 teaspoon

Fried egg
1 egg
Oil 4.2 teaspoon

Stewed pork leg with rice 1 dish
Oil 6 teaspoon

Barbecued red pork in sauce with rice 1 dish
Oil 5 teaspoon

Shrimp-paste fried rice 1 dish
Oil 5 teaspoon

Metabolism boosting meals

- No CHO, No sugar
- Low fat
- High protein - metabolism boosting
- 1 day cheating in a week - metabolism boosting
- Limitation
  - Susceptible to hypoglycemia

2. Calories reduction

E intake < E expenditure

Energy Expenditure

= BMR + physical activity

= BMR x activity factor (1.25)

BMR Estimation by Harris-Benedict Equation

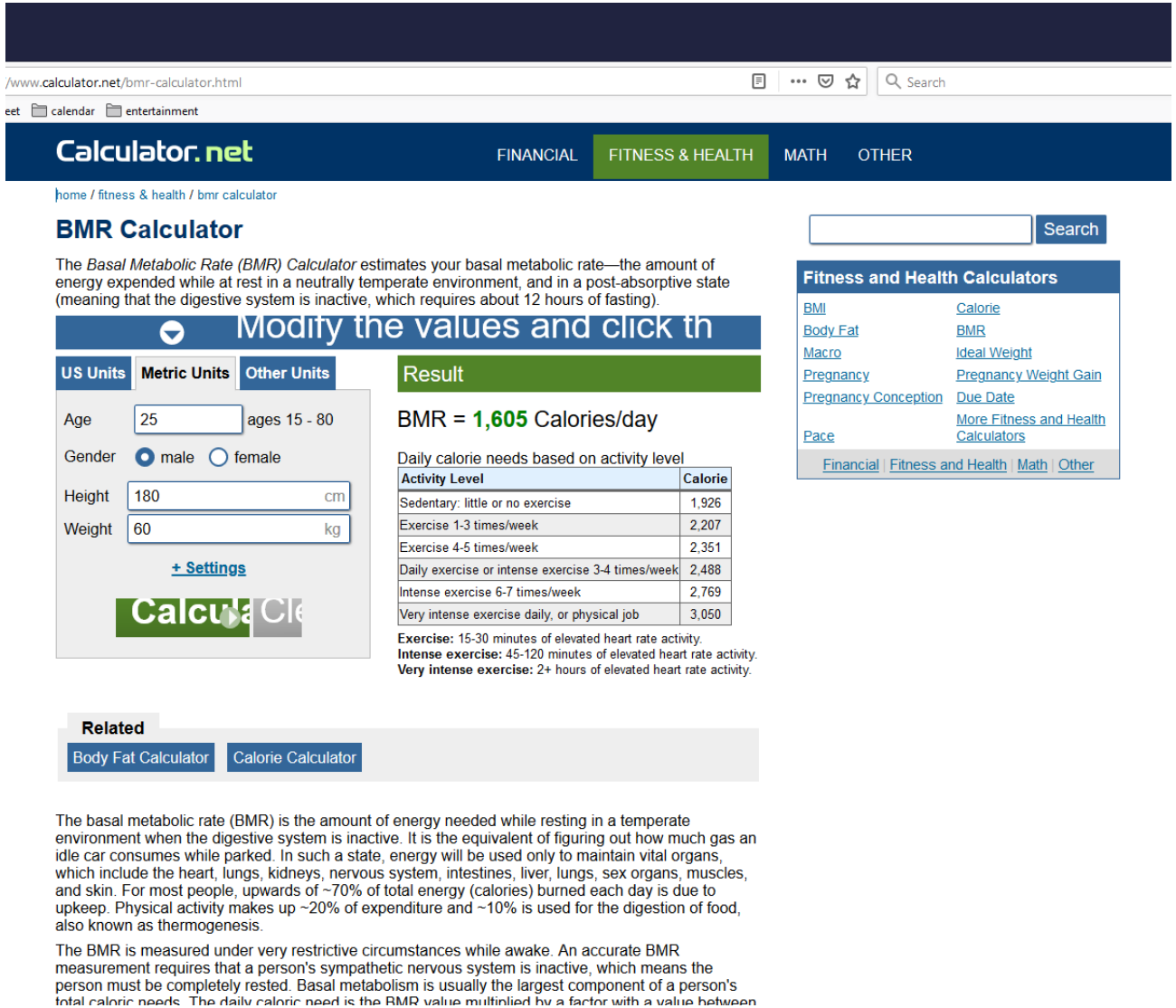
M: 66.5 + (13.75 x kg) + (5.003 x cm) - (6.775 x age)

F: 655.1 + (9.563 x kg) + (1.850 x cm) - (4.676 x age)

BMR calculator

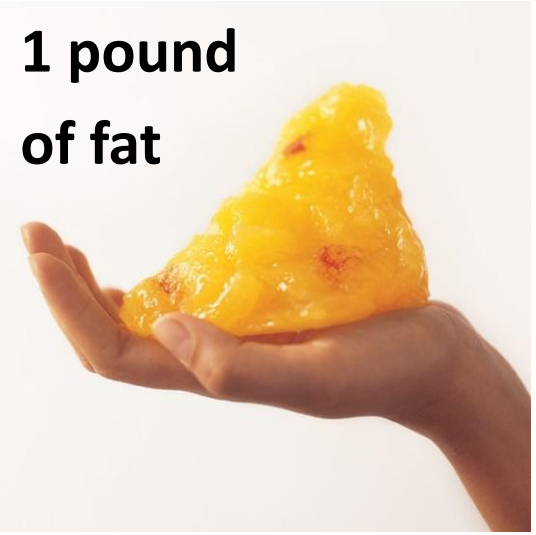
https://www.calculator.net/bmr-calculator.html

BMR Calculator



Calories reduction

“3,500 kcal per pound rule”



= 3,500 kcal

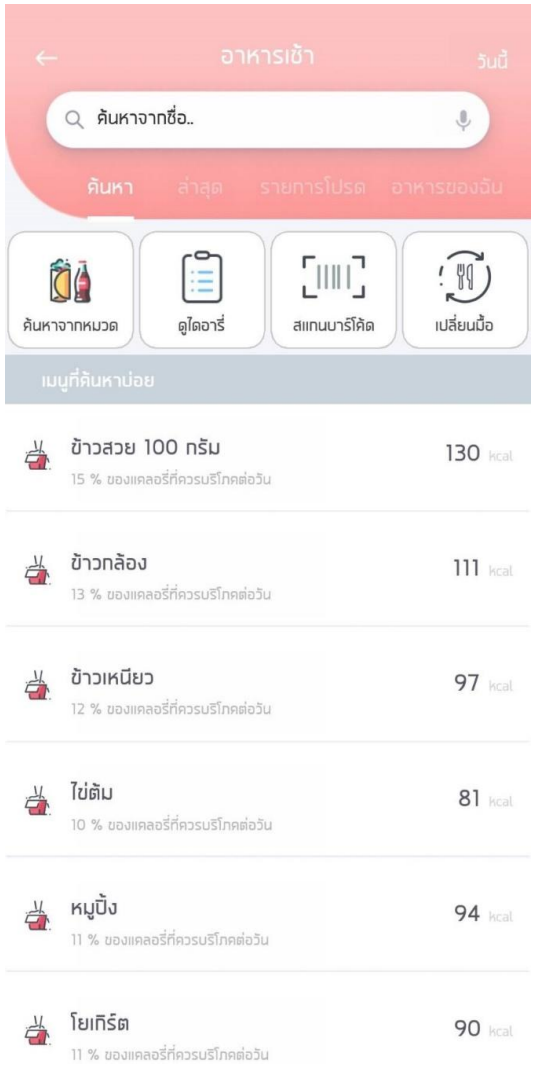
Negative

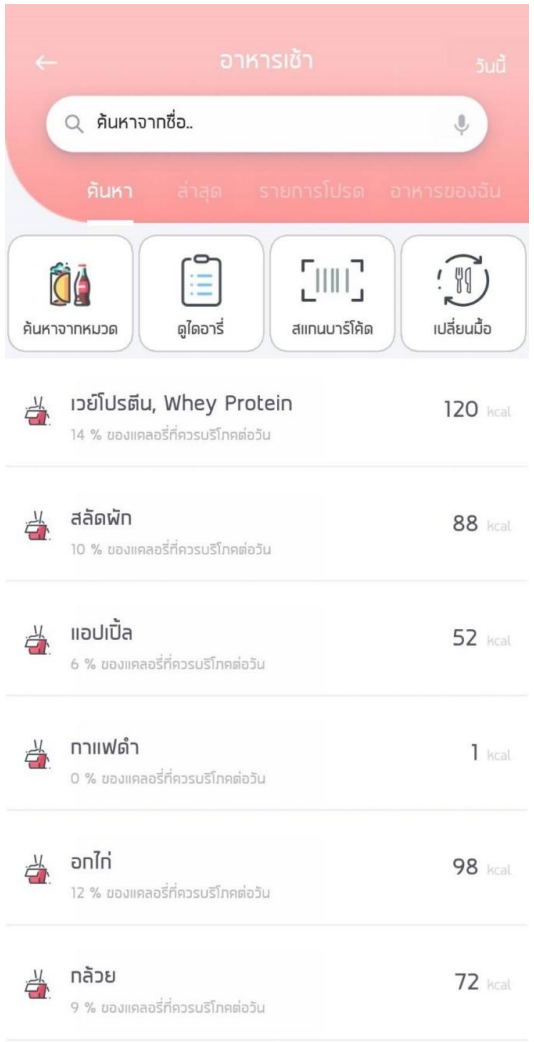
- 3,500 kcal/wk
- 500 kcal/day
- Weight loss 1 pound/wk
- ~(0.5 kg/wk)

Minimum weight loss to achieve health benefits

- 5 - 10% of initial body weight

Calorie counter Application





Caloric restriction

- ↓Energy intake 20-40 %
- ↓Body weight, BMI, body fat, fat mass, waist circumference
- ↓Blood sugar and lipid levels
- ↓Blood pressure
- ↓Fat-free mass
- ↓5-7 % resting energy expenditure
- ↓Total daily energy expenditure
- ↓T3
- ↓Fat mass 75-80% and fat-free mass 20-25 %

Longo VD, et. al. Nature Aging. 2021;1(1):47-59.

Napoleão A, et. al., Nutrients. 2021;13(4).; Golbidi S, et. al., Curr Diab Rep. 2017;17(12):123.; Varady KA., Obesity Reviews. 2011;12(7):e593-e601.; Luscombe ND, Tsopelas C, et. al., Asia Pac J Clin Nutr. 2006;15(3):307-16.; Redman LM, et al., PLoS One. 2009;4(2):e4377.; Jiménez Jaime T, et al., Nutr Hosp. 2015;31(6):2428-36.

3. Paleolithic diet

- Hunter-gatherer diet or stone-age diet
- The paleolithic era, ~2.5 million to 10,000 years ago
- Consumption of meat, fish, eggs, vegetables, fruits, roots, and nuts,
- No consumption of many cultivated products, such as dairy products, oils, cereals, and legumes (as well as salt and refined sugars)
- A traditional paleolithic diet ~35% fat, 35% CHO, and 30% proteins
- A low-carbohydrate diet, high fiber
- Weight loss
- Improvement of lipid profile, carbohydrate metabolism, and insulin sensitivity
- ↓Blood pressure
- ↓Oxidative stress
- Anti-inflammatory benefits

Jamka M, et al. J Clin Med. 2020;9(2); de Menezes EVA, et. al.. Nutrition journal. 2019;18(1):41-.

3. Paleolithic diet

- A systematic review and meta-analysis
- In overweight and obese individuals with or without calorie restriction

- ↓Weight (-3.52 kg)
- ↓BMI
- ↓Blood glucose HbA1c and insulin levels
- ↓HOMA-IR
- No different from other diets, including the Mediterranean diet, the diabetes diet, and the diet recommended by the Dutch health council

Jamka M, et al. J Clin Med. 2020;9(2); de Menezes EVA, et. al.. Nutrition journal. 2019;18(1):41-.

4. Mediterranean diet

- **Food traditionally eaten by countries bordering the Mediterranean Sea (Greece, Italy, France, Spain, etc.)**

https://images.everydayhealth.com/images/diet-nutrition/mediterranean-diet/mediterranean-diet-recipes-01-722x406.jpg?w=768

https://images.everydayhealth.com/images/diet-nutrition/mediterranean-diet/mediterranean-diet-recipes-mediterranean-sheet-pan-baked-shrimp-and-vegetables-406x406.jpg?w=768

- **High consumption**
  - Fruits and vegetables
  - Monounsaturated fats (primarily from olive oil)
  - Legumes and grains
- **Moderate consumption**
  - Poultry
  - Fish
  - Dairy products
- **Little to no consumption of red meat**

Am J Med. 2016 Apr;129(4):407-415.e4.

4. Mediterranean diet

- Grains, Vegetables, Fruits should be eaten at most meals.
  - Important sources of vitamins, minerals, energy, antioxidants, and fiber
- Grains
  - The majority → whole grains (wheat, oats, rice, rye, barley, and corn)
  - Best consumed in whole, minimally-processed forms (refining and processing can remove many valuable nutrients, including vitamins, minerals, and fiber)
  - Common → barley, buckwheat, bulgur, farro, millet, oats, polenta, rice, wheatberries, breads, couscous, and pastas
- Vegetables
  - Important (valuable nutrients and satiety)
  - Common → artichokes, arugula, beets, broccoli, brussels sprouts, cabbage, carrots, celery, celeriac, chicory, collard greens, cucumbers, dandelion greens, eggplant, fennel, kale, leeks, lemons, lettuce, mache, mushrooms, mustard greens, nettles, okra, onions (red, sweet, white), peas, peppers, potatoes, pumpkin, purslane, radishes, rutabaga, scallions, shallots, spinach, sweet potatoes, turnips, zucchini
- Fruits
  - Whole fresh or No-sugar-added fruit juices (portion and total calories control)
  - Common → apples, apricots, avocados, cherries, clementines, dates, figs, grapefruits, grapes, melons, nectarines, olives, oranges, peaches, pears, pomegranates, strawberries, tangerines, tomatoes

https://oldwayspt.org/traditional-diets/mediterranean-diet/traditional-med-diet

4. Mediterranean diet

- **Olives & Olive Oil**

  - Olives → eaten whole and widely used for cooking and flavoring
  - Olive oil → principal source of dietary fat used for cooking, baking, and for dressing salads and vegetables (extra virgin olive oil → highest in health-promoting fats, phytonutrients and other important micronutrients)
- **Nuts, Beans, Legumes & Seeds**

  - Good sources of healthy fats, protein, and fiber (add flavor and texture)
  - Common → almonds, cannellini beans, chickpeas, cashews, fava beans, green beans, hazelnuts, kidney beans, lentils, pine nuts, pistachios, sesame seeds, split peas, tahini sauce, walnuts
- **Herbs & Spices**

  - adding flavors and aromas to foods, ↓need to add salt or fat when cooking
  - rich in a broad range of health-promoting antioxidants
  - Common → anise, basil, bay leaf, chiles, cloves, cumin, fennel, garlic, lavender, marjoram, mint, oregano, parsley, pepper, pulbiber, rosemary, sage, savory, sumac, tarragon, thyme, za'atar
- **Cheese & Yogurt**

  - Eaten regularly, but low to moderate amounts
  - The calcium in cheese and yogurt → important for bone and heart health
  - Common → brie, chevre, corvo, feta, haloumi, manchego, Parmigiano-Reggiano, pecorino, ricotta, yogurt (including Greek yogurt)

https://oldwayspt.org/traditional-diets/mediterranean-diet/traditional-med-diet

4. Mediterranean diet

- **Fish and shellfish**
  - Important sources of healthy protein
  - Tuna, herring, sardines, salmon and bream → rich in essential heart-healthy omega-3 fatty acids (also shellfish and crustaceans including mussels, clams and shrimp)
  - Common seafood → abalone, clams, cockles, crab, eel, flounder, lobster mackerel, mussels, octopus, oysters, salmon, sardines, sea bass, shrimp, squid, tilapia, tuna, whelk, yellowtail

- **Eggs**
  - Good source of high-quality protein
  - Common → chicken, duck, and quail eggs

- **Meats**
  - Eaten in small portions
  - Poultry → good source of lean protein without the high levels of saturated fat
  - With ground meats (90% lean/10% fat)
  - Common poultry and red meat → beef, chicken, duck, goat, guinea fowl, lamb, mutton, pork

- **Wine**
  - Consumed regularly but moderately
    (Women, up to 1/5, Men, up to 2/5-ounce glass of wine/day)

https://oldwayspt.org/traditional-diets/mediterranean-diet/traditional-med-diet

4. Mediterranean diet

- A systematic review of randomized controlled trials (RCTs)
- Long-term effects (at ≥ 12 months)
- In overweight and obese individuals with or without calorie restriction

- ↓Weight (-4.1 to -10.1 kg)
  - >Low-fat diet (-2.9 to -5.0 kg)
  - ~Low-CHO diet (-4.7 to -7.7 kg)

- ↓BMI (-1.0 to -3.3 kg/m^2)
  - >Low-fat diet (1.4 to -1.8 kg/m2)
  - ~Low-CHO diet (-1.5 to -2.8 kg/m2)
  - Similar trend with waist circumference

Am J Med. 2016 Apr;129(4):407-415.e4.

4. Mediterranean diet

- Compared to low-fat diet, low-CHO diets
  - ~↓Glycemic control
  - >Significant improvement in DM type 2 patients
    - ↓Fasting glucose, HbA1c, serum insulin, and the homeostatic model assessment of insulin resistance
    - ↓Fasting glucose levels (-0.89 to -4.30 mmol/L vs 0.67 to -3.10 mmol/L)
  - ~↓LDL, ↑HDL
  - >↓TG (-0.25 to-1.50 vs -0.03 to -0.70 mmol/L)
  - ~↓Blood pressure (some)

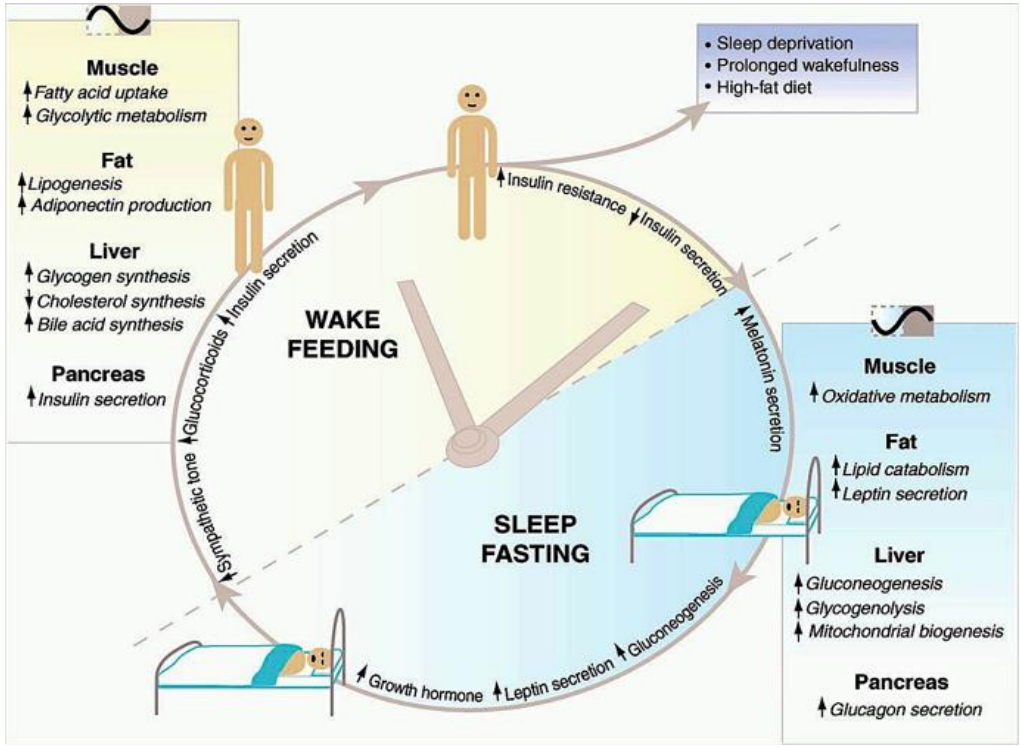
Am J Med. 2016 Apr;129(4):407-415.e4.

5. “Eating breakfast like a king, lunch like a prince, and dinner like a pauper”

- A seminal randomized controlled trial (Silver Spring) 2013;21: 2504–2512
- Overweight and obese women randomized to eat isocaloric diet ~1400 kcal for 12 weeks
  - A large breakfast compared to A large dinner
  - 700/200 kcal breakfast vs. dinner, 500 kcal lunch
  - >↓Weight 5.1 kg (8.7±1.4 kg vs. 3.6±1.5 kg)
  - >↓Waist circumference
  - > Fasting glucose, insulin, and HOMA-IR
  - ↓TG 33.6% vs. ↑14.6%
  - ↓Ghrelin and Hunger scores
  - ↑Satiety scores
- Several other interventional and cohort studies
  - Shifting food intake to earlier during the daytime increases weight loss.

J Nutr 1997; 127: 75–82, Cell Metab 2015;22: 789–798, Clin Nutr 2016;35: 1308–1314, Int J Obes (Lond) 2013;37: 604–611, Nutr Healthy Aging 2018, Diabetologia 2014;57: 1552–1560

The circadian system



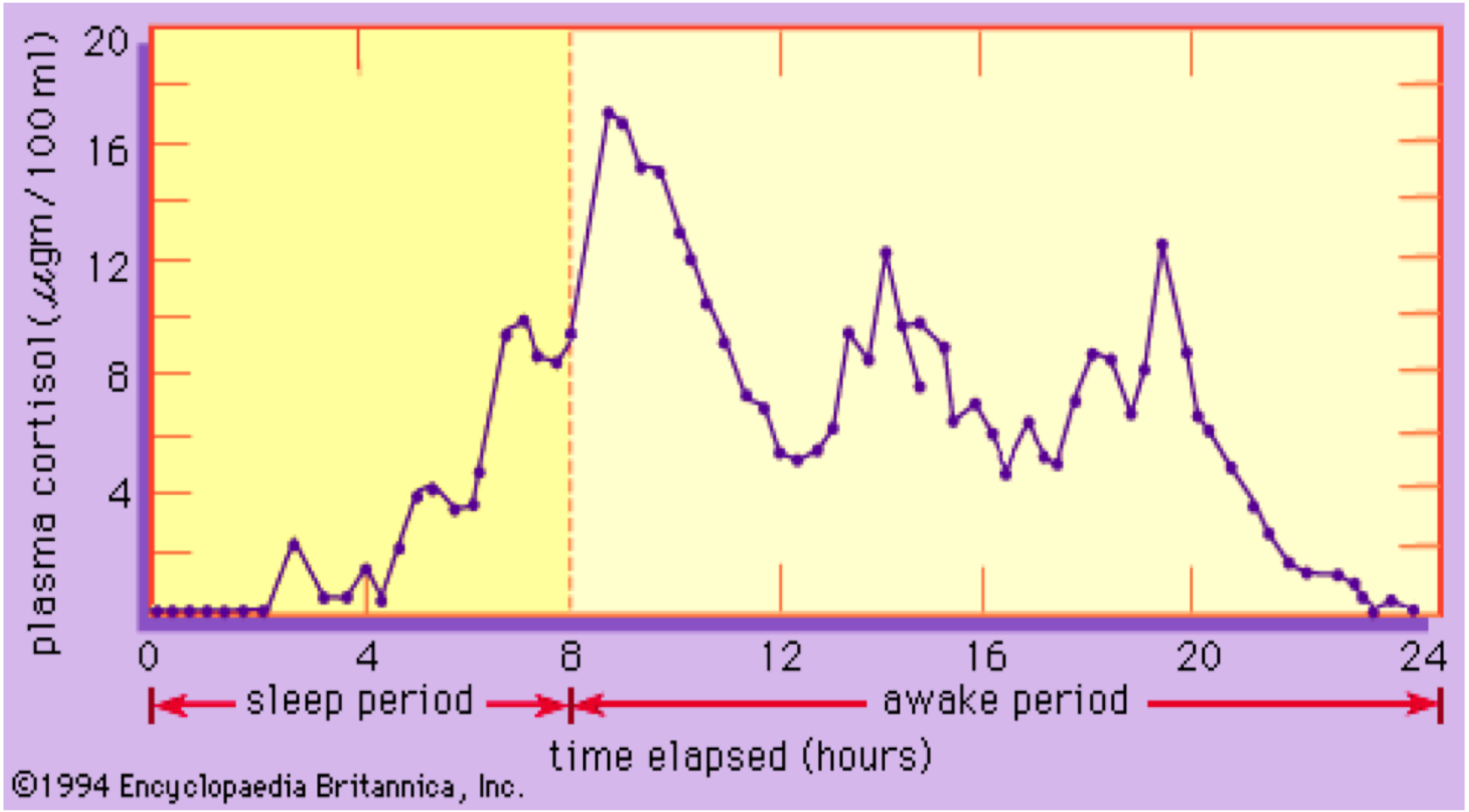
Joseph Bass, 2010

- In humans, ↑insulin sensitivity, beta cell responsiveness, and the thermic effect in the morning than in the afternoon or evening
- Human metabolism is optimized for food intake in the morning.

Morris et al., 2015a, 2015b; Poggiogalle et al., 2018; Scheer et al., 2009

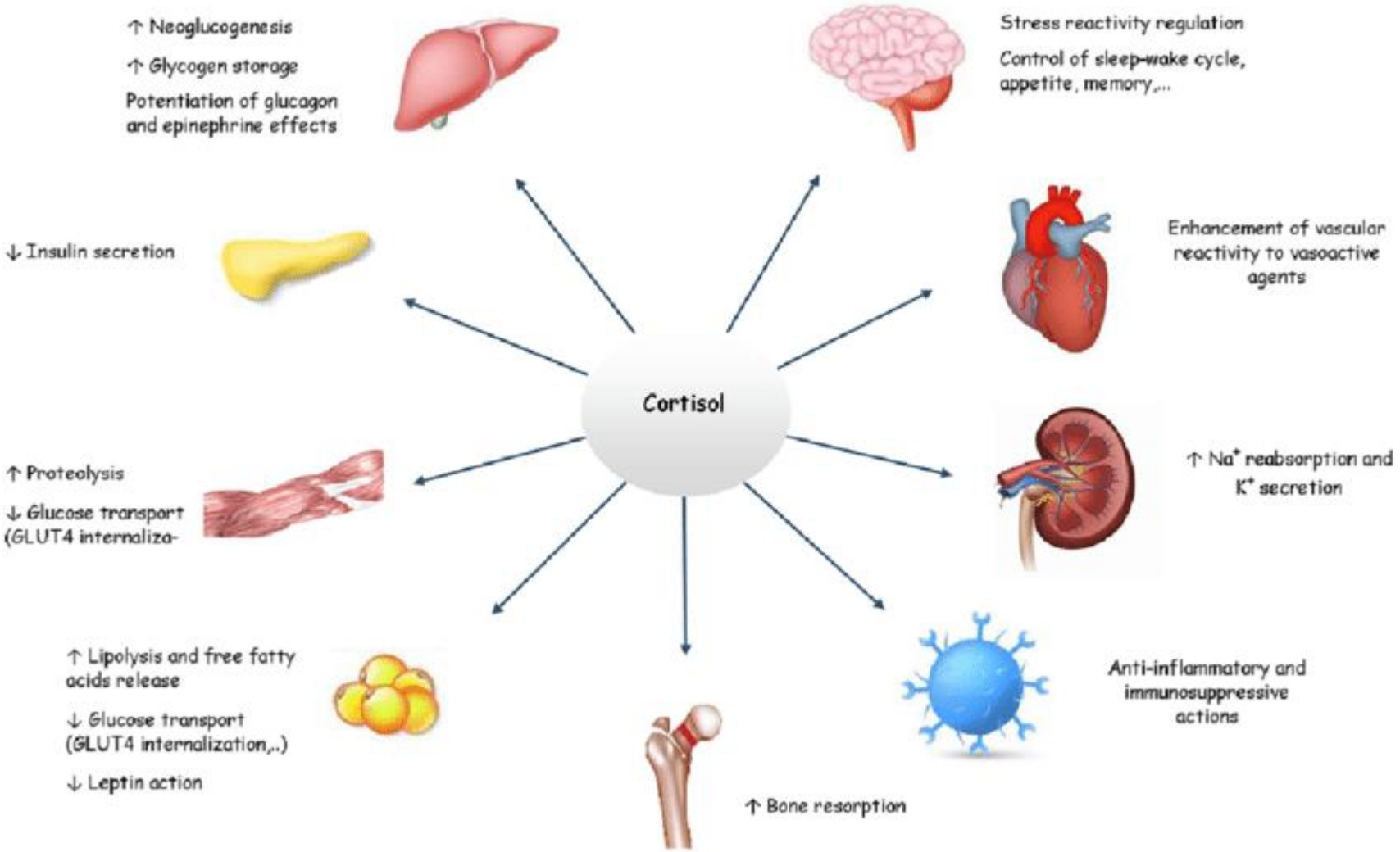
Obesity (Silver Spring). 2019 August ; 27(8): 1244–1254

Plasma Cortisol Levels



http://www.precisionnutrition.com/wordpress/wp-content/uploads/2009/03/cortisol-time.png

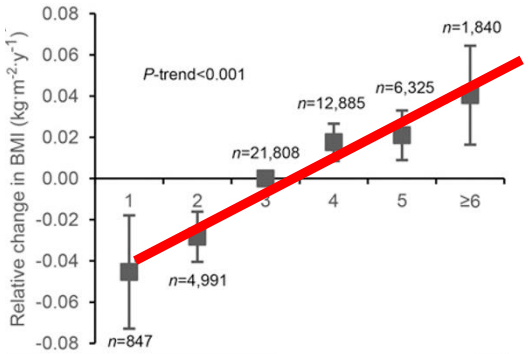
Cortisol



Ther Adv Endocrinol Metab. 2019; 10: 2042018818821294.

A Longitudinal Study Over 7 Years

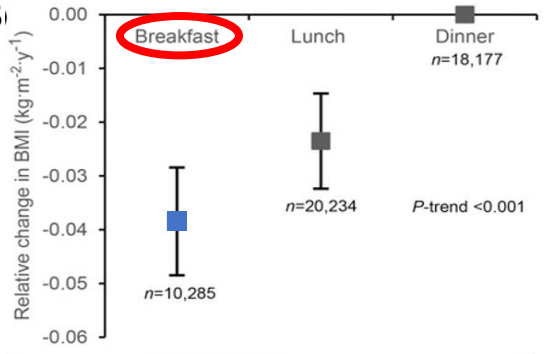
Number of meals



Meals and snacks (*n*/d)	1	2	3	4	5	≥6
Cohort %	1.74	10.3	44.8	26.5	13.0	3.78

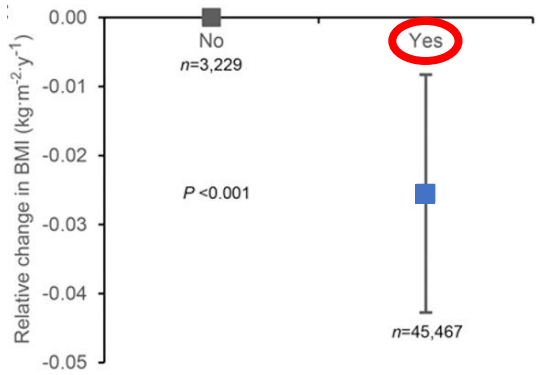
48,696 subjects

Largest meal



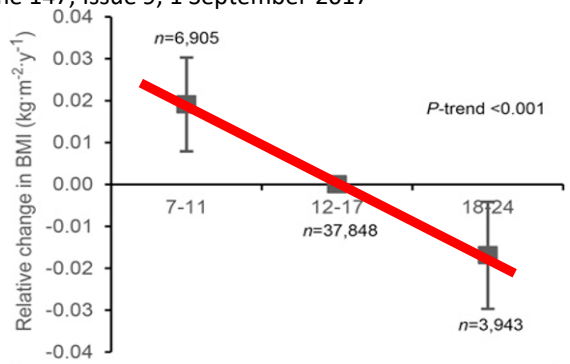
Time of largest meal	0500 –1100 h	1200 –1600	1700 –2300 h
Cohort %	21.1	41.6	37.3

The Journal of Nutrition, Volume 147, Issue 9, 1 September 2017



Breakfast	No	Yes
Cohort %	6.63	93.4

Breakfast Consumption

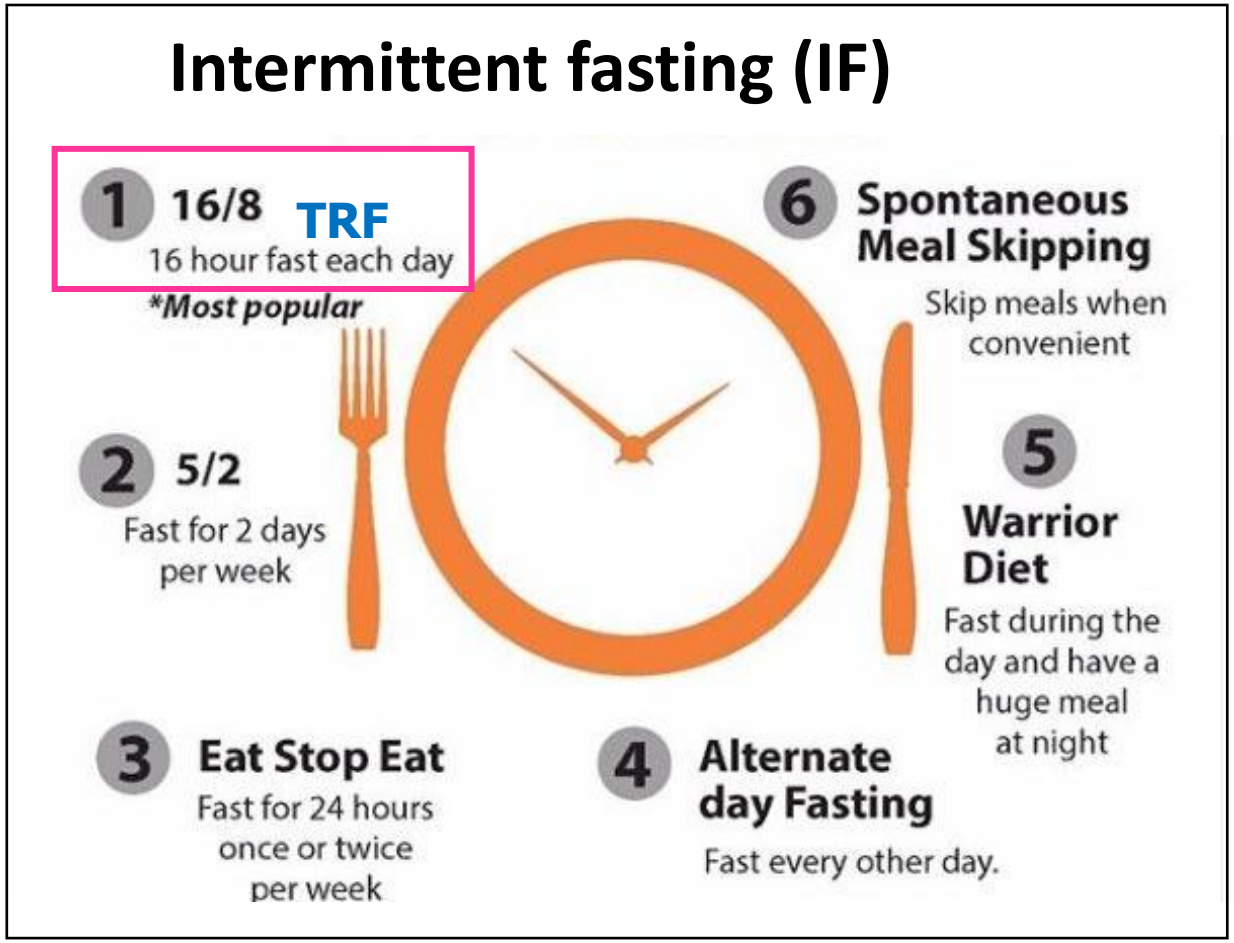


Length of night fast (hours)	7-11	12-17	18-24
Cohort %	14.2	77.7	8.10

Overnight Fast

6. Intermittent fasting (IF)

Any diet that alternates between periods of restricting calories and eating normally



- Complete alternate day fasting
- Modified alternate day fasting
- 5:2 intermittent fasting
- TRF

TRF = Time-restricted feeding

Garaulet et al., 2013

Intermittent fasting (IF)

Eating patterns that alternate between periods of restricting calories and eating normally

"Fasting" no consumption of energy-containing foods or beverages

"Feeding" consumption of foods and beverages ad libitum

Protocols of IF

- **Complete alternate-day fasting (ADF): eating ad libitum days alternating with no-energy food days**
- **Modified alternate-day fasting (MADF): eating ad libitum days alternating with <25% of baseline energy need days**
- **5:2 IF: 5 days/week of ad libitum feeding alternating with 2 days/week of absolute fasting which can be consecutive or not consecutive**
- **Time-restricted feeding (TRF): ad libitum intake during specific times (few hours) followed by fasting for a prolonged time during each day**

Patikorn C, et al. JAMA Netw Open. 2021;4(12):e2139558.; Halpern B, et al. Arch Endocrinol Metab. 2021;65(1):14-23.; Saad R. N Engl J Med. 2020;382(18):1773.; Anton SD, et al. Obesity (Silver Spring). 2018;26(2):254-68.; Welton S, et al. Can Fam Physician. 2020;66(2):117-25.

6. Intermittent fasting (IF)

Benefits of IF (Data from rodents and humans trials)

- ↓Body weight/BMI/body fat
- ↑Oxygen consumption/energy expenditure
- ↓Blood Glucose/insulin levels
- Improved insulin sensitivity
- Improved lipid profiles
- ↓Blood pressure
- ↓Markers of inflammation and oxidative stress
- Reverse type 2 Diabetes
- Slows and reverses aging and disease processes
- Increases longevity and survival in many species (animal models)

Am J Clin Nutr 2005;81:69-73; Carlson et al., 2007; Gill and Panda, 2015; Moro et al., 2016; Stote et al., 2007; Tinsley et al., 2017; Gill and Panda, 2015; Moro et al., 2016; Carlson et al., 2007; Stote et al., 2007; Tinsley et al., 2017; Cell Metab 2018;27(4):805.e4-815.e4., R de Cabo, MP Mattson. N Engl J Med 2019;381:2541-2551;

The fasting state

- ↓Blood glucose → ↓Insulin
- ↑Counter regulatory hormones (oppose the action of insulin) → ↑Blood sugar
  - Glucagon
  - Epinephrine
  - Norepinephrine
  - Cortisol
  - GH

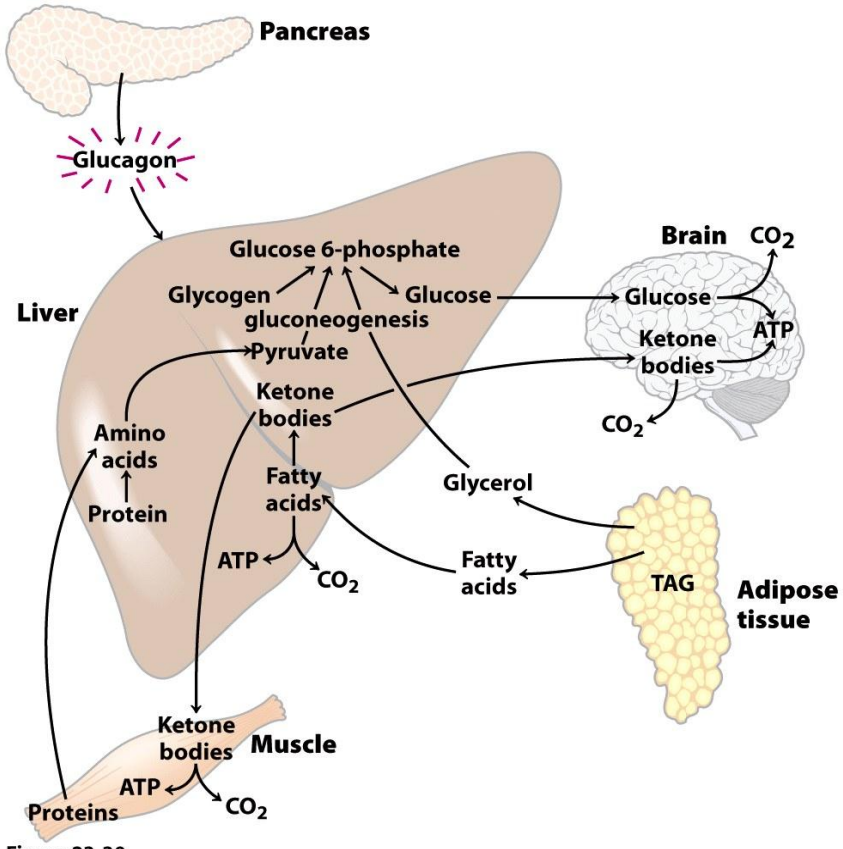
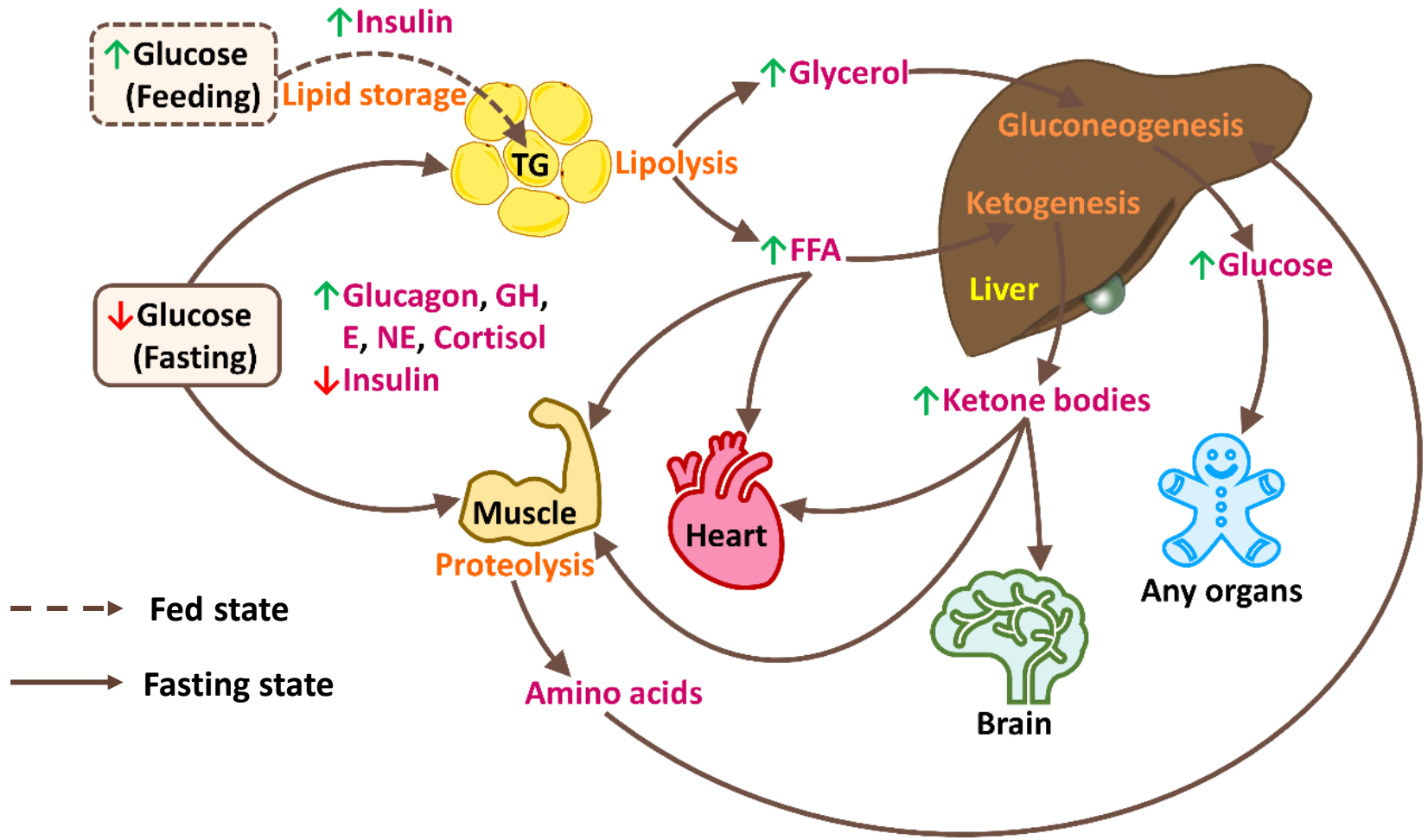


Figure 23-30
Lehninger Principles of Biochemistry, Fifth Edition

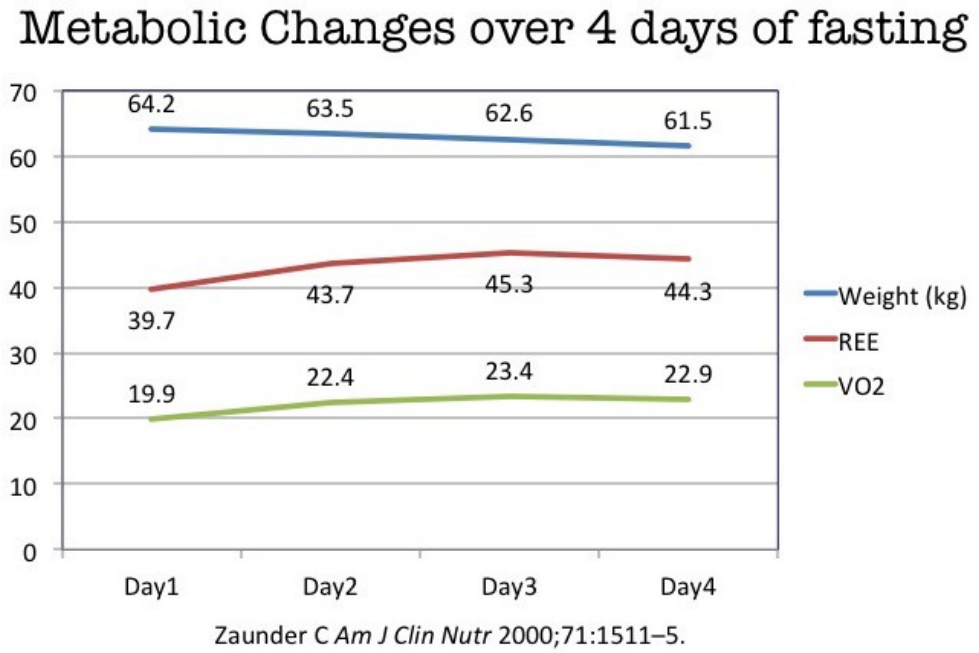
The fasting state



TG: triglyceride; FA: free fatty acid; GH: growth hormone; E: epinephrine; NE: norepinephrine

Fasting in humans

- The first 36-60 hours
  - ↑BMR
  - ↑NE and GH production
- Afterwards (72 or more)
  - ↓BMR
  - ↓NE and GH production



Zaunder C *Am J Clin Nutr* 2000;71:1511–5.

BMR = basal metabolic rate

NE = noradrenaline

GH = growth hormone

Plasma concentrations of fatty acids, glucose, and ketone bodies during the first week of starvation

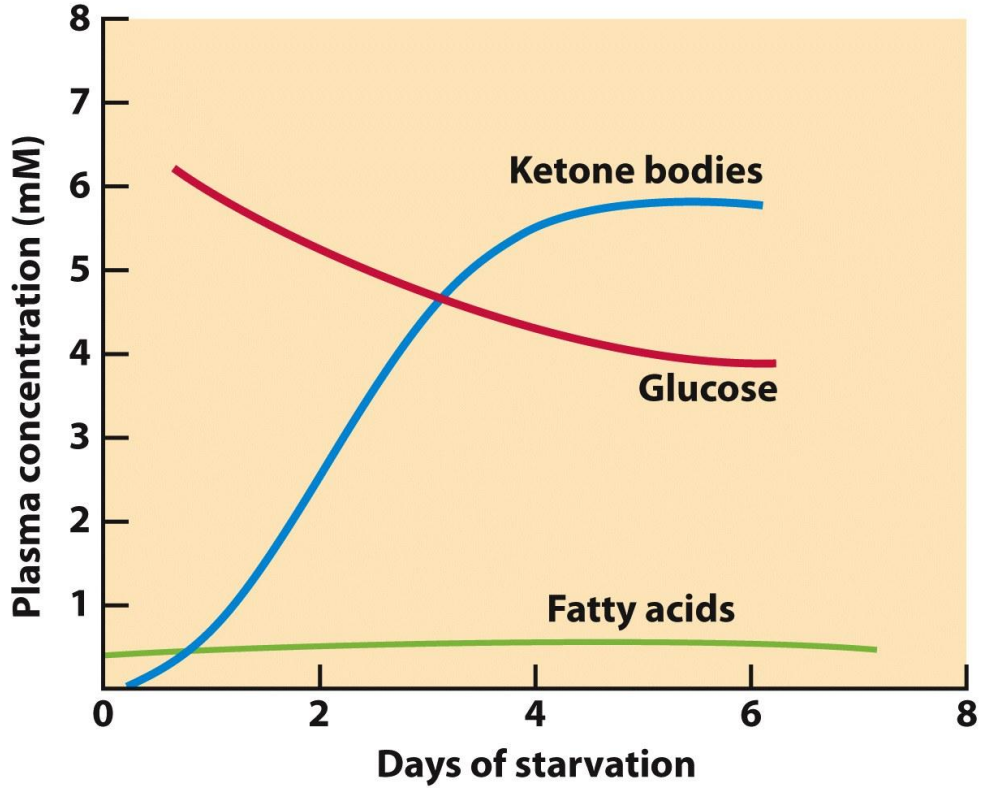


Figure 23-32
Lehninger Principles of Biochemistry, Fifth Edition

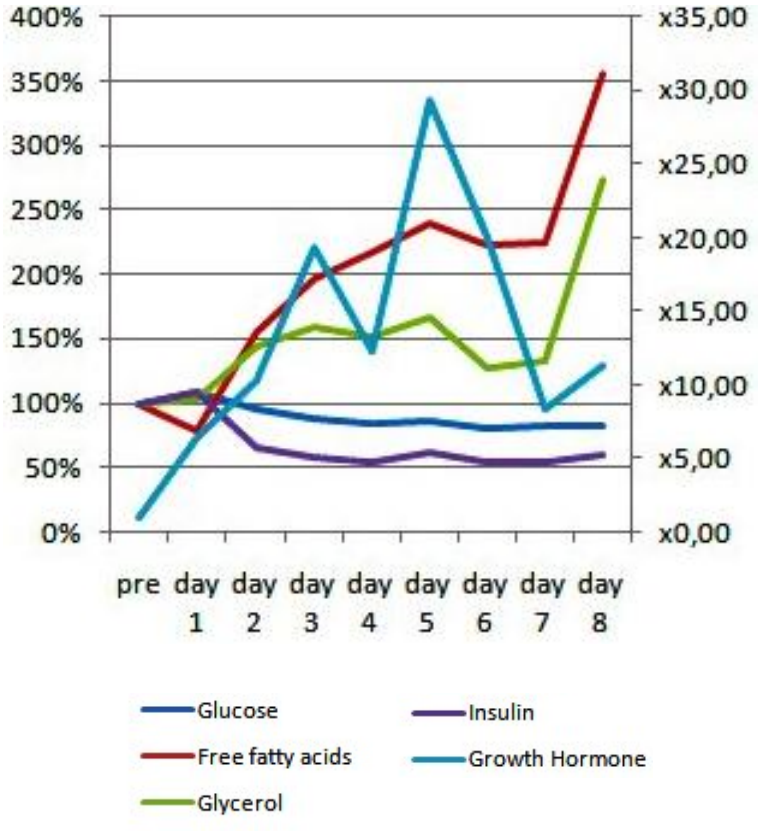
↓Glucose after 2 days of fasting

Fatty acids cannot serve as a fuel for the brain; they do not cross the blood-brain barrier.

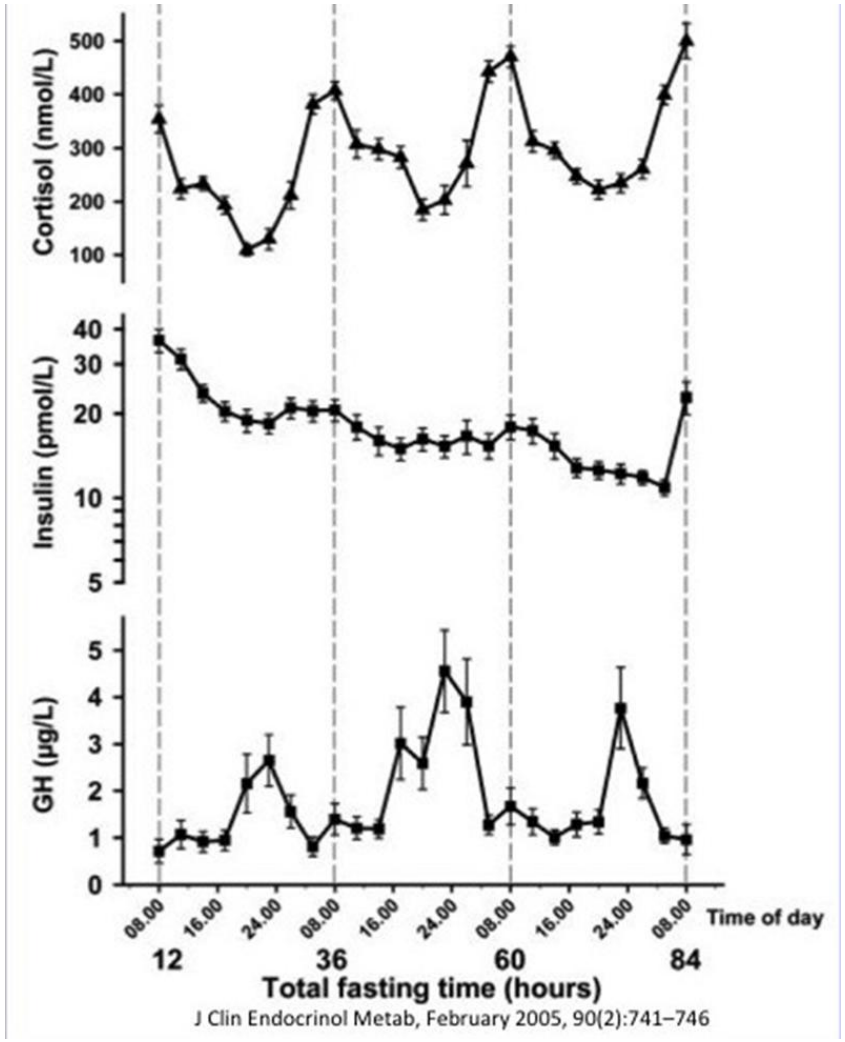
Ketone bodies, almost unmeasurable before the fast, rises dramatically after 2 to 4 days of fasting. These water-soluble ketones, acetoacetate and *β*-hydroxybutyrate, supplement glucose as an energy source during a long fast.

Fasting in humans

Effects of 8 days of fasting in 6 perfectly healthy subjects

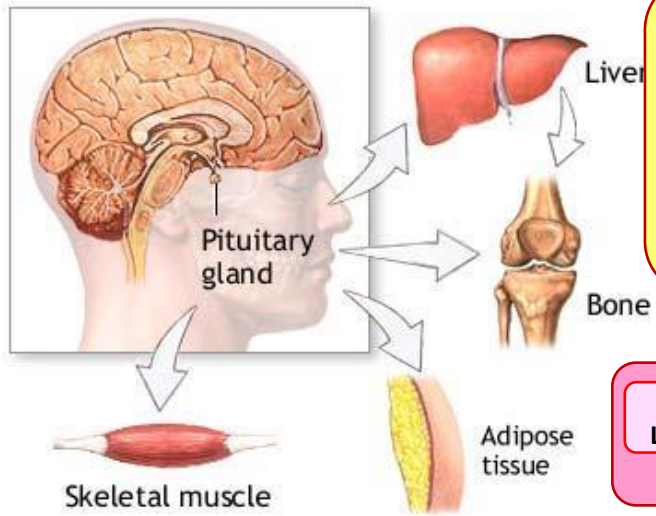


K Y Ho,et al. 1988., Wook-chul Choi et al. 2016



J Clin Endocrinol Metab, February 2005, 90(2):741–746

Growth Hormone (GH)



↑Hepatic glucose production

↓Cellular glucose uptake & utilization

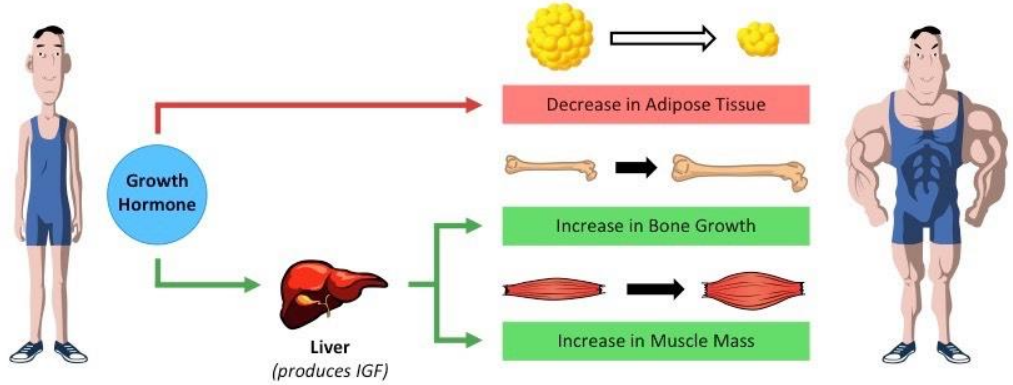
↑Blood glucose

GLUCOSTATIC EFFECT

Fat Lipolysis → ↑Blood FFA

LIPOLYTIC EFFECT

↑Protein synthesis → ↑Lean body mass PROTEIN ANABOLIC EFFECT



https://ib.bioninja.com.au/_Media/growth-hormone_med.jpeg

↑GH

- Plasma amino acids (Arginine)
- ↓Blood sugar/Hypoglycemia/Fasting
- ↓Blood FFA
- Exercise/Excitement
- Acute stress/Trauma
- Deep sleep
- GHRH
- Sex hormones, Thyroid hormone
- Ghrelin

↓GH

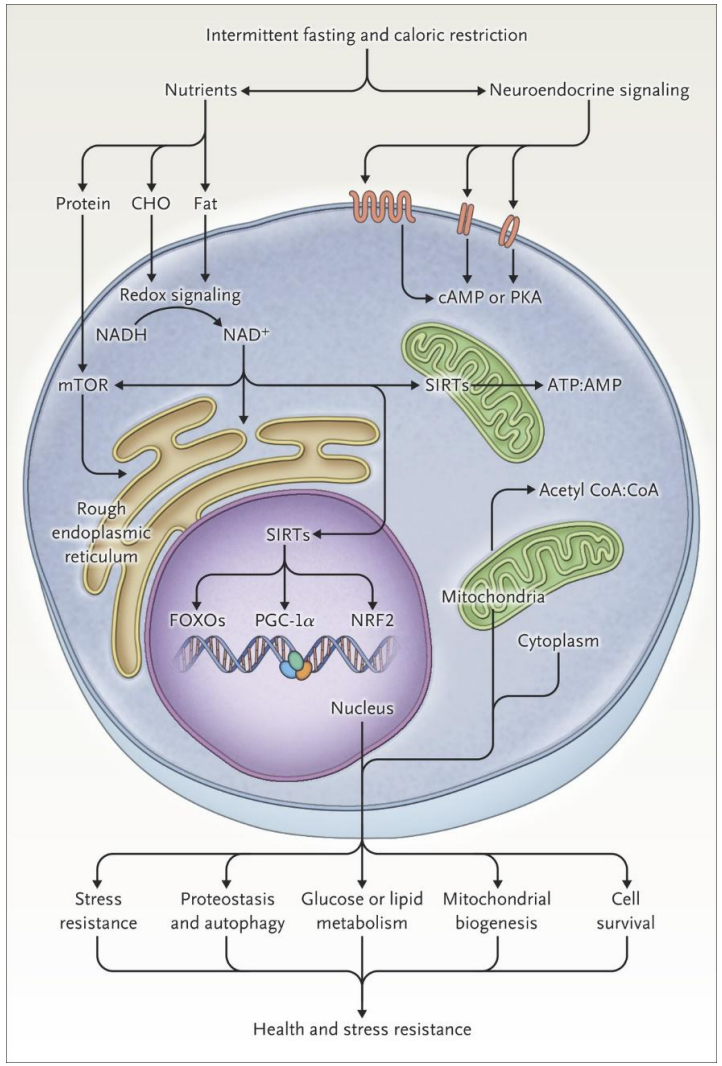
- ↑Blood sugar/Hyperglycemia/↑FFA
- Aging/Obesity/Chronic stress
- GHIH (somatostatin)/IGFs

The fasting state

- Energy restriction for 10-14 hours or more
  - Depletion of liver glycogen
  - ↑Lipolysis
  - ↑Production of ketone bodies
- β-hydroxybutyrate (β-HB) has signaling functions
  - ↑Transcription factors such as cyclic adenosine monophosphate (cAMP) response element–binding protein (CREB) and nuclear factor κB (NF-κB)
  - ↑Expression of brain-derived neurotrophic factor (BDNF) in neurons
- ↓Glucose and amino acids during fasting
  - ↓Activity of the mammalian target of rapamycin (mTOR) pathway
  - Up-regulation of autophagy
- Energy restriction stimulates
  - Mitochondrial biogenesis
  - Mitochondrial uncoupling

R de Cabo, MP Mattson. New England Journal of Medicine. 2019;381:2541-2551

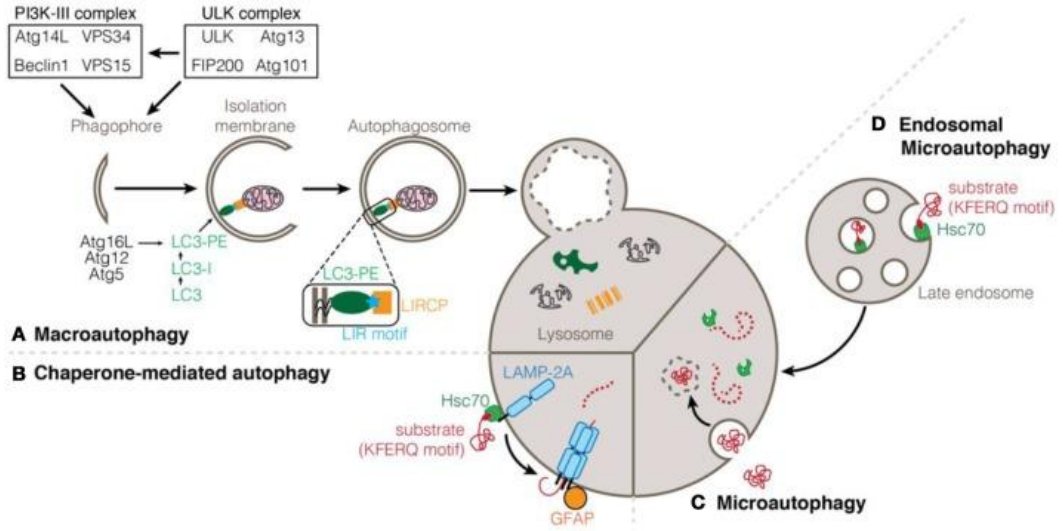
Cellular Responses to Fasting



- Intermittent fasting triggers neuroendocrine responses and adaptations.
- ↓Circulating glucose, insulin, and amino acids
- ↓Circulating amino acids → repress the activity of mammalian target of rapamycin (mTOR) → inhibition of protein synthesis → stimulation of autophagy
- Down-regulation of the insulin-like growth factor1 (IGF-1) signaling pathway
- Minimizing anabolic processes (synthesis, growth, and reproduction)
- Favoring maintenance and repair systems
- Enhancing stress resistance
- Recycling damaged molecules
- Stimulating mitochondrial biogenesis
- Promoting cell survival
- Improvements in health and diseases

R de Cabo, MP Mattson. New England Journal of Medicine. 2019;381:2541-2551

Autophagy

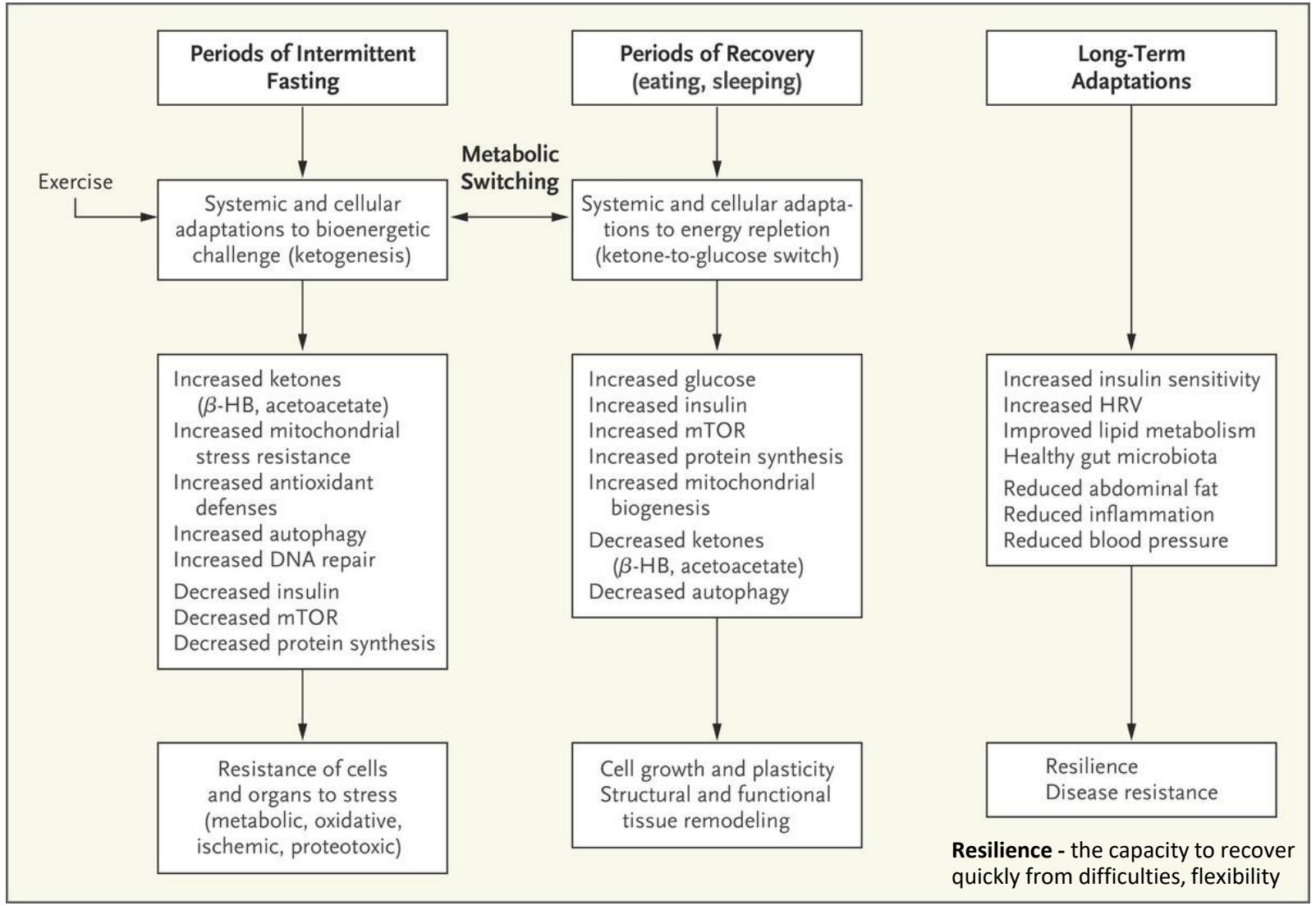


- Cellular self-digestion
- An adaptive response to stress, particularly in the condition of nutrient deprivation, allowing for cell and organism survival
- Cytoplasmic catabolic process that protects the cell against stressful conditions

- Damaged cellular components are funneled by autophagy into the lysosomes, where they are degraded and can be re-used as alternative building blocks for protein synthesis and cellular repair.
- When nutrient resources are restricted, cells are able to break down and reprocess all sort of macromolecules including proteins, lipids, and carbohydrates which can then be reused as essential building blocks for the synthesis of new macromolecules and the production of energy.
- Autophagic dysfunction is associated with cancer, neurodegeneration, microbial infection, and ageing.

Nature. 2008 Feb 28; 451(7182): 1069–1075.

Cellular and Molecular Mechanisms Underlying Improved Organ Functions and Resistance to Stresses and Diseases with Intermittent Metabolic Switching



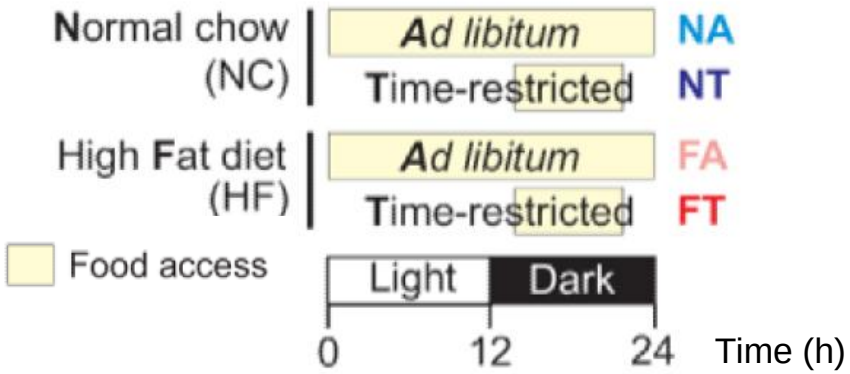
Resilience - the capacity to recover quickly from difficulties, flexibility

R de Cabo, MP Mattson. N Engl J Med 2019;381:2541-2551.

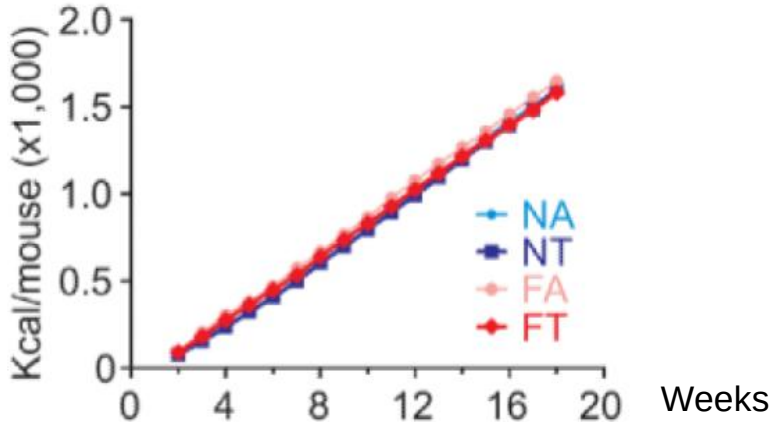
HRV = heart-rate variability

Time-restricted feeding (TRF) in mice

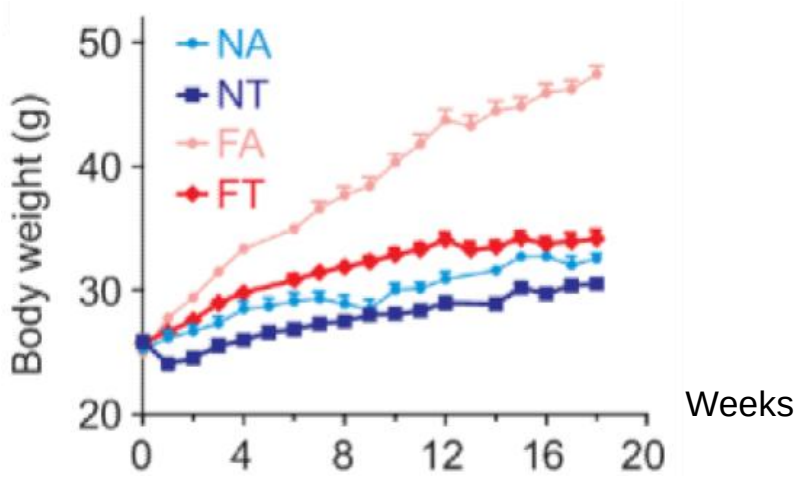
A) Four feeding regimens



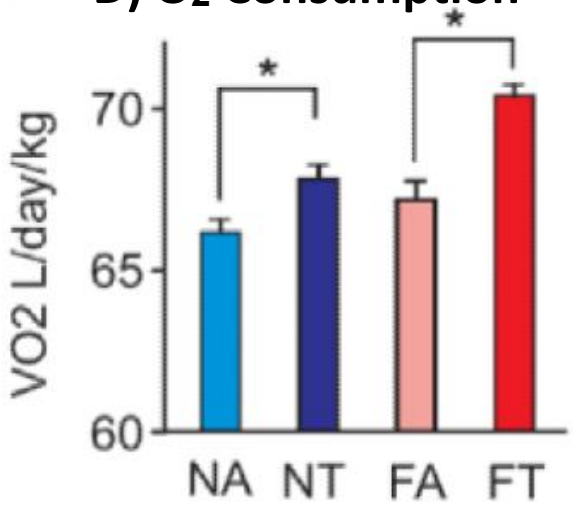
B) Cumulative average energy intake



C) Average body weight



D) O_2 Consumption



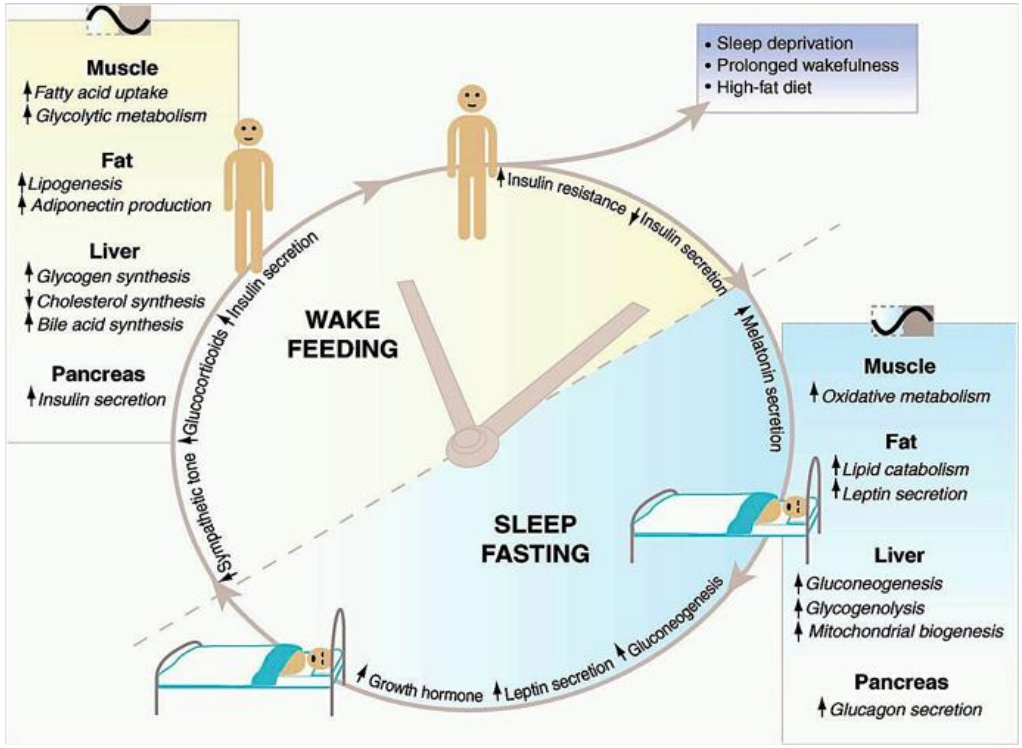
Hatori M et al., 2012

Time-restricted feeding (TRF) in humans

- Appears to depend on the time of day of the eating window
- Restricting food intake to the middle of the day (“mid-day TRF’’)
  - ↓Body weight or body fat, fasting glucose and insulin level, insulin resistance, hyperlipidemia, inflammation
- Restricting food intake to the late afternoon or evening (‘‘late TRF’’)
  - Produced mostly null results or worsened postprandial glucose levels, β-cell responsiveness, blood pressure, and lipid levels

Carlson et al., 2007; Gill and Panda, 2015; Moro et al., 2016; Stote et al., 2007; Tinsley et al., 2017;
Gill and Panda, 2015; Moro et al., 2016; Carlson et al., 2007; 9) Stote et al., 2007; Tinsley et al., 2017

The circadian system



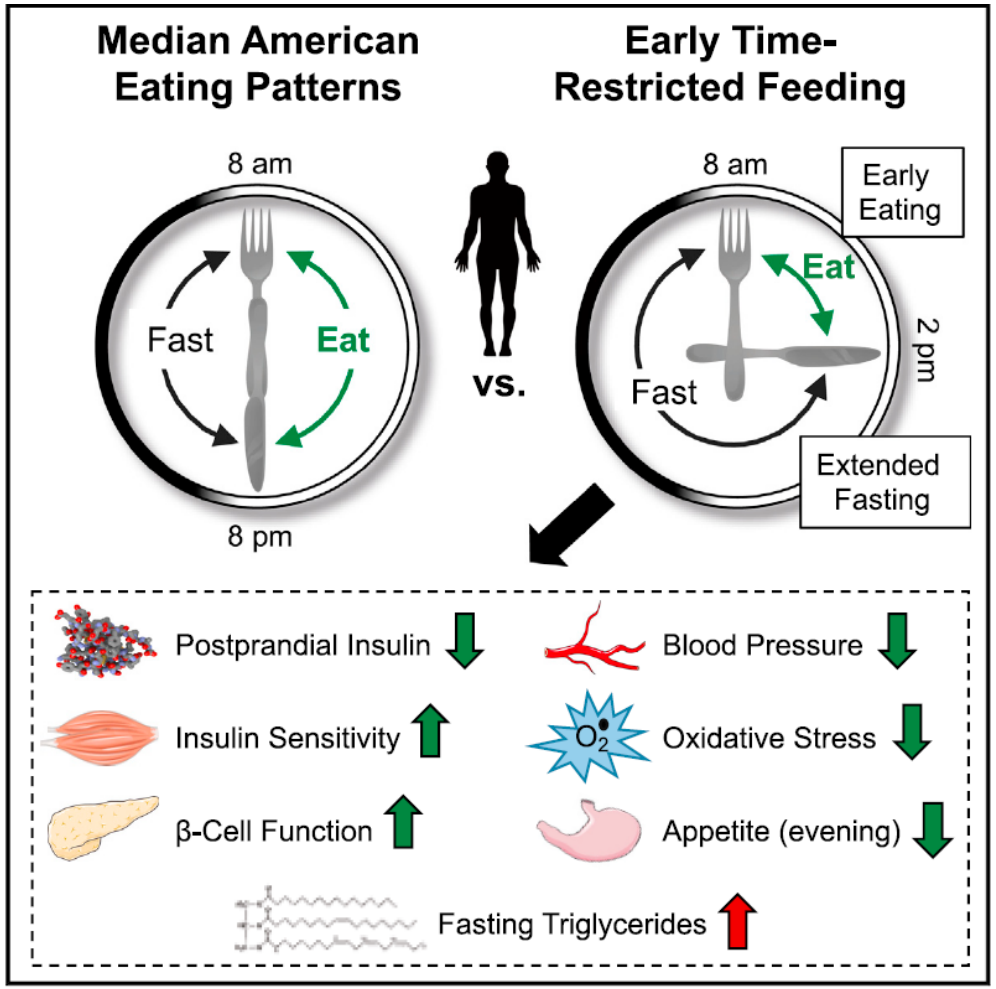
Joseph Bass, 2010

- In humans, ↑insulin sensitivity, beta cell responsiveness, fat oxidation, and the thermic effect of food in the morning than in the afternoon or evening
- Human metabolism is optimized for food intake in the morning.

Morris et al., 2015a, 2015b; Poggiogalle et al., 2018; Scheer et al., 2009

Obesity (Silver Spring). 2019 August ; 27(8): 1244–1254

Early Time-Restricted Feeding



Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes
Elizabeth F.Sutton1RobbieBeyl1Kate S.Early2William T.Cefalu13EricRavussin1Courtney M.Peterson
Cell Metabolism Volume 27, Issue 6, 5 June 2018, Pages 1212-1221.e3

7. Ketogenic diet

- High-fats, moderate-proteins, and very-low-carbohydrates
- approximately 55-60% fat, 30-35% protein, and 5-10% CHO
- The most common and relatively minor short-term side effects
  - Nausea, vomiting, headache, fatigue, dizziness, insomnia, difficulty in exercise tolerance, and constipation, sometimes referred to as keto flu
  - Ensuring adequate fluid and electrolyte intake → counter some of these symptoms
- Long-term adverse effects
  - Hepatic steatosis, hypoproteinemia, kidney stones, and vitamin and mineral deficiencies

Masood W, Annamaraju P, Uppaluri KR. Ketogenic Diet. [Updated 2020 Jun 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-.
Available from: https://www.ncbi.nlm.nih.gov/books/NBK499830/

7. Ketogenic diet

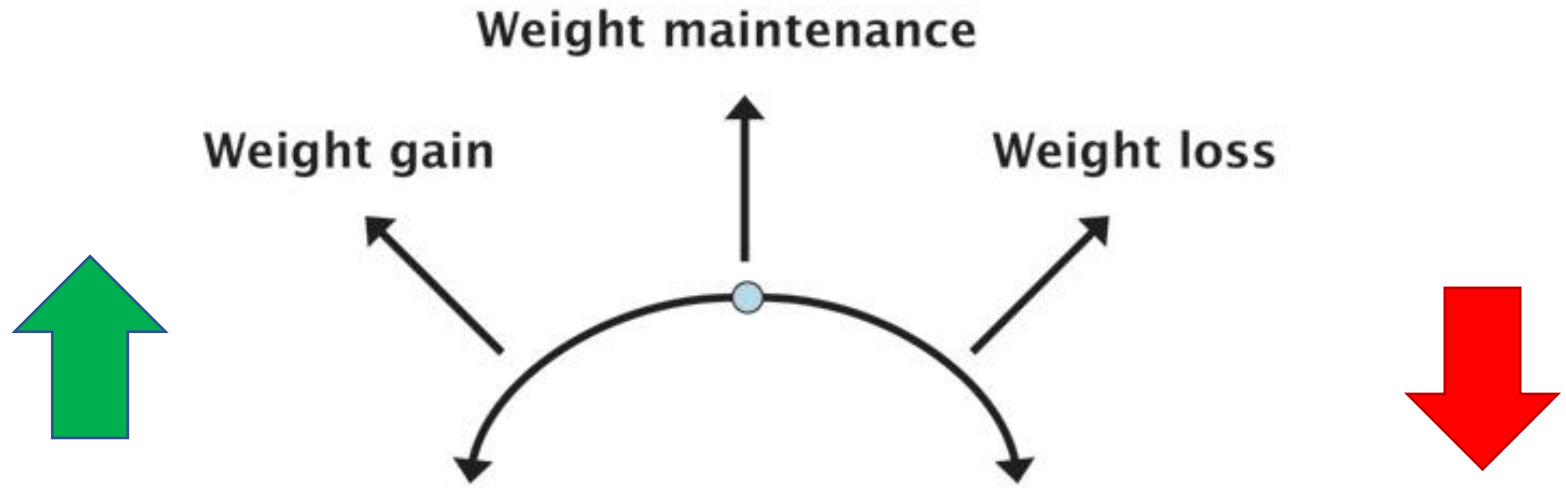
- Most systematic reviews and meta-analysis
  - Confounded by low-CHO diets that were likely not ketogenic

Saslow LR, et. al. PLoS One. 2014;9(4):e91027.

- ↓Fat mass 66.15% and fat-free mass 33.85%
- No systematic reviews or RCTs examined mortality or cardiovascular disease

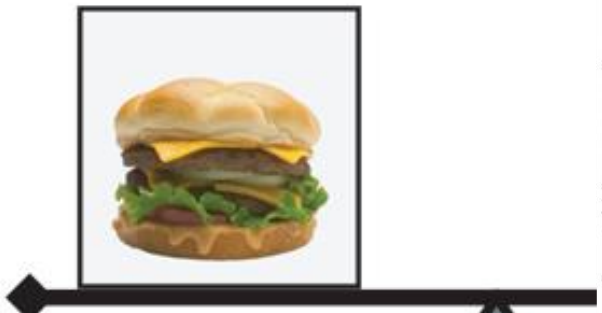
Can Fam Physician. 2018 Dec; 64(12): 906; Foster GD, et. Al. N Engl J Med. 2003;348(21):2082-90.; Dashti HM, et. al. Exp Clin Cardiol. 2004;9(3):200-5; Moreno B, et. al. Endocrine. 2016;54(3):681-90.; Yancy WS, Jr., et. al. Ann Intern Med. 2004;140(10):769-77.; Goday A, et. al. Nutrition & Diabetes. 2016;6(9):e230-e.; Jabekk PT, et. al. Nutrition & Metabolism. 2010;7(1):17.; Partsalaki I, et. al. Endocrinol Metab. 2012;25(7-8):697-704.; Saslow LR, et. al. Nutrition & Diabetes. 2017;7(12):304.; Westman EC, et. al. Nutrition & metabolism. 2008;5:36-.

Energy balance

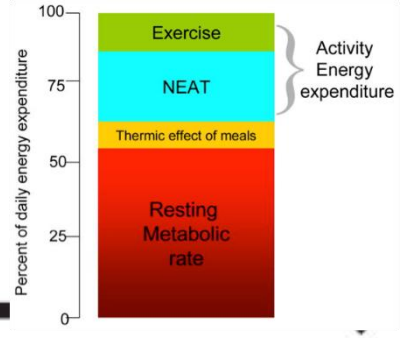


Obesity!!!

Food intake



Energy expenditure



http://4.bp.blogspot.com/-obEju6EGjzo/T6FmPh8cgoI/AAAAAAAAExA/euaH3NKQBss/s1600/NEAT_graph.png

http://www.precisionnutrition.com/wordpress/wp-content/uploads/2009/04/energy-balance-continuum.jpg

Principle of Weight Management

ฉันทชา สิทธิจรูญ. ใน: ฉันทชา สิทธิจรูญ, บรรณาธิการ. ภาวะอ้วนและการลดน้ำหนัก.

พิมพ์ครั้งที่ 1. กรุงเทพฯ: บริษัท ไอดี ออล ดิจิตอลพริ้นท์ จำกัด; 2565.

Principle of Weight Management

1. Inspiration and determination
2. Goal setting: short-term goal & long-term goal
3. Choosing a diet that's right for you
4. Increased energy expenditure
5. Self-monitoring
6. Sleep
7. Probiotics
8. Stress
9. Support
10. Positive attitude

Principle of Weight Management

1. Inspiration and determination
   - The most important factor
   - Drives behavior

2. Goal setting
   - Short term-goal for goal achievement
   - Long term-goal for optimum BW/BMI
   - Limit setting

3. Choosing a diet that's right for you
   - Could be done continuously in a long term
   - Too hungry → over-eating!!!
   - Method alternating

Weight loss diet regimens

1. General Recommendation (↓Carbohydrate, ↓Sugar, ↑Protein, ↓Fat, ↑Vegetable/Fiber, ↑Drinking water)
   - Metabolism boosting meals (High protein, Low fat, No carb with 1 day cheating/week)
   - Plate method
2. Calories reduction
3. Paleolithic diet
4. Mediterranean diet
5. "Eating breakfast like a king, lunch like a prince, and dinner like a pauper"
6. Intermittent fasting (including Time-restricted eating, TRF)
7. Ketogenic Diet

Principle of Weight Management

4. Increased energy expenditure

- ↑EAT or exercise
  - ↑EE, lean mass, BMR, lipolysis, GH
- ↑NEAT
- Aerobic exercise
  - Moderate intensity 150 min/week (walking)
  - Vigorous intensity 75 min/week (running)
- Muscle strengthening, all muscle groups
  - ≥2 days/week (8-12 repetitions, 2-3 sets)
- Pedometer goal:
  - 5,000-10,000 steps/day

Moderate- and Vigorous-intensity Physical Activity

Moderate-intensity Physical Activity (Approximately 3-6 METs)	Vigorous-intensity Physical Activity (Approximately >6 METs)
Requires a moderate amount of effort and noticeably accelerates the heart rate.	Requires a large amount of effort and causes rapid breathing and a substantial increase in heart rate.
Examples of moderate-intensity exercise include:	Examples of vigorous-intensity exercise include:
• Brisk walking	• Running
• Dancing	• Walking / climbing briskly up a hill
• Gardening	• Fast cycling
• Housework and domestic chores	• Aerobics
• Traditional hunting and gathering	• Fast swimming
• Active involvement in games and sports with children / walking domestic animals	• Competitive sports and games (e.g. Traditional Games, Football, Volleyball, Hockey, Basketball)
• General building tasks (e.g. roofing, thatching, painting)	• Heavy shovelling or digging ditches
• Carrying / moving moderate loads (<20kg)	• Carrying / moving heavy loads (>20kg)

http://www.who.int/dietphysicalactivity/physical_activity_intensity/en/

HR max = 208-0.7 x age

Heart rate reserve = HR max-HR basal

Moderate exercise intensity

- **(Heart rate < 0.7 X Heart rate reserve, HRR)**
  - **Your breathing quickens, but you're not out of breath.**
  - **You develop a light sweat after about 10 minutes of activity.**
  - **You can carry on a conversation, but you can't sing.**

Vigorous exercise intensity

- **(Heart rate 0.7- 0. 85 X Heart rate reserve)**
  - **Your breathing is deep and rapid.**
  - **You develop a sweat after only a few minutes of activity.**
  - **You can't say more than a few words without pausing for breath.**

https://www.mayoclinic.org/healthy-lifestyle/fitness/in-depth/exercise-intensity/art-20046887

Exercise

NEAT

is movement activities of the body caused by skeletal muscle causing energy consumption such as walking, cleaning the house, etc.

Exercise

is a subtype of physical activity that is structured, repetitive and intended to either strengthen a skill or maintain a fitness level, either or all.

Exercise should be at least 30-45 minutes, 5-7 days/week.

Principle of Weight Management

5. Self-monitoring

- Weighing
  - Bathroom scale
  - Feedback (self-awareness)
  - Fat → light weight → stepwise
- Food Record
  - Calories
  - Response
  - Feedback

6. Sleep

- Deep sleep → GH → ↑lipolysis GH = growth hormone
- Lack of sleep
- Sleep deprived people → ↓leptin, ↑ghrelin → ↑appetite

Principle of Weight Management

7. Probiotics

- Faster gut & colonic transit time
- ↑Stool frequency
- ↑ Stool consistency
- ↓Flatulence
- ↑recovery of tight junction between epithelial cells → prevent bacterial movement & ↓inflammation from LPS → ↑insulin sensitivity at hypothalamus → ↑satiety
- ↑GLP-1 & PPY in intestine → ↓ appetite, ↑fullness

LPS = lipopolysaccharide, GLP-1 = glucagon-like peptide 1, PYY = peptide YY

Principle of Weight Management

8. Adjust behavior when stressed

- Stress ⌦ eat

9. Support

- Friend, family
- Social
- Environment

10. Positive attitude

- Don’t give up
- Can always start over

Weight regain

Weight Regain

- Weight reduction 5-10% within 3-6 months
- Weight Regain
  - Obvious in ~6-12 months after weight loss
  - >25% within the first year
  - >50% within 2 years
  - >80% within 5 years
- Causes
  - ↓Fat → ↓Insulin & leptin → ↑appetite
  - ↓TEE (REE & non-REE) from ↓body composition (↓ metabolically active component e.g. FFM)
  - ↓FFM → high risk of weight regain or even ↑BW

TEE = total energy expenditure, REE = resting energy expenditure, FFM = fat-free mass

Weight Regain

- Causes
  - ↓Thermogenesis not associated with BW & body composition called "adaptive thermogenesis" (AT) or ↓EE > ↓body composition
    - Occurring
      - Eating less >2 weeks
      - Optimum ~10% weight loss of initial BW or after 12-20 weeks of loosing weight
  - ↓T3
  - ↓SNS
  - Unlimited eating → rapid weight regain
    - ↑Energy intake
    - ↓Energy expenditure from ↓FFM and prolong AT
    - 4 weeks → normal BMR (new body composition)

AT = adaptive thermogenesis

EE = energy expenditure

BW = body weight

T3 = Triiodothyronine

SNS = sympathetic nervous system

FFM = fat-free mass,

BMR = basal metabolic rate

Diet break or Cheat days

Diet break or Cheat days

- Eating less >2 weeks
  - ↓RMR
  - Adaptive thermogenesis
    - Could be normal after diet refeed
- Diet break or cheat days
  - Eucaloric or ~5-10% a little bit ↑ or ↓ than current BW, not initial BW
  - Diet control, not over eating
  - Short term ~1-3 days
  - Or prolong >4 days to several weeks
  - Maintain BW to stimulate RMR & thermogenesis
  - More effectiveness in weight loss

RMR = resting metabolic rate, BW = body weight

Weight loss maintenance

Weight loss maintenance

- Voluntary weight loss at least 10% of initial BW and maintain at least 1 year
- Voluntary weight loss at least 5% of initial BW and maintain at least 2 years
- Generally, weight loss ~7-10% of initial BW in 6 months after that ~5-6% of initial BW
- Within 5 years, 13-20% of people can maintain weight loss

BW = body weight

Factors associated with successful weight maintenance

1. Inspiration
2. Reaching a self-determined goal weight
3. Autonomy
4. Initial weight loss → more initial weight loss, more successful weight maintenance
5. Calorie Reduction and Portioning of food eaten
6. Eating breakfast regularly
7. Control of over-eating with eating restraint
8. Physically active lifestyle

Elfhag K, Rössner S. Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. Obes Rev. 2005;6(1):67-85.
Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. Med Clin North Am. 2018;102(1):183-97.
Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr. 2005;82(1 Suppl):222S-5S.

Factors associated with successful weight maintenance

9. Self-monitoring → weighing & food record
10. Psychological strength and stability
11. Self-efficacy
12. Ability to handle life stress & coping strategy
13. Socialization & thinking flexibility
14. Social support
15. Being able to maintain weight after prolong weight loss

Elfhag K, Rössner S. Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. Obes Rev. 2005;6(1):67-85.
Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. Med Clin North Am. 2018;102(1):183-97.
Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr. 2005;82(1 Suppl):222S-5S.

Example

Example

Example

Example

Percentage of total weight loss

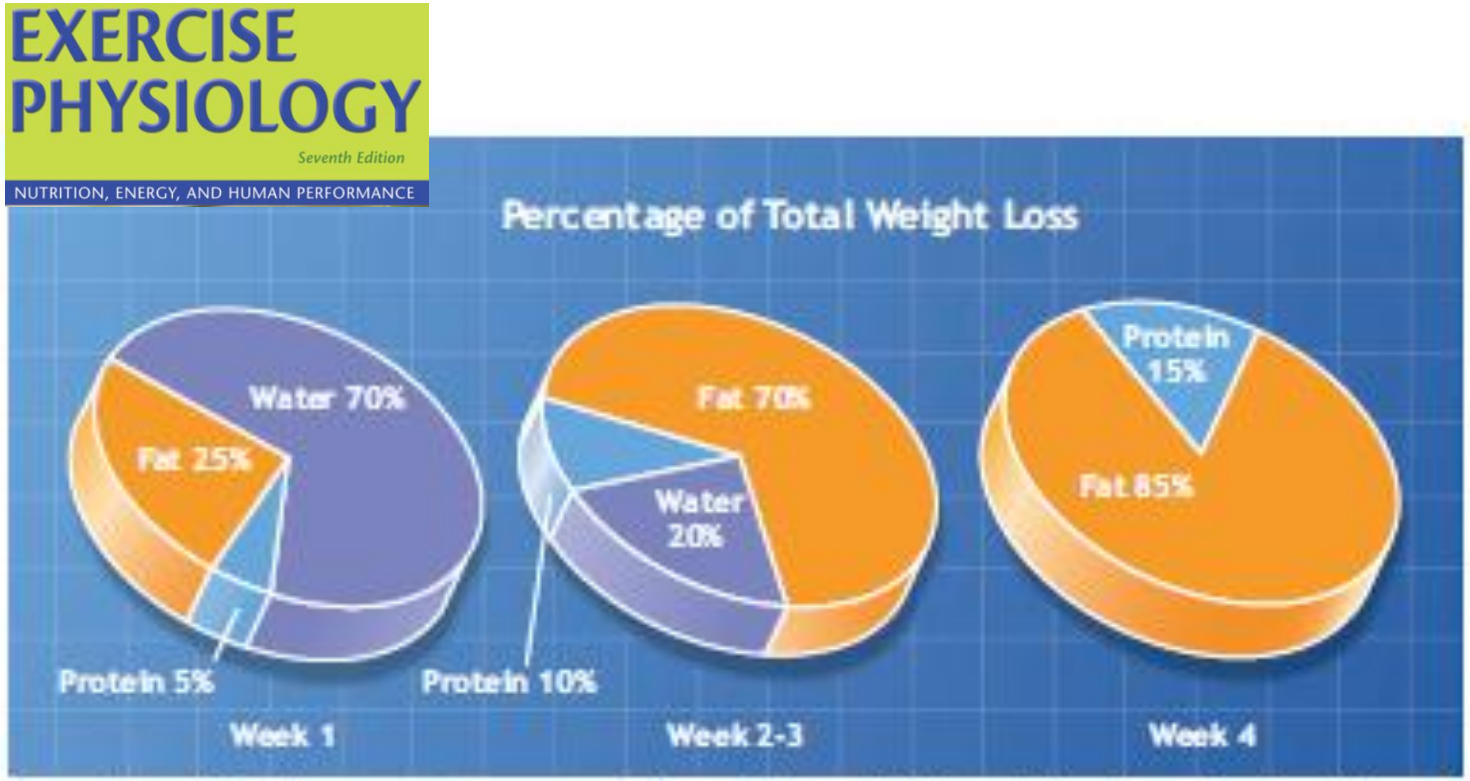


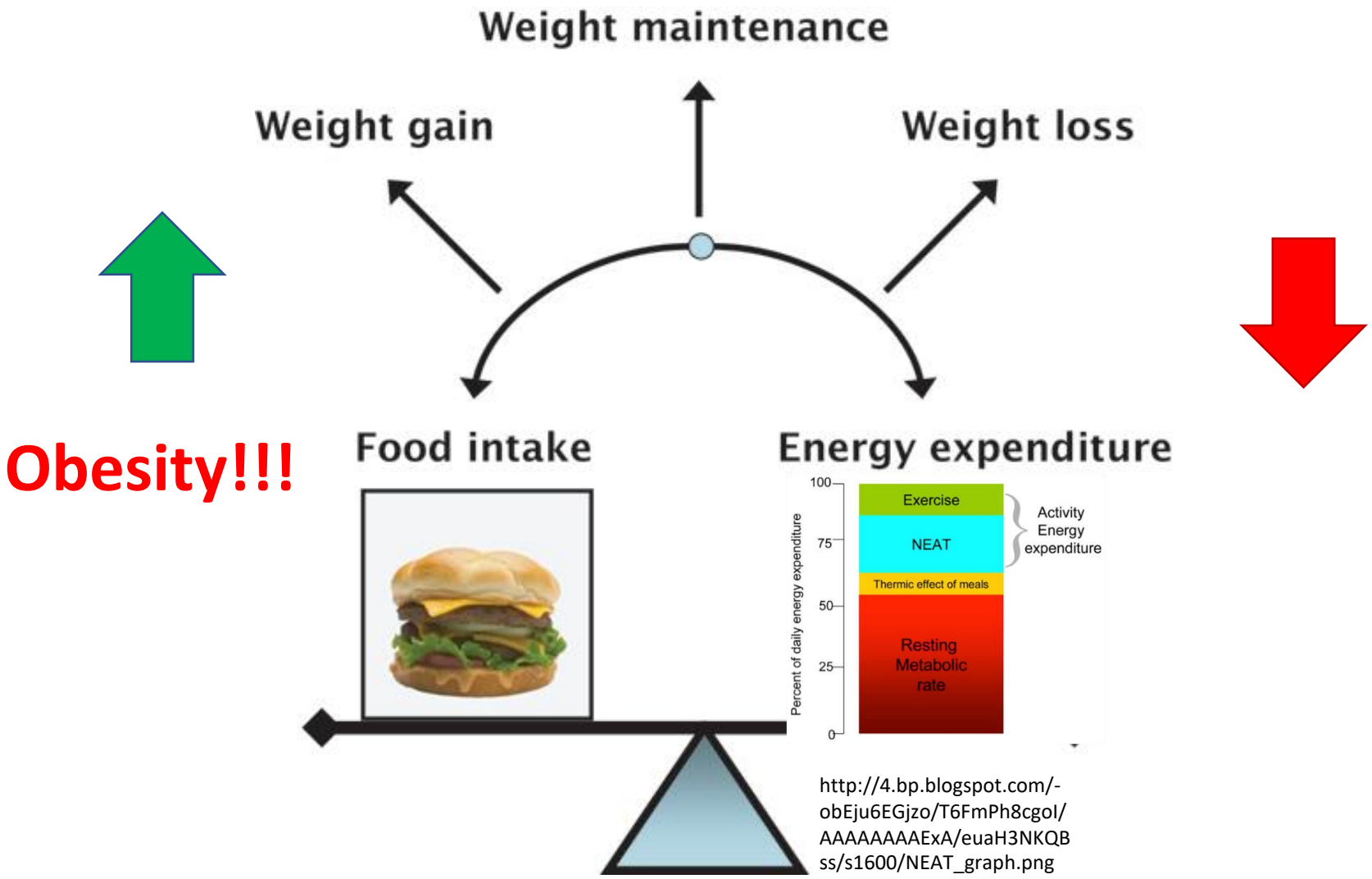
Figure 30.22 • General trend for the percentage composition of the weight lost during 4 weeks of caloric restriction.

The fasting state

- When fat reserves are gone.
  - Degradation of essential proteins begins
  - Loss of heart and liver function
  - Prolonged starvation → death

- Stored fat → provides adequate energy during fast or rigid diet, but vitamins and minerals must be provided.
- Sufficient dietary glucogenic amino acids are needed to replace those being used for gluconeogenesis.
- Rations for those on a weight-reduction diet are commonly fortified with vitamins, minerals and amino acids or proteins.

Energy balance



http://4.bp.blogspot.com/-obEju6EGjzo/T6FmPh8cgoI/AAAAAAAAExA/euaH3NKQBss/s1600/NEAT_graph.png

http://www.precisionnutrition.com/wordpress/wp-content/uploads/2009/04/energy-balance-continuum.jpg

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