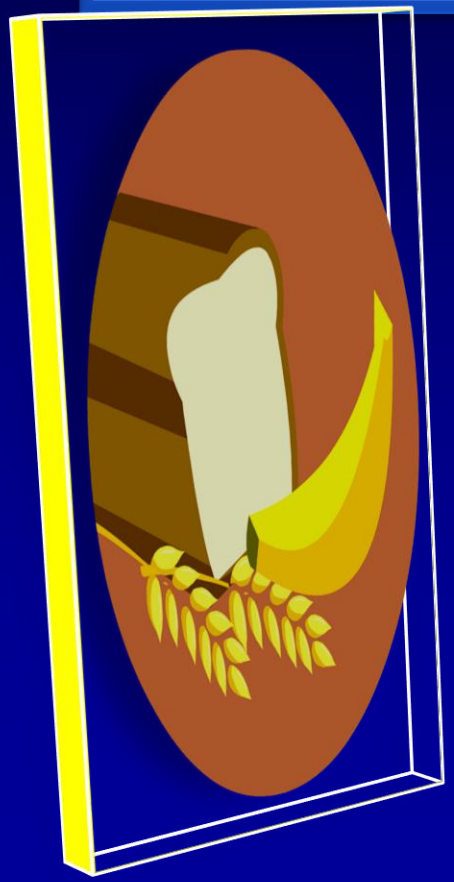
In The Name Of God

Obesity

Weight-Regulation



Dr. Majid Hassan Ghomi(PhD)

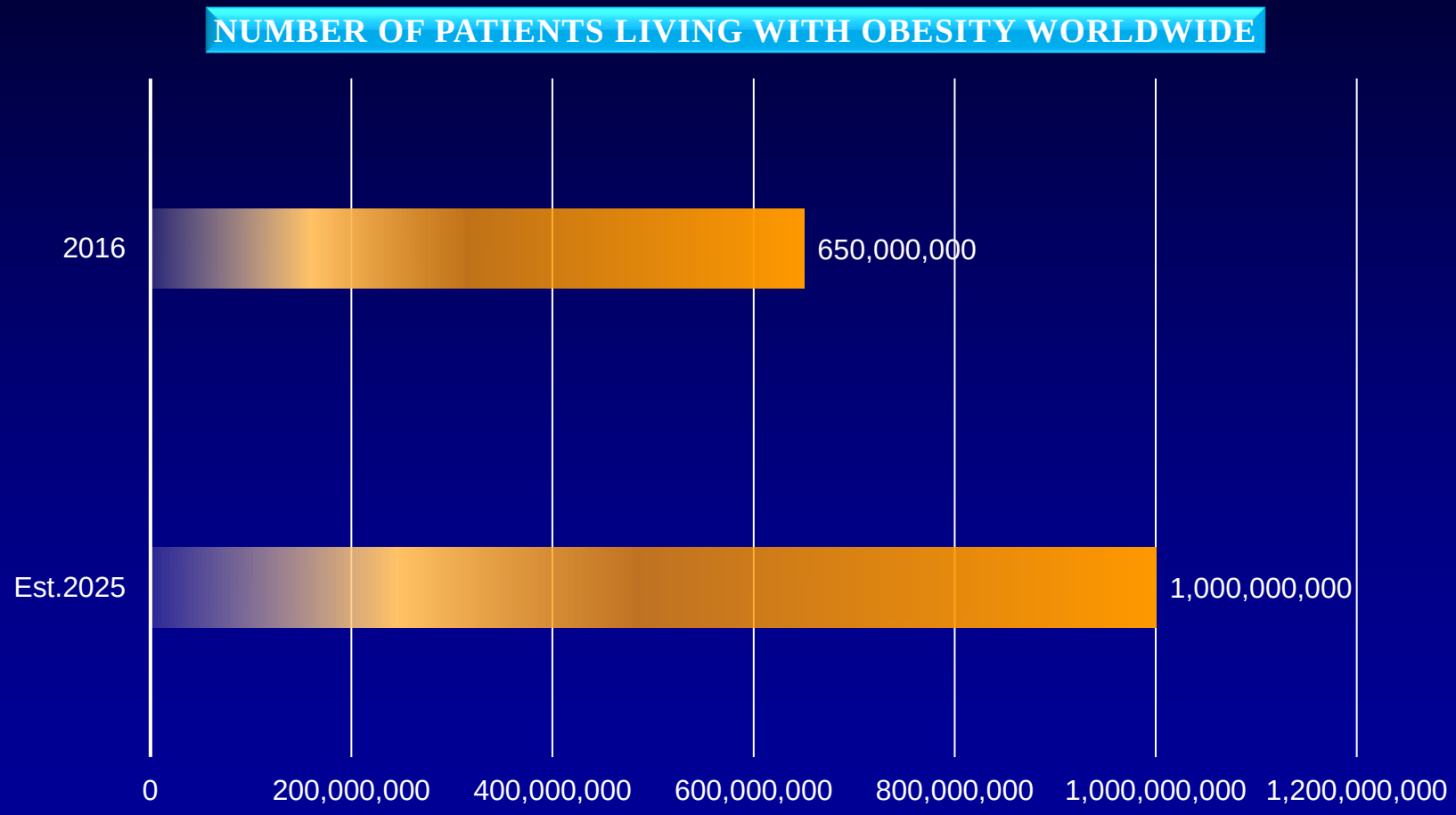
Obesity as a Relapsing, Chronic Disease

Kushner, R. *Circ*. 2012;126: 2870-2877.

Obesity Recognized as a Chronic Disease

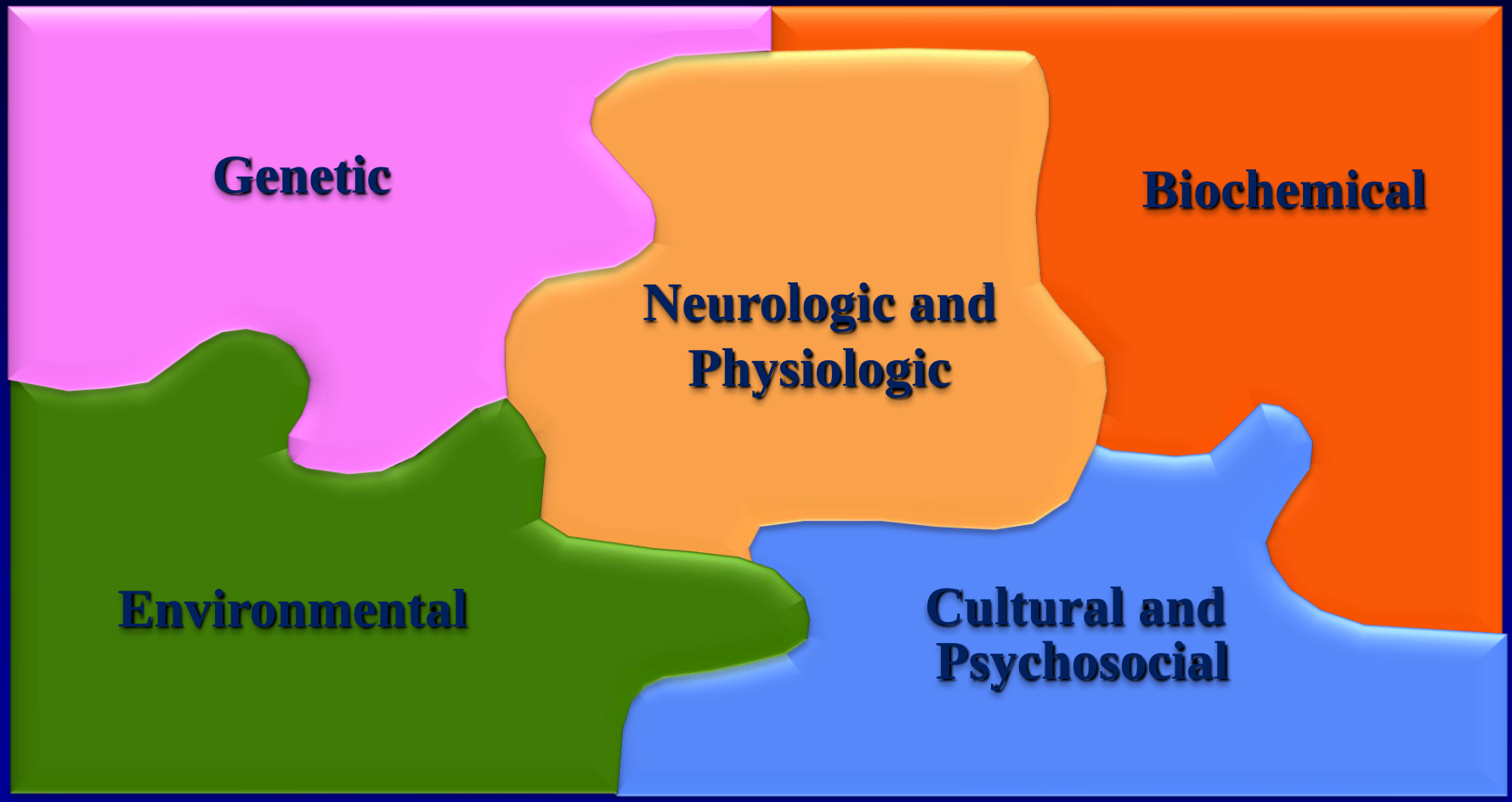
Kyle T et al. *Endocrinol Metab Clin North Am*. 2016; 45(3): 511-520.

Increasing Prevalence Worldwide



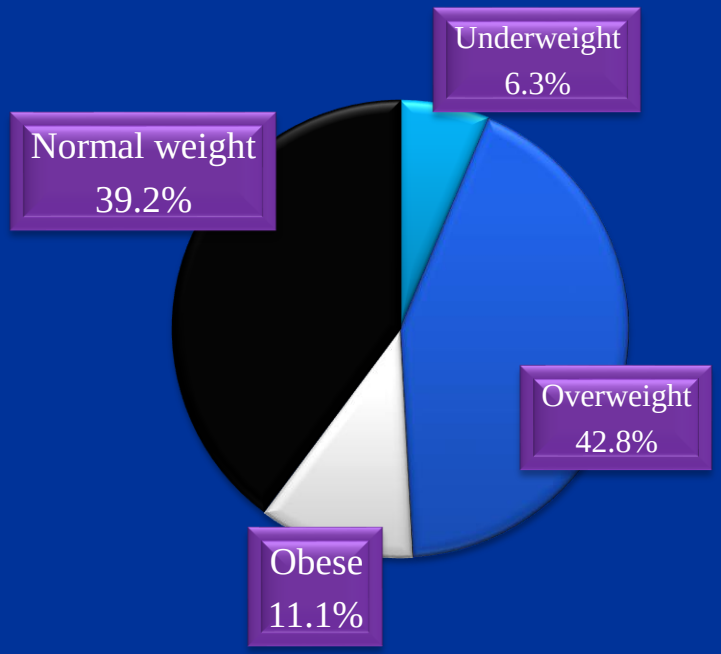
World Obesity Federation. 2019. December 18, 2021. https://www.worldobesity.org/about/about-obesity/prevalence-of-obesity

Aetiology of Obesity: Numerous Complex and Interrelated Factors

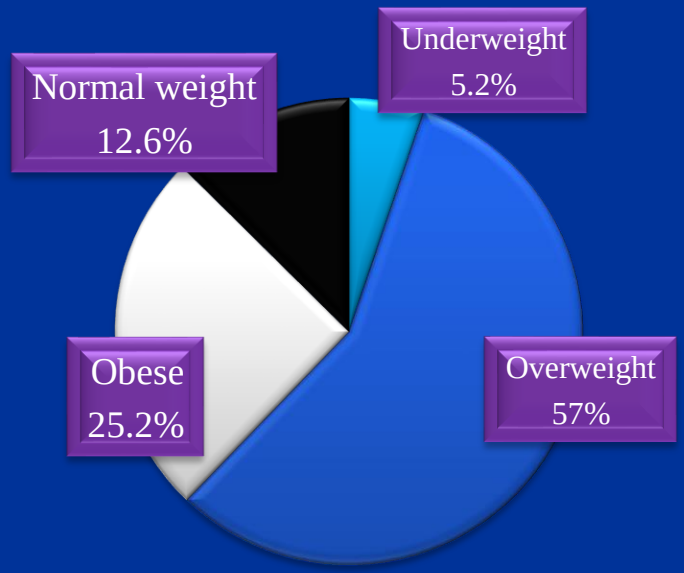


مطالعه ملی شیوع اضافه وزن و چاقی در بزرگسالان ایران

89,404 men and women 15 to 65 years of age



Men



Women

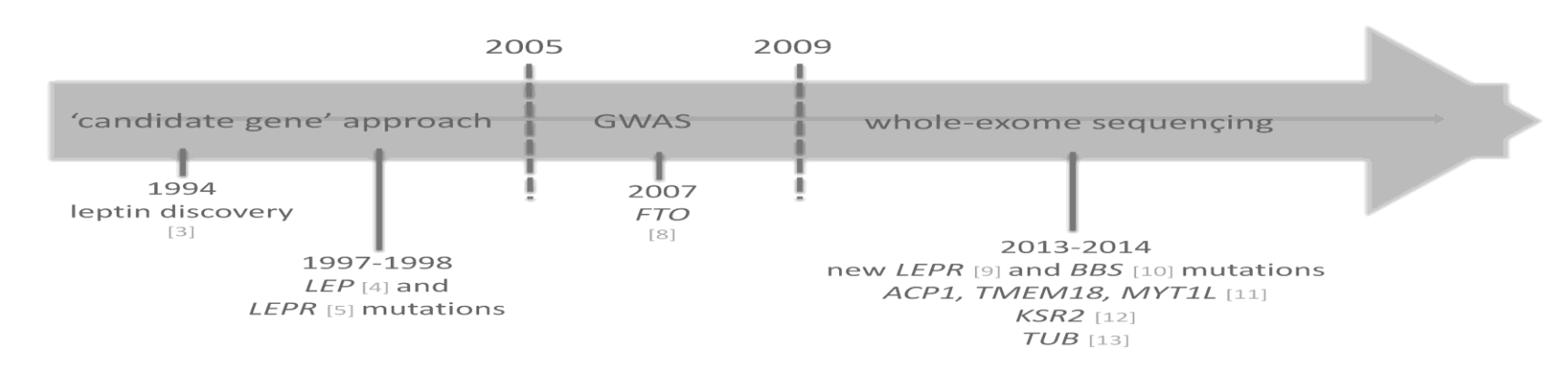
Janghorbani M, Obesity (Silver Spring). 2007;15(11):2797-808

شیوع جهانی چاقی در بزرگسالان رتبه بندی کشورها در سال ۲۰۱۰

Rank	Country	Male %	Female %
1	Papua New Guinea	74.8	79.5
7	Egypt	-	46.6
9	Qatar	34.6	45.3
18	USA	32.2	35.5
22	UAE	17.1	31.4
25	Kuwait	27.5	29.9
26	Turkey	16.5	29.4
38	England	24.1	24.9
66	**Iran**	**9.1**	**19.2**
89	Finland	14.9	13.5
91	Brazil	8.9	13.1
107	Italy	10.5	9.1
136	China	2.4	3.4
137	Japan	2.3	3.4

Source: International Obesity Task force

- Studies suggest that genetics contribute to 30-50% of obesity.
- More than 50 genes are discovered that are strongly associated with obesity.



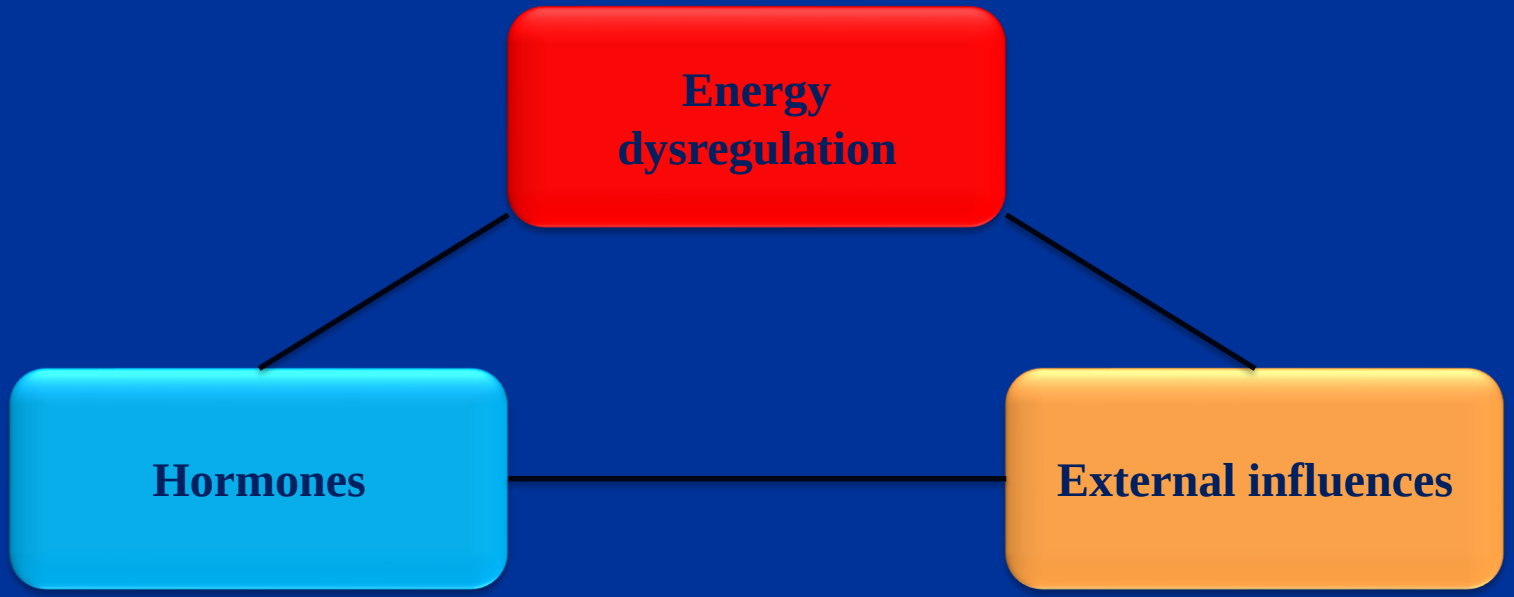
on genes موتاسیون در ژن ob و یا ژن آدیپونکتین به چاقی و یا سندرم متابولیک

Adiponectin

FTO(افزایش استعداد ابتلا به دیابت)

Adrenergic receptor, GAD2,

Complex System Interplay



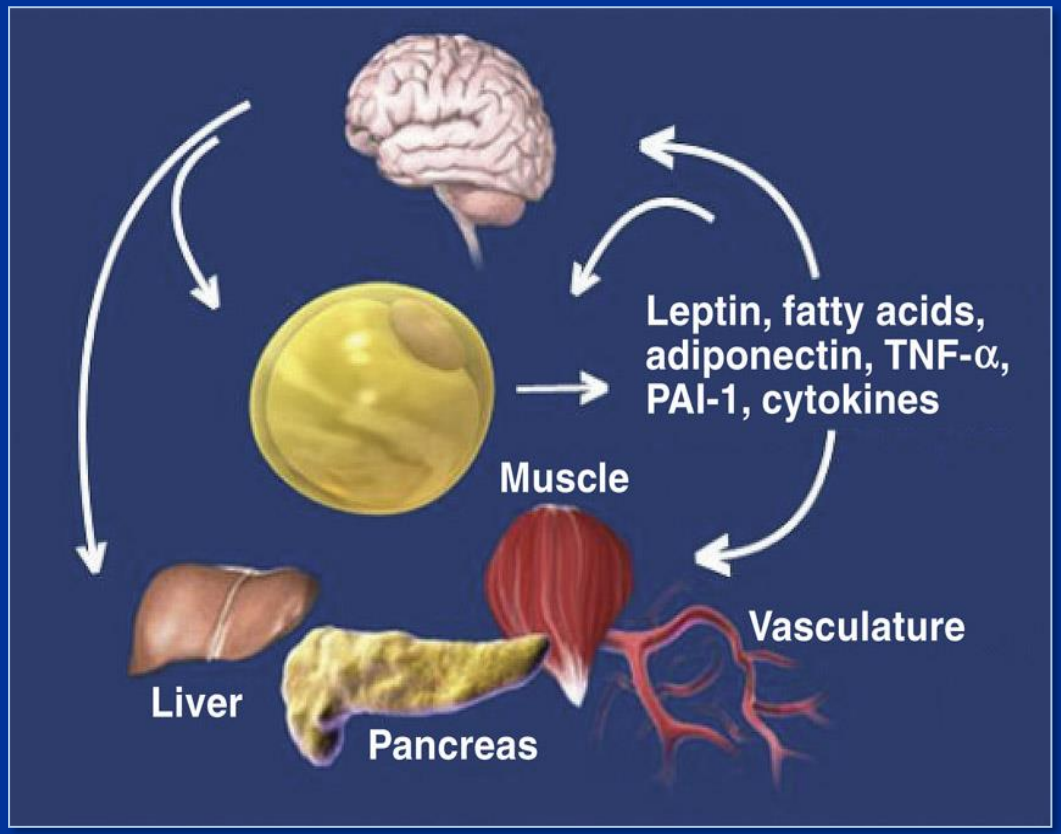
Berthoud HR, et al. *Gastroenterology*. 2017;152(7):1728-1738.

Food Regulation Hormones

Hunger	Satiety
• Ghrelin	• Glucagon-like peptide 1 (GLP-1) • Gastric inhibitory polypeptide (GIP) • Leptin • Amylin • Insulin

Greenway F. *Int J Obes. 2015;*39: 1188–1196

Endocrine Functions of Adipose Tissue

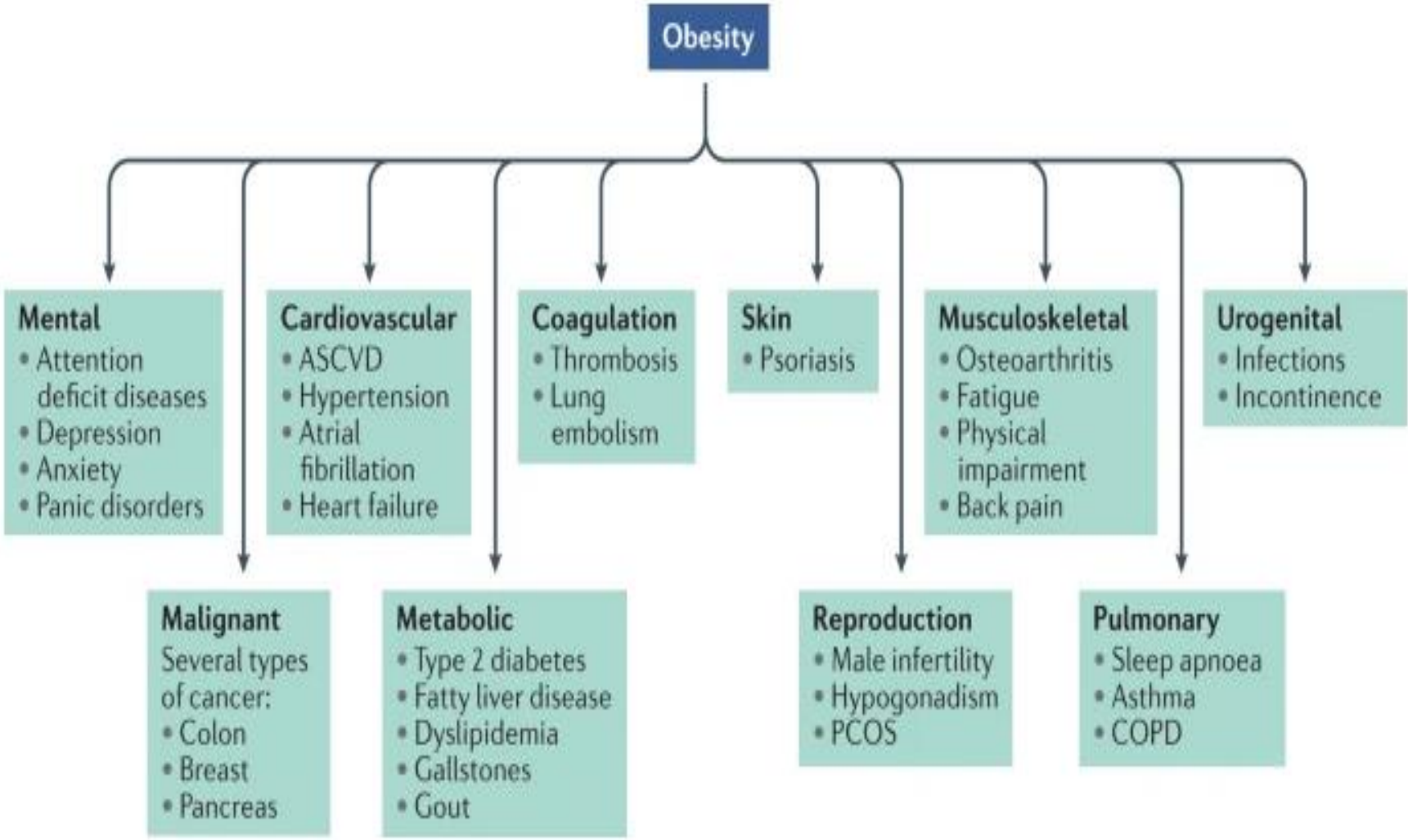


- Not just fat storage
- Secretory endocrine organ

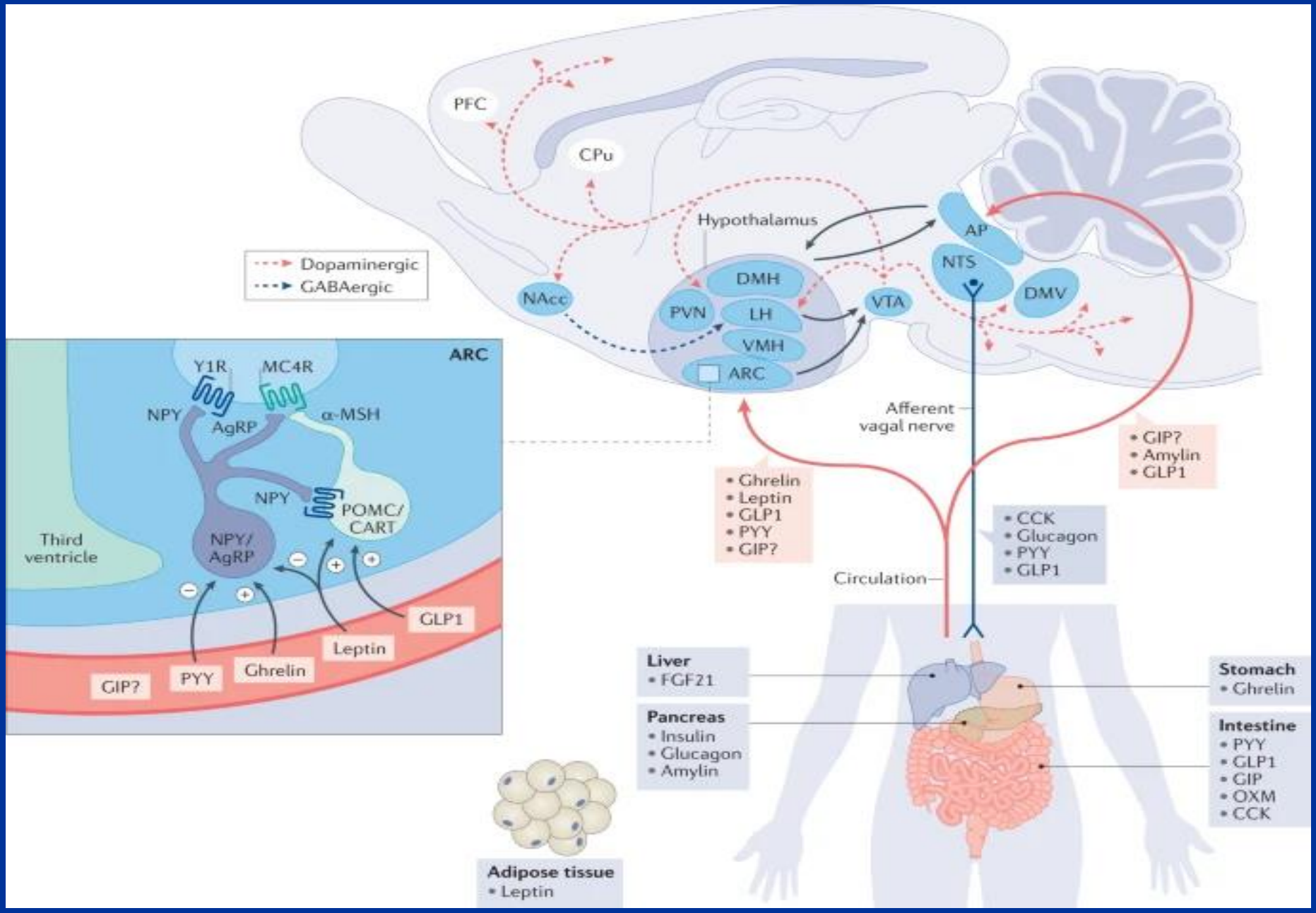
PAI-1, Plasminogen Activator Inhibitor-1; TNF-α, Tumor Necrosis Factor

Kershaw E, et al. *J. Clin. Endocrinol. Metab.* 2004;89(6): 2548-2556.

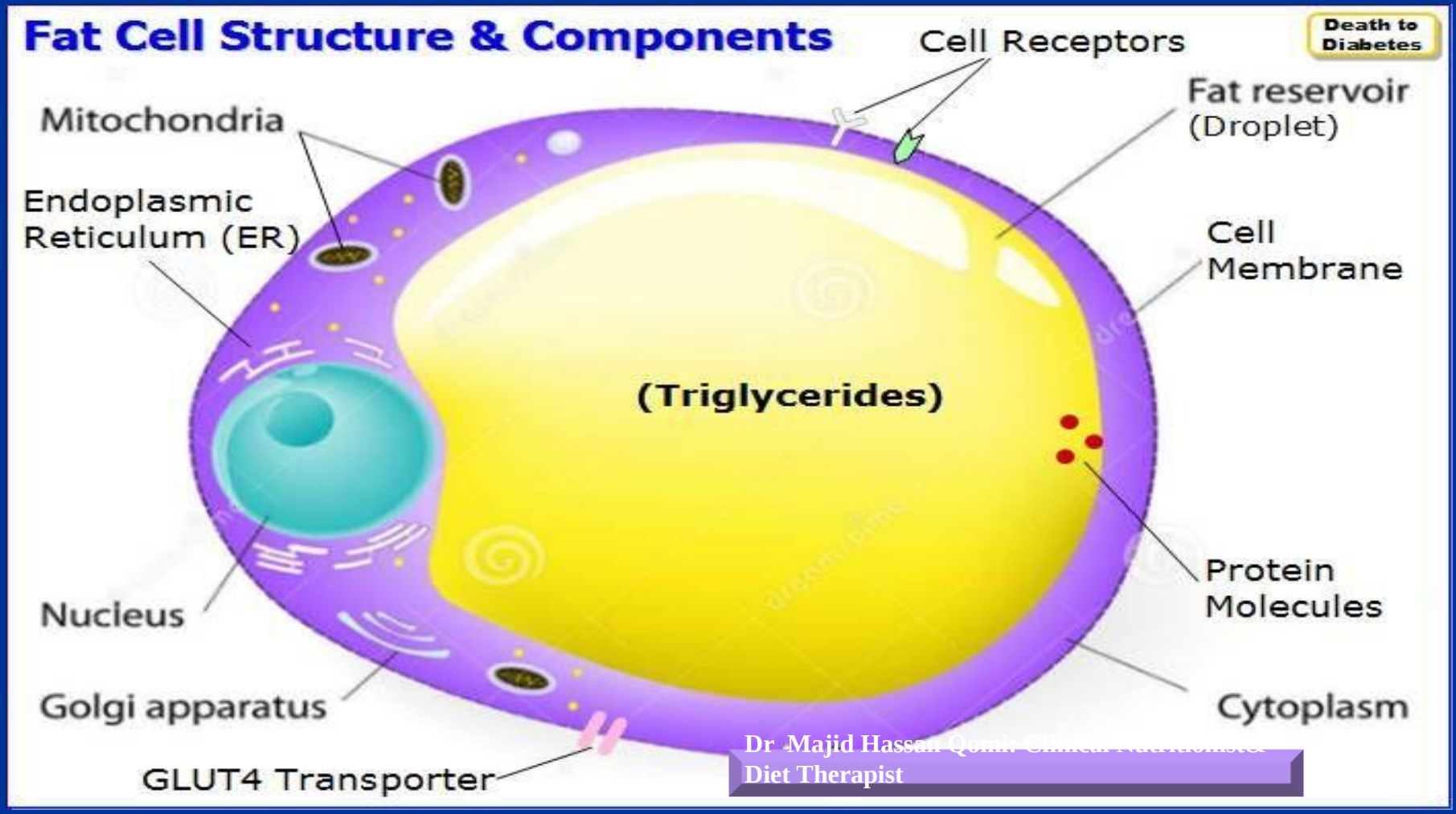
Obesity-associated metabolic disturbances

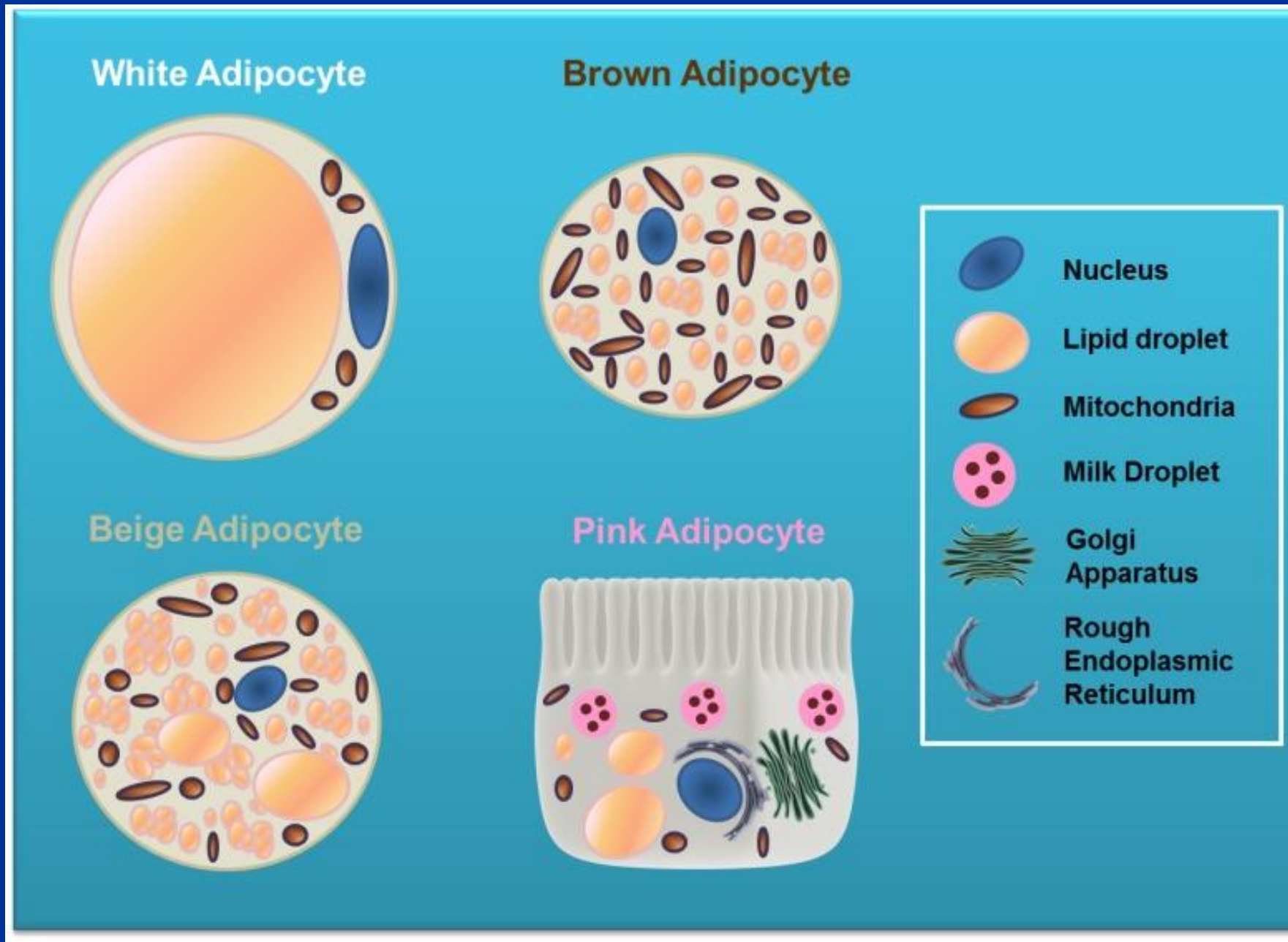


Most prominent metabolic and psychological comorbidities associated with morbid obesity. Atherosclerotic Cardiovascular Disease(ASVCD); Chronic Obstructive Pulmonary disease(COPD); Polycystic Ovary Syndrome(PCOS).



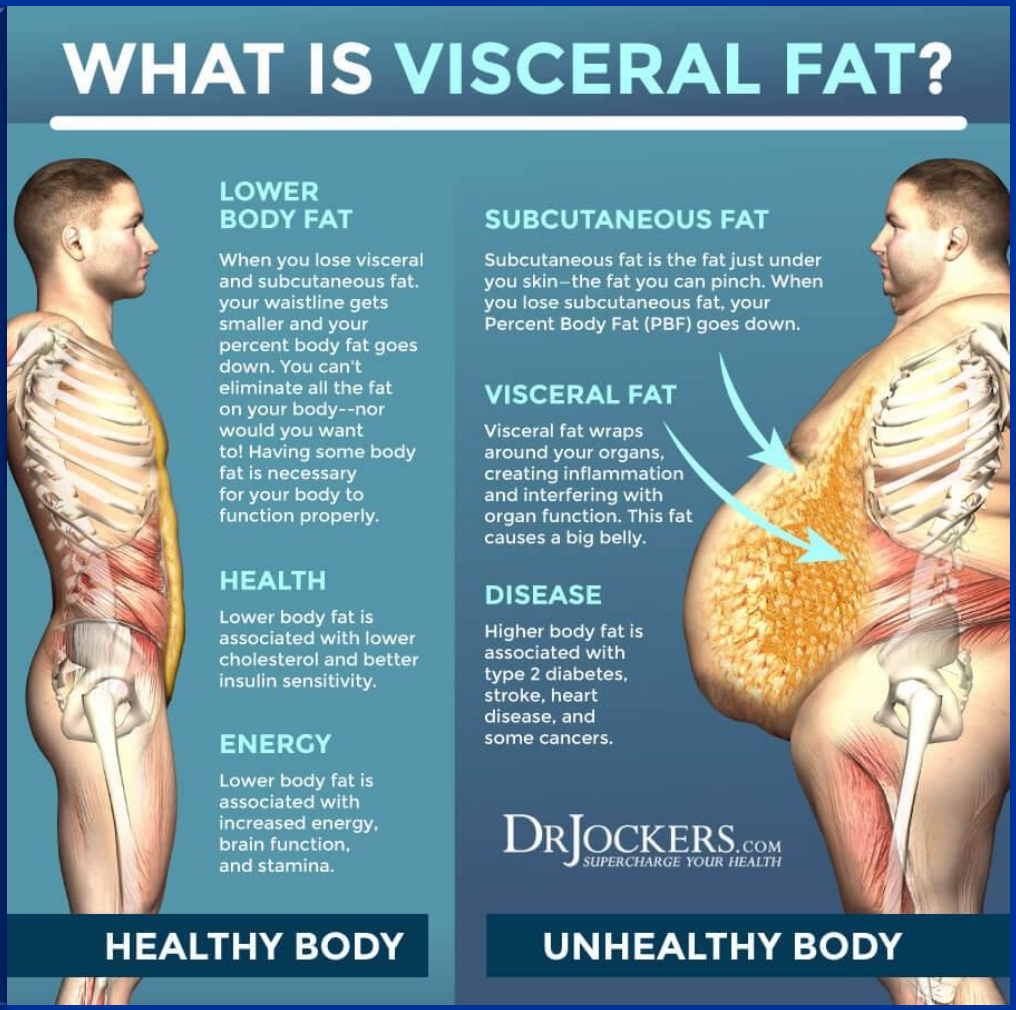
Gut–brain regulation of food intake


Fat Cell Structure & Components
Death to Diabetes
Cell Receptors
Fat reservoir (Droplet)
Mitochondria
Endoplasmic Reticulum (ER)
Cell Membrane
(Triglycerides)
Protein Molecules
Nucleus
Golgi apparatus
Cytoplasm
GLUT4 Transporter
Dr .Majid Hassan Qunly Clinical Nutritionist
Diet Therapist


White Adipocyte
Brown Adipocyte
Beige Adipocyte
Pink Adipocyte
Nucleus
Lipid droplet
Mitochondria
Milk Droplet
Golgi Apparatus
Rough Endoplasmic Reticulum

Visceral

- Visceral fat, is what most people know as ‘belly fat’. This is the white fat that is stored in your abdomen, surrounding your major organs.
- Visceral fat can increase the risk of an array of health issues, including:
- Obesity
- Coronary heart disease
- Stroke
- Diabetes
- Cancer
- Dementia
- Arthritis
- Sleep disorders
- Sexual dysfunction
- Depression
- Hormonal health issues



obesity reviews

doi: 10.1111/j.1467-789X.2009.00623.x

Etiology and Pathophysiology

Subcutaneous and visceral adipose tissue: structural and functional differences

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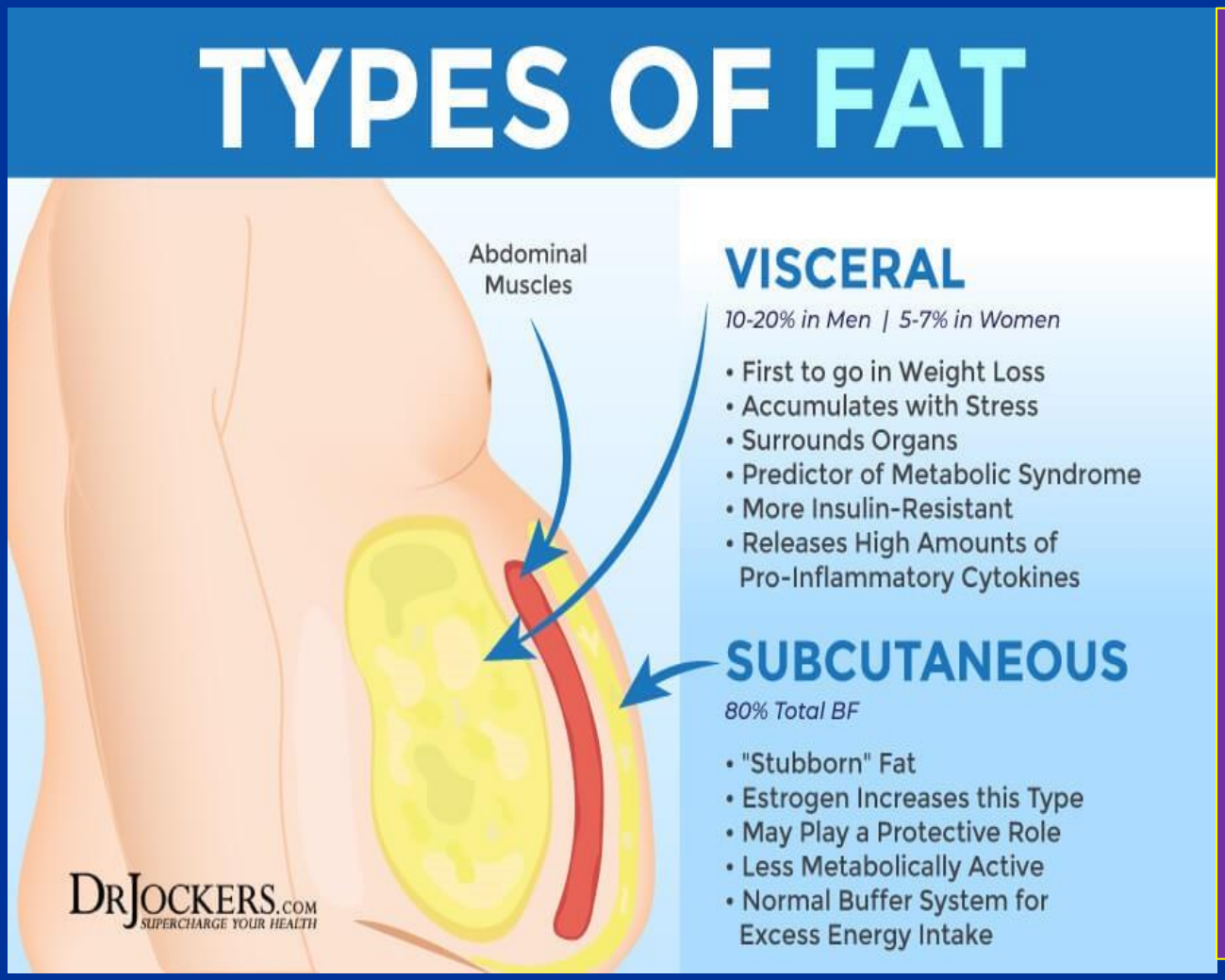
Cardiology Department, Cairo University, Cairo, Egypt

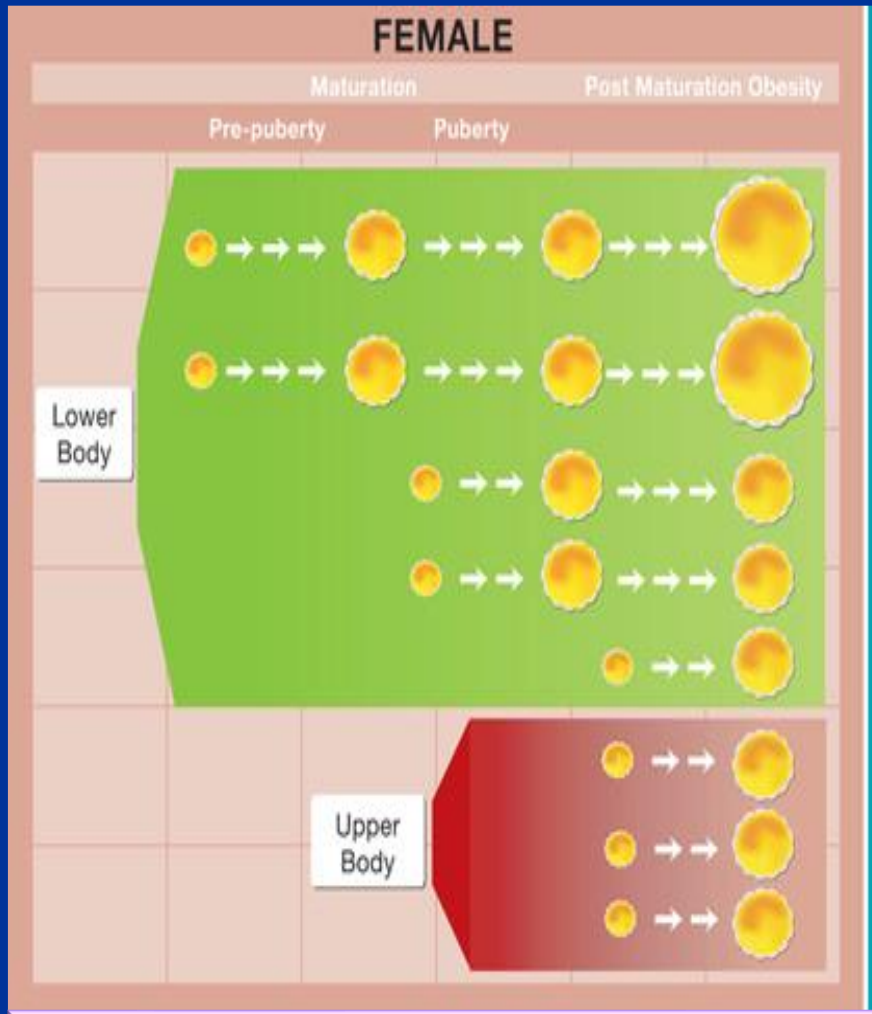
Received 14 January 2009; revised 10 May 2009; accepted 15 May 2009

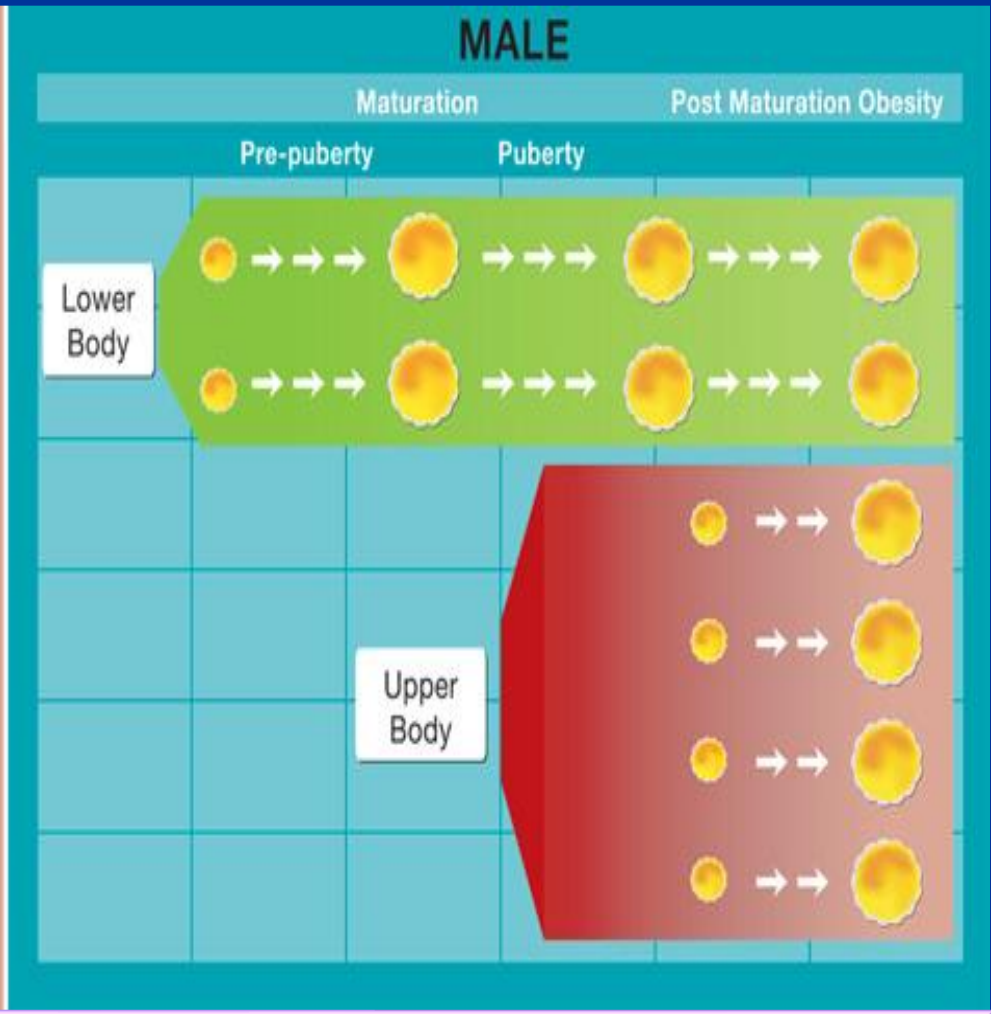
Summary

Obesity is a heterogeneous disorder. Obese individuals vary in their body fat distribution, their metabolic profile and degree of associated cardiovascular and metabolic risk. Abdominal obesity carries greater risk of developing diabetes and future cardiovascular events than peripheral or gluteofemoral obesity. There



Anatomical differences The main areas for subcutaneous fat deposition are the femerogluteal regions, back and anterior abdominal wall. About 80% of all body fat is in the subcutaneous area. The abdominal fat is present in two main depots: subcutaneous and intra-abdominal. Intra-abdominal fat Visceral fat accounts for up to 10–20% of total fat in men and 5–8% in women. The amount of visceral fat increases with age in both genders.





در زنان قبل از بلوغ، سلول‌های چربی کوچک هستند. همزمان با گسترش توده بافت چربی در دوران بلوغ، هم اندازه و هم تعداد آنها افزایش می‌یابد. این انبساط در درجه اول در قسمت پایین بدن رخ می‌دهد. بنابراین، به طور کلی، شار(جریان) FA غشایی کم است. در چاقی پس از بلوغ (بزرگسالان) سایز سلول‌های چربی در هر دو قسمت پایین و فوقانی بدن به منظور تأمین نیازهای ذخیره شده افزایش می‌یابند. این باعث افزایش ظرفیت سنتتیک و هیدرولیتیک تری آسیل گلیسرول در بافت چربی شده و باعث افزایش جریان مایع به کبد و ترشح apoB می‌شود. بافت چربی در مردان قبل از بلوغ مشابه زنان قبل از بلوغ است. در دوران بلوغ، انبساط کمی در بافت چربی وجود دارد. با چاقی پس از بلوغ، سلول‌های چربی فوقانی بدن از نظر تعداد و اندازه افزایش می‌یابند و منجر به شار(جریان) FA غشایی و در نتیجه افزایش ترشح apoB می‌شوند.

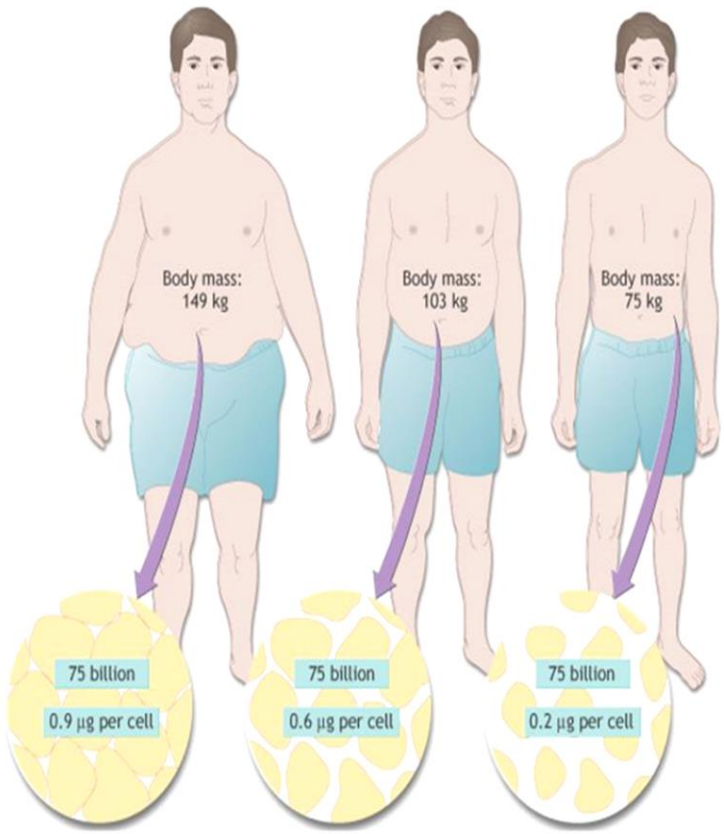
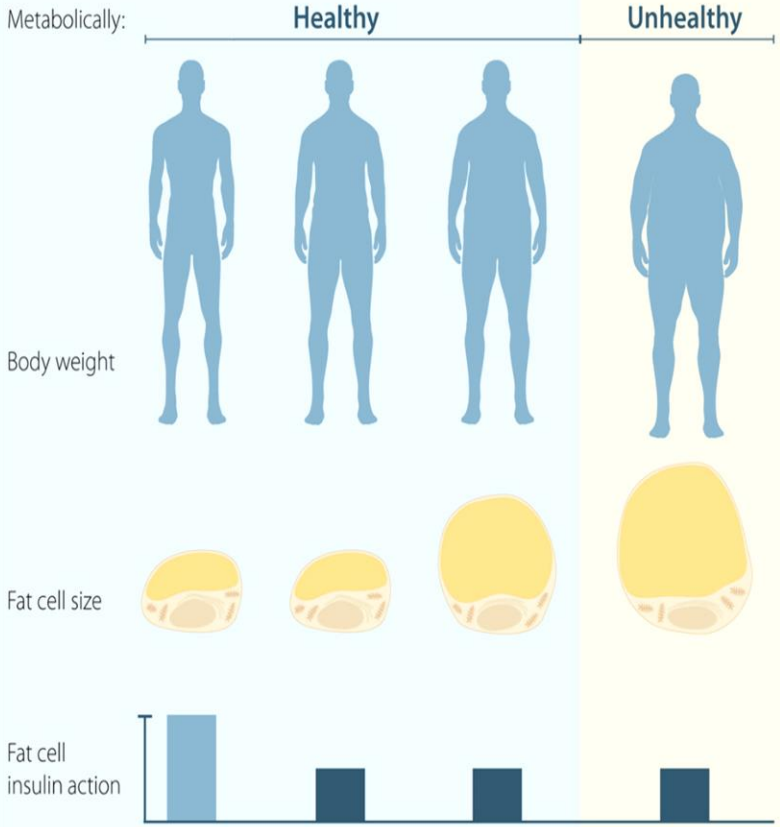


Figure 30.13. Changes in adipose cellularity with weight reduction in obese subjects. (Data from Hirsch J. Adipose cellularity in relation to human obesity. In: Stollerman GH, ed. Advances in internal medicine, vol 17. Chicago: Year-Book, 1971.)

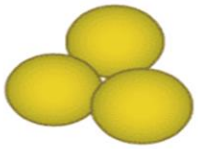
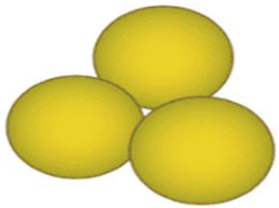
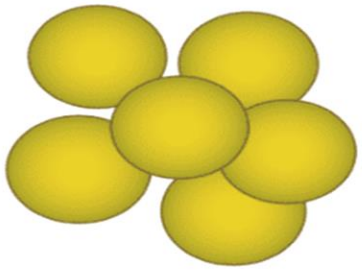
Impaired insulin action already in apparent healthy subjects

JIM Journal of Internal Medicine
Founded in 1863



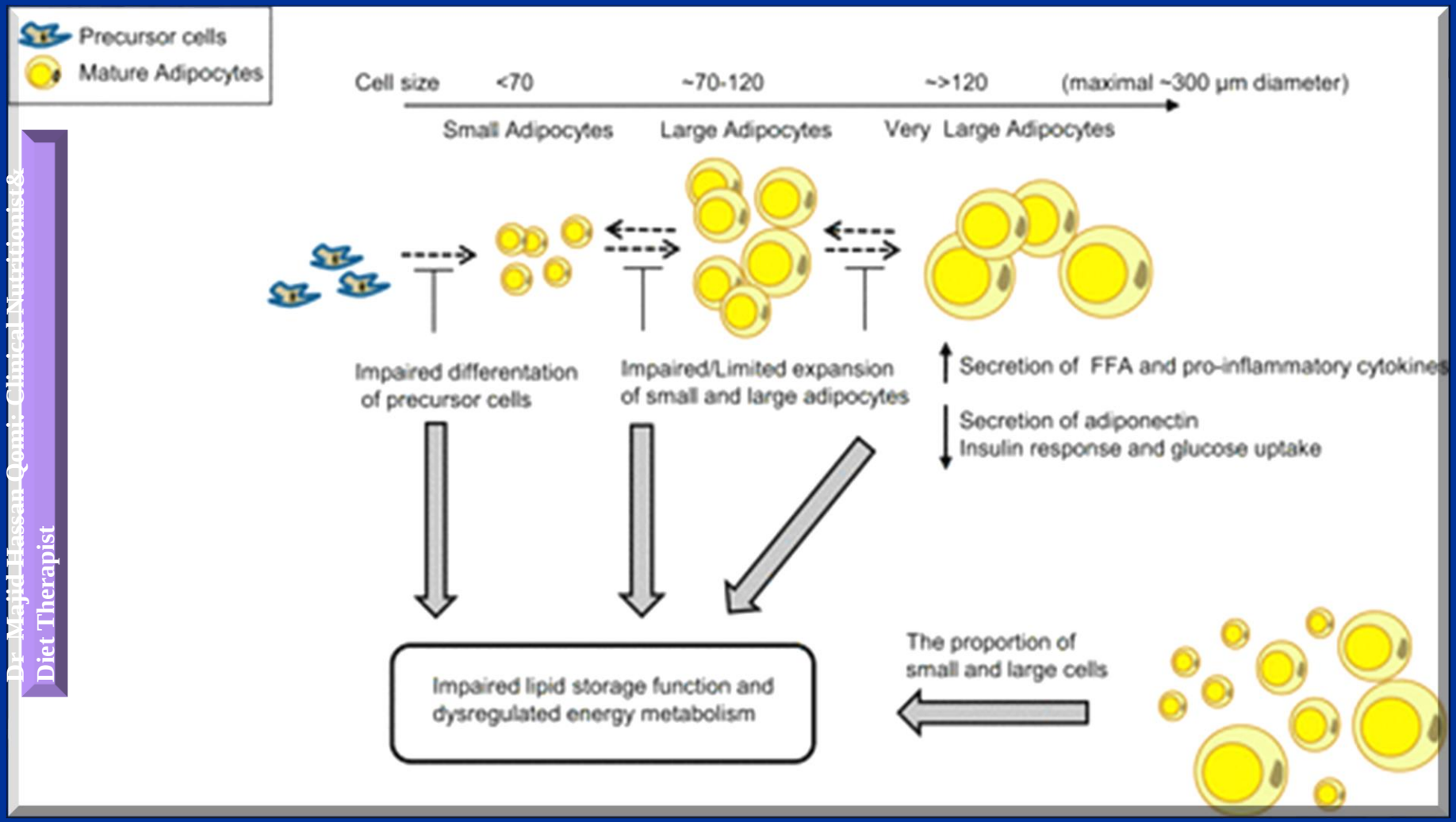
Human Weight Gain Illustration

= 10 Billion Fat Cells (about 10 lbs. of Body Fat)

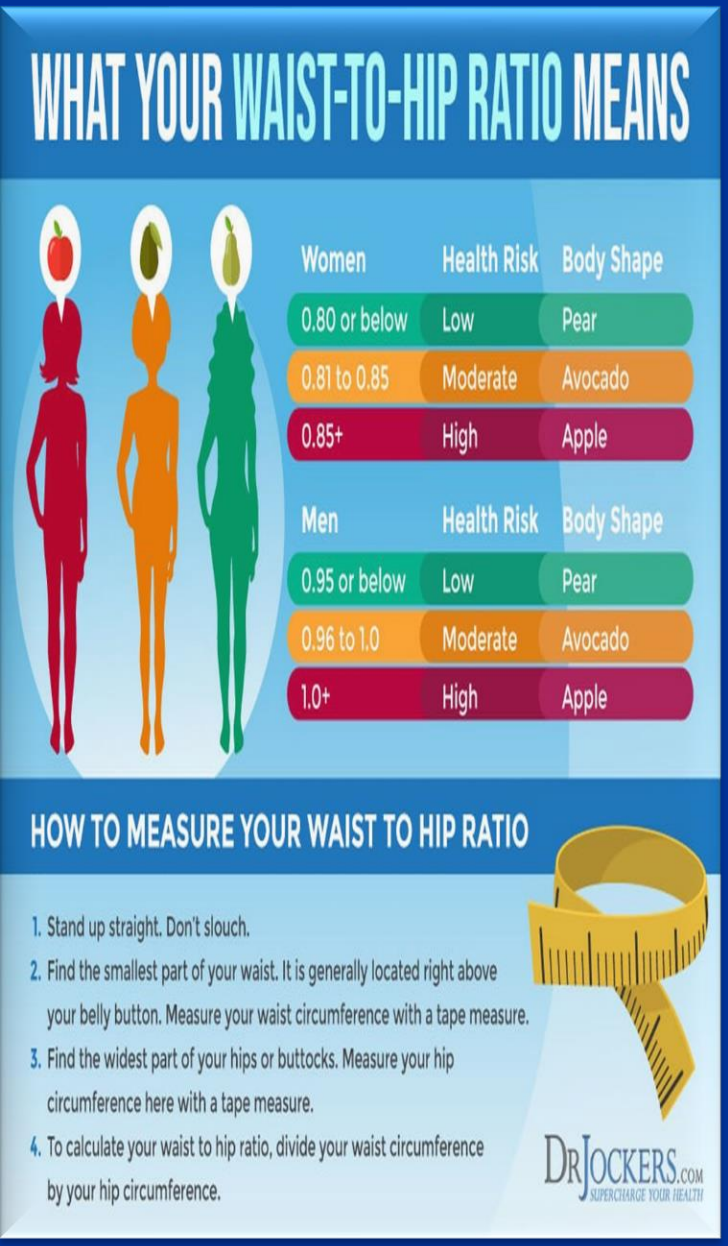
Normal Weight	Normal Weight + 15 lbs.	Normal Weight + 60 lbs.
		
Fat Cells Normal Size, Normal Number Total Body Fat = 30 lbs.	Fat Cells Increase in Size, Normal Number Total Body Fat = 45 lbs.	Fat Cells Increase in Size and Number Total Body Fat = 90 lbs.

This model is conceptual in nature. It is representative of the disease process of abnormal weight gain in humans and may not correlate exactly with an individual

Dr. Majid Hassan Qomi: Clinical Nutritionist& Diet Therapist



نسبت دور کمر به باسن

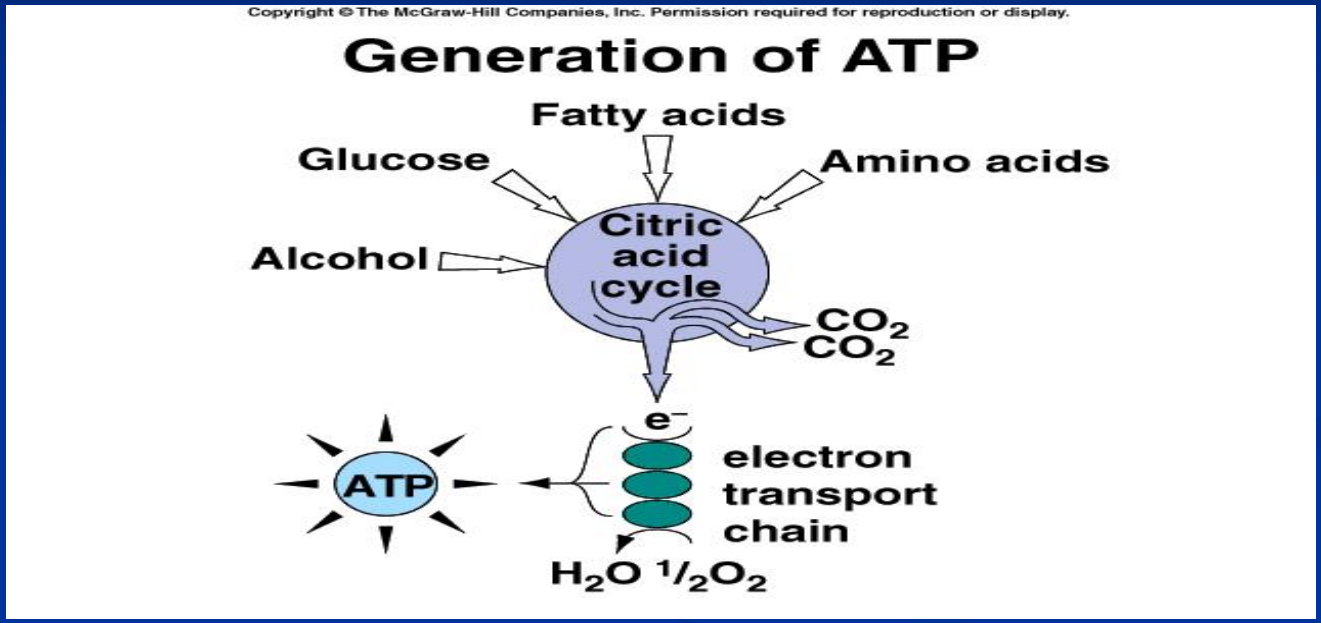


شکم و ران ها عمده ترین محل تجمع چربی های بدن هستند ، توده چربی شکمی خطر ساز تر از توده چربی است که در ران ها تجمع یافته است .

این شاخص تناسب بدن را از نظر وضعیت تجمع چربی ها نشان می دهد .

حد مطلوب این معیار در مردان کمتر از ۰/۹ و در زنان کمتر از ۰/۸ است. مقادیر بیش از ۱ با خطر ابتلا به بیماری ها مرتبط است.

شاخص توده بدنی(BMI)



- به تعبیری مناسب ترین معیار جهت تعیین چاقی است
- این معیار تناسب وزن را برای قد مشخص می نماید .

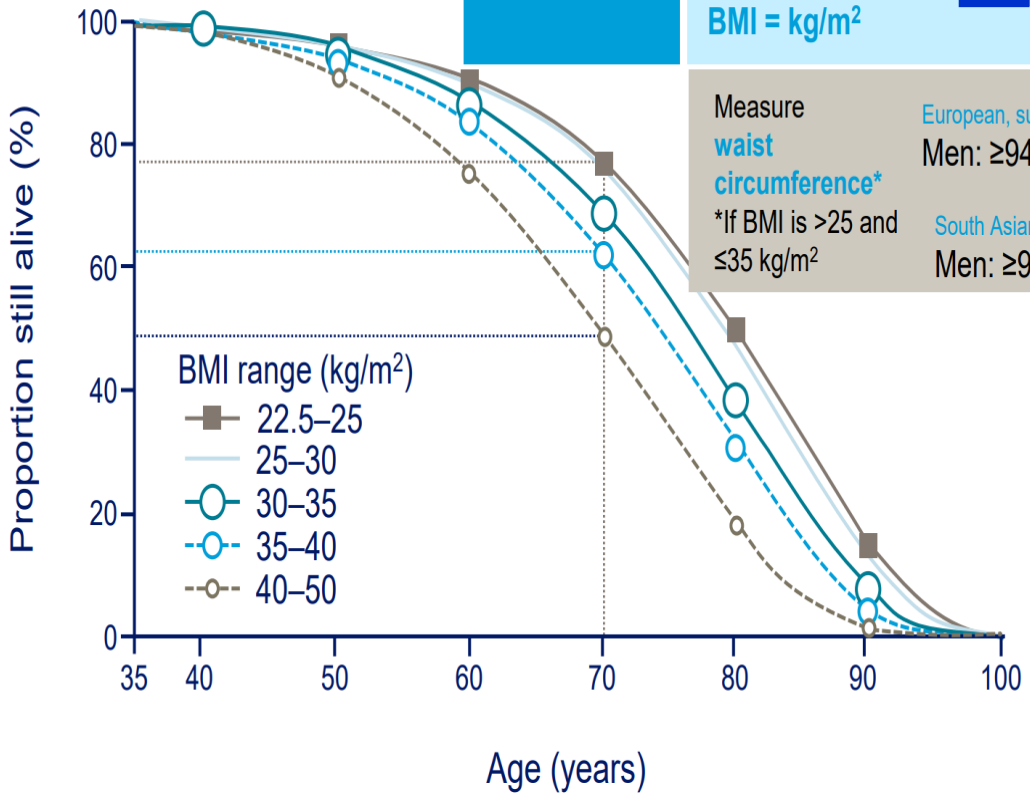
Classification	BMI(kg/m2)	
	Principal cut - off points	Additional cut - off points
Underweight	<18.50	<18.50
Severe thinness	<16.00	<16.00
Moderate thinness	16.00 - 16.99	16.00 - 16.99
Mild thinness	17.00 - 18.49	17.00 - 18.49
Normal range	18.50 - 24.99	18.50 - 22.99
		23.00 - 24.99
Overweight	≥25.00	≥25.00
Pre -obese	25.00 - 29.99	25.00 - 27.49
		27.50 - 29.99
Obese	≥30.00	≥30.00
Obese class I	30.00 - 34.99	30.00 - 32.49
		32.50 - 34.99
Obese class II	35.00 - 39.99	35.00 - 37.49
		37.50 - 39.99
Obese class III	≥40.00	≥40.00

Mc Ardle & Katch - Essentials of exercise physiology,
ACSM's - Resource manual for guidelines for exercise testing and prescription

طبقه بندی اضافه وزن و چاقی براساس نمایه توده بدن، دور کمر و خطرات بیماری‌های همراه

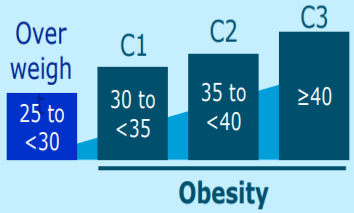
طبقه بندی	BMI	درجه چاقی	خطربیماری های مرتبط با دورکمر	
			مردان >102Cm زنان >88Cm	مردان >102cm زنان >88cm
کم وزن	<18/5	–	–	–
طبیعی	18/5-24/9	–	–	–
اضافه وزن(پیش چاق)	25-29/9	–	افزایش	افزایش
چاقی متوسط	30-34/9	I	بالا	بالا
چاقی شدید	35-39/9	II	بسیار بالا	بسیار بالا
چاقی بیماری زا	>40	III	بی نهایت بالا	بی نهایت بالا

Life Expectancy Decreases as BMI Increases



Obesity definition:

Measure **height**
Measure **weight**
Calculate **BMI**
BMI = kg/m²



BMI **does not consider** muscle or fat distribution
(not for children, elderly, highly muscular adults & others)

Measure **waist circumference***
*If BMI is >25 and ≤35 kg/m²

European, sub-Saharan African, Mediterranean & Middle Eastern
Men: ≥94 cm, Women: ≥80 cm

South Asian, Chinese, Japanese, South & Central American
Men: ≥90 cm, Women: ≥80 cm

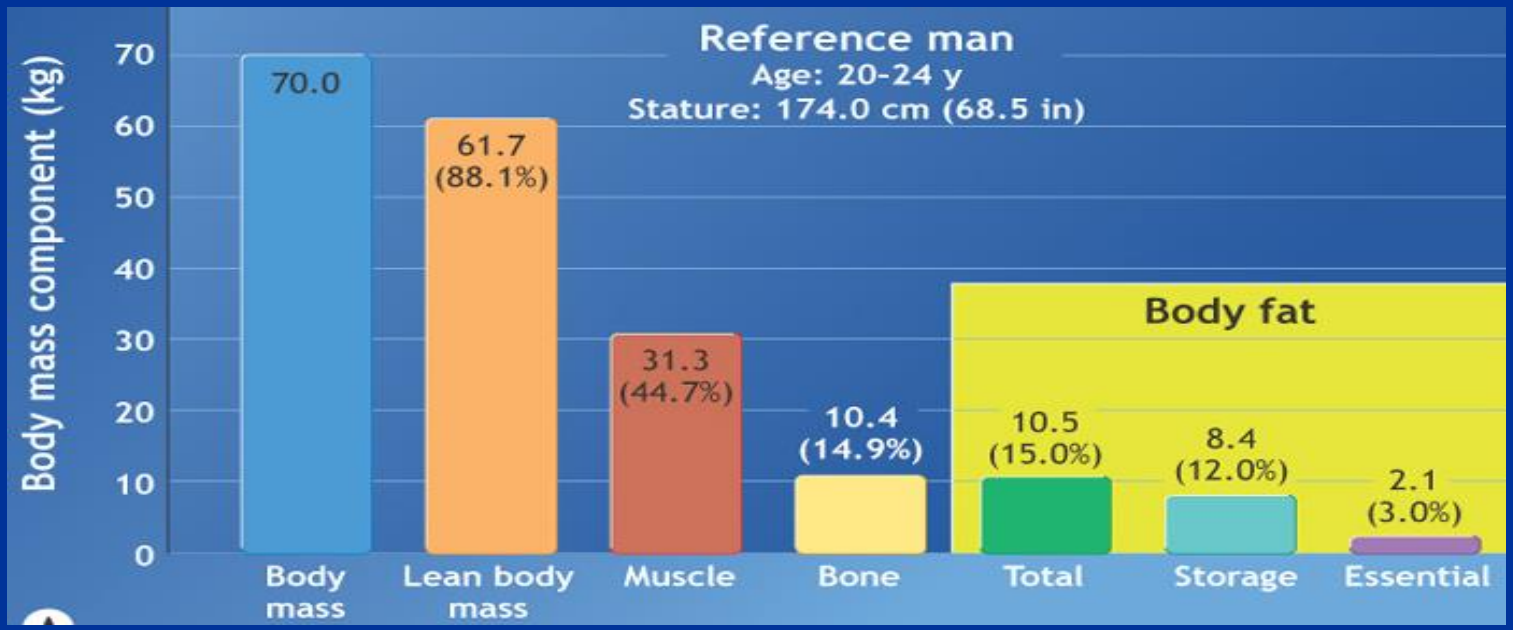
Waist circumference reflects **visceral adiposity** in adults

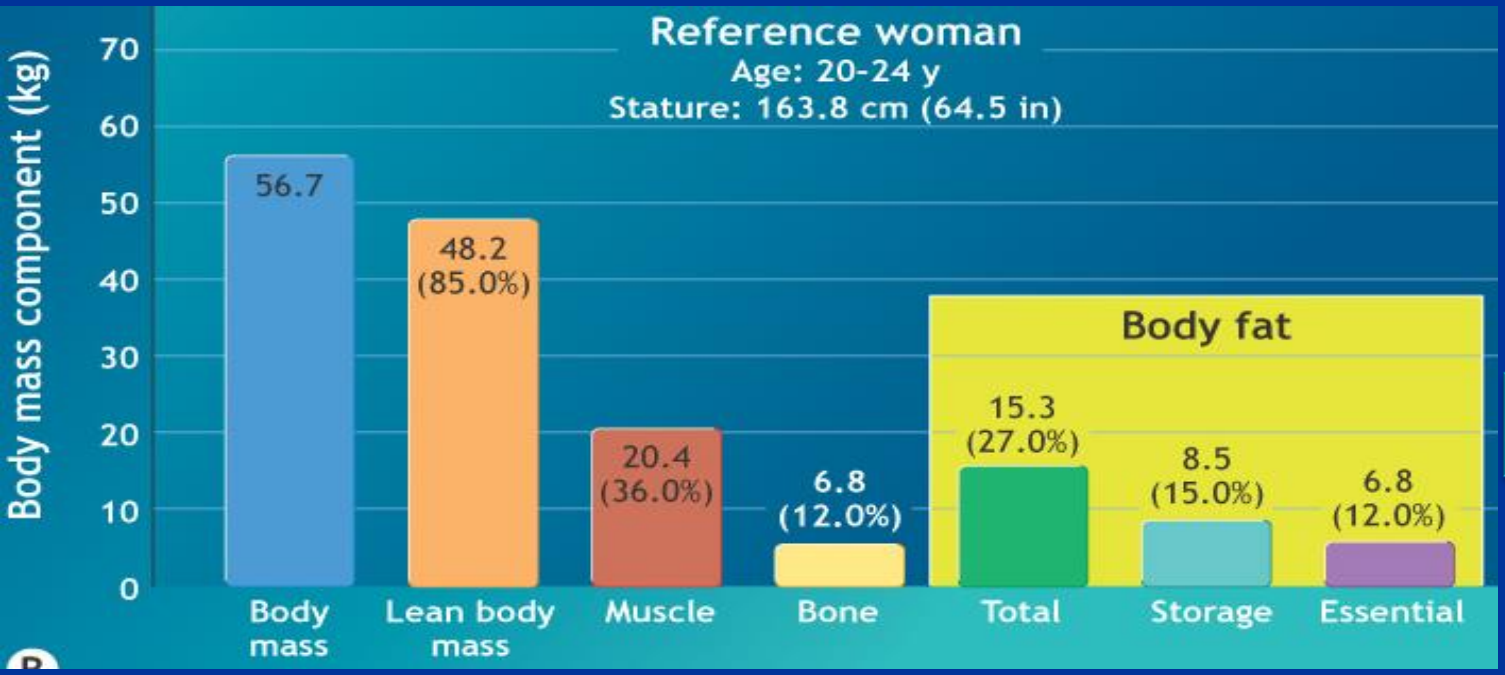
BMI 35–40 kg/m² = ~60% chance of reaching age 70

BMI 40–50 kg/m² = ~50% chance of reaching age 70

Data are based on male subjects; n=541,452.
Prospective Studies Collaboration. *Lancet* 2009;373:1083–96.

Western





Male

vs

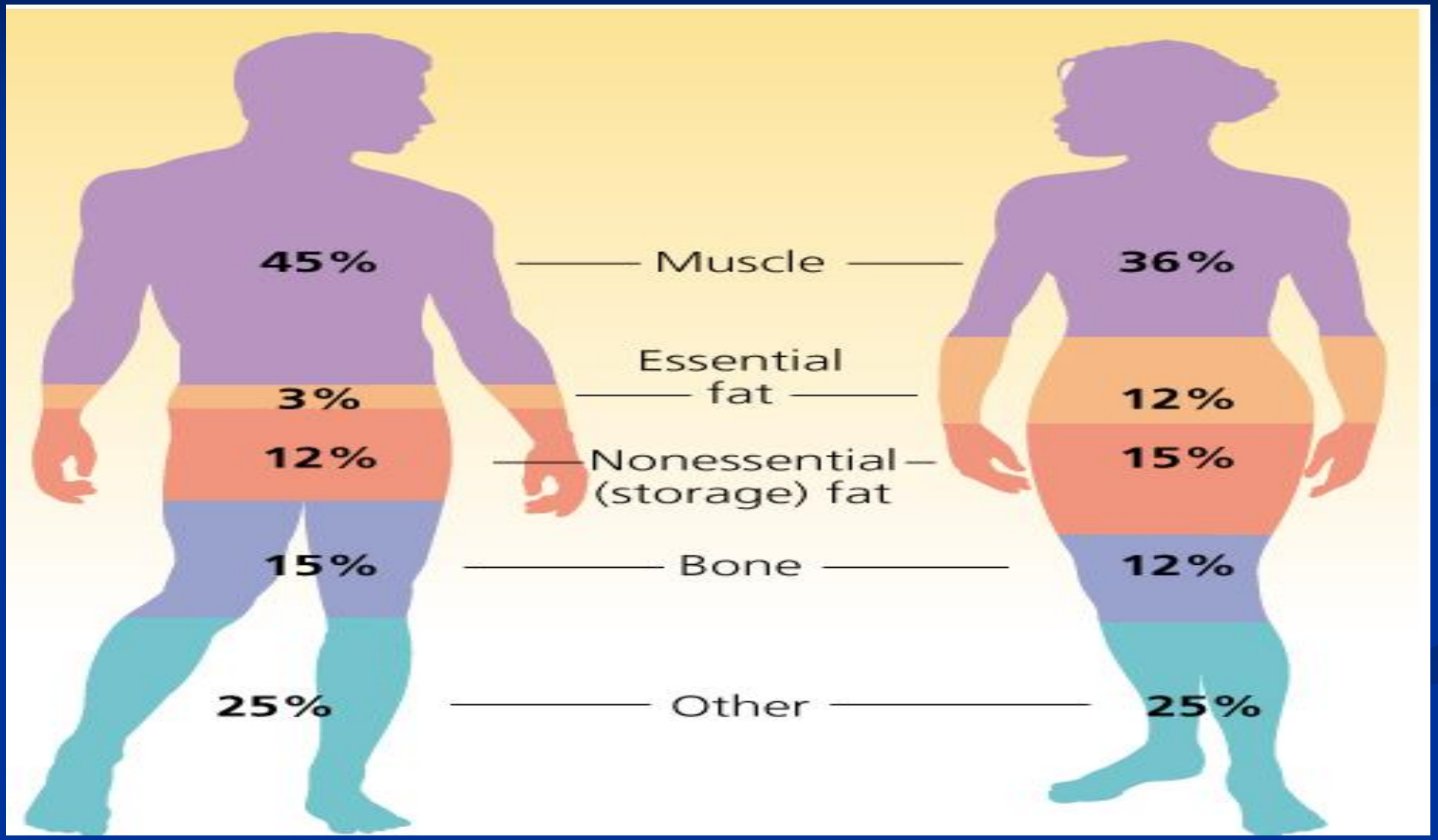
Female

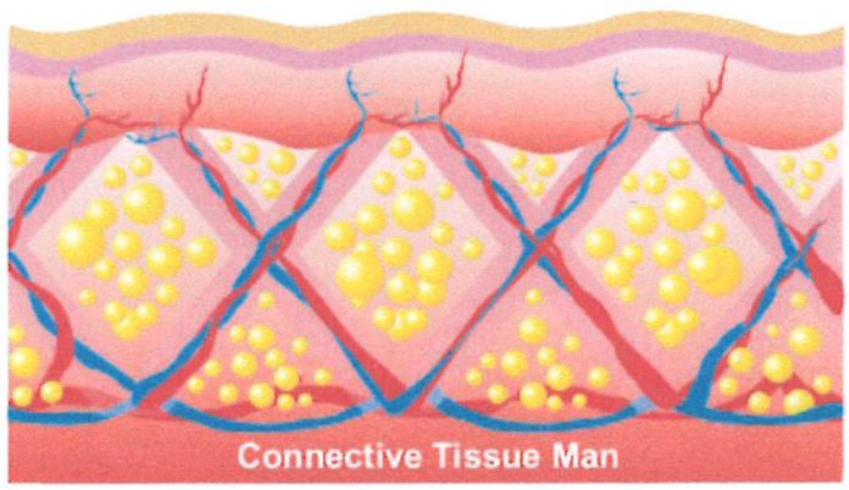
(Note differences in fat and muscle content)

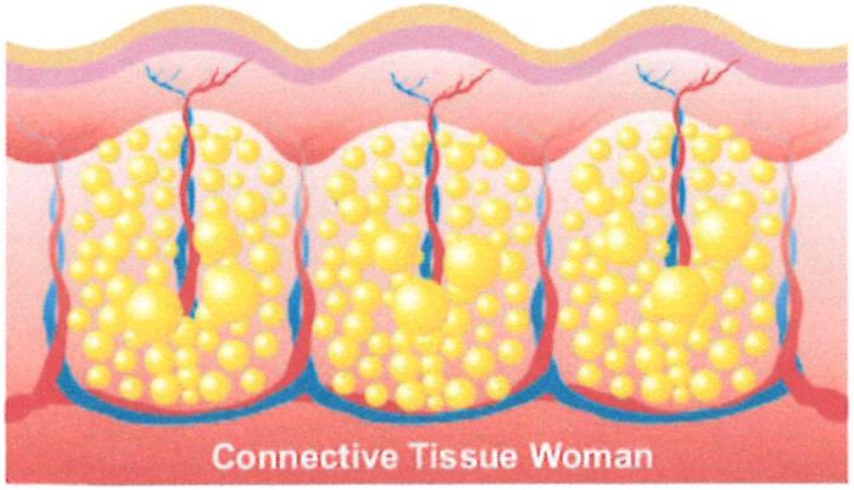
درصدهای چربی بدن

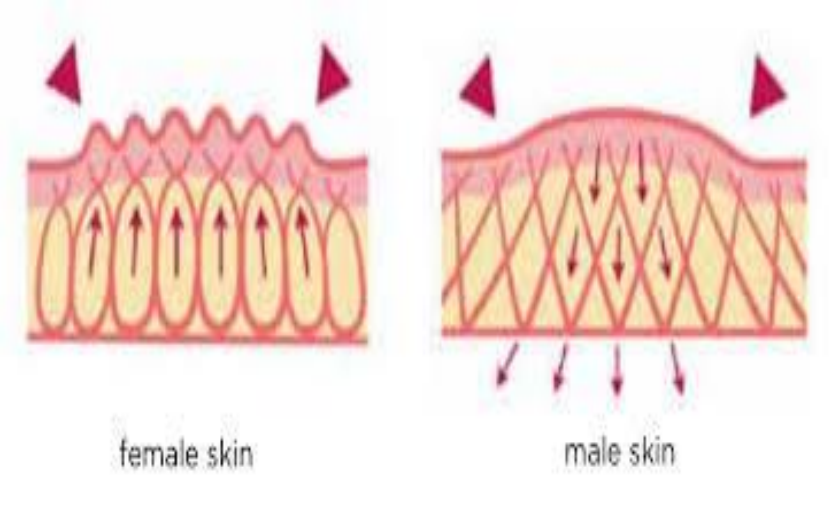
نوع چربي	مرد	زن	ملاحظات
ضروري	3	12	برای عملکرد فیزیولوژیکی نرمال ضروری بوده و در مقادیر کم در ارگان هایی نظیر مغز استخوان،ریه، قلب ،طحال، کلیه ،عضلات ، سیستم عصبی
ذخيره اي	7-21	6-18	ذخیره انرژی در بدن و عمدتا به شکل تری گلیسرید،در زیر پوست و اطراف ارگان های داخلی بدن قرار گرفته و نقش محافظتی در برابر ضربه ها،بیشتر چربی های ذخیره ای بدن قابل افزایش می باشند.
كل	10-25	18 -30	
ورزشكار	12-18	16-25	

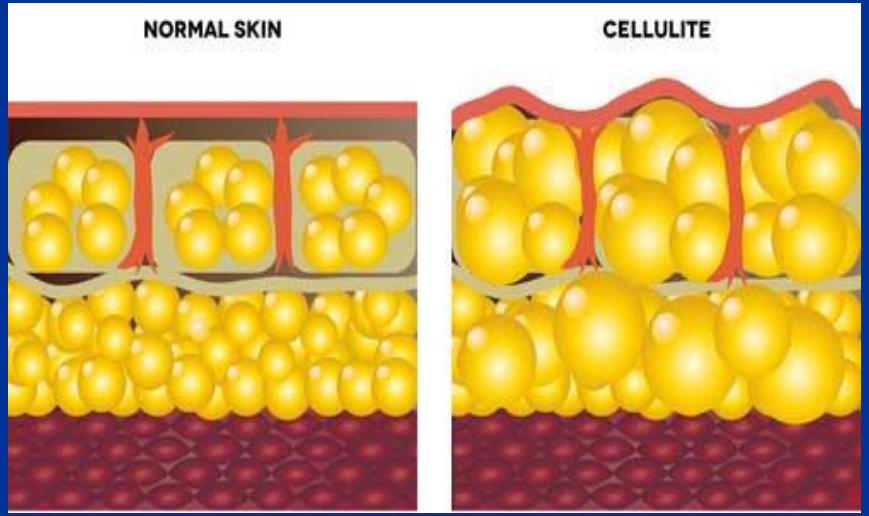
BODY COMPOSITION TYPICAL




Connective Tissue Man


Connective Tissue Woman

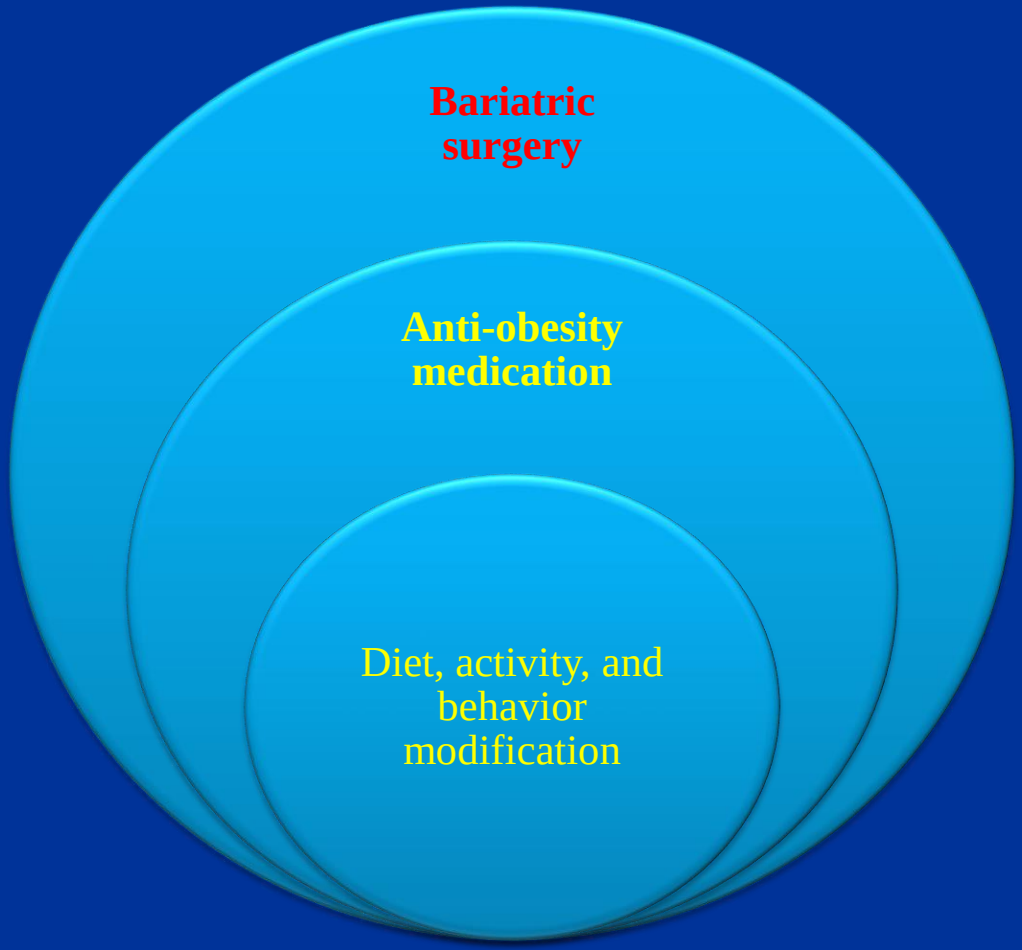

female skin
male skin


NORMAL SKIN
CELLULITE

توزیع رسپتور های آلفا و بتا در زنان

موقعیت	رسپتور های آلفا ۲ (بلوک کننده لیپولیز)	رسپتور های بتا ۳و۲و۱ (تحریک لیپولیز)
در ناحیه باسن	۸۹۰±۸۶	۱۳۰±۲۵
در ناحیه شکم	۵۴۰±۴۹	۱۸۰±۳۰
چربی احشایی	۲۲۰±۳۰	۱۹۰±۴۰

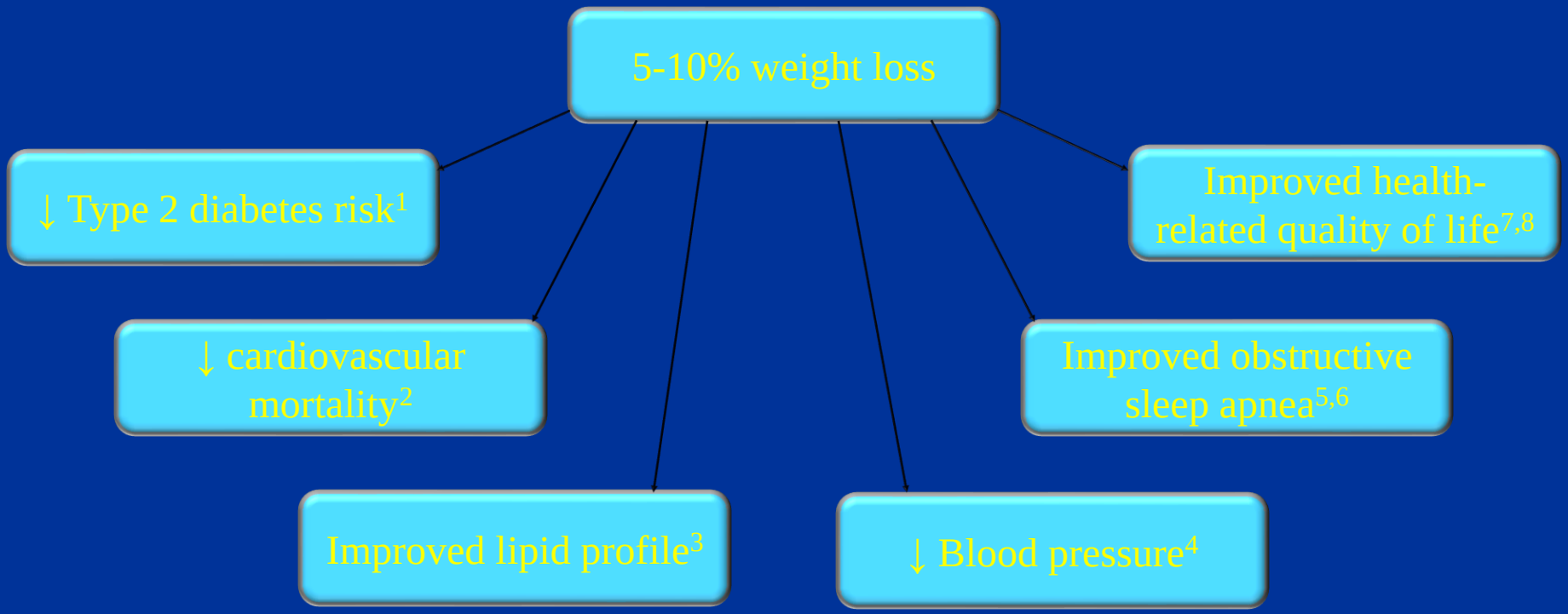
Escalation from Lifestyle Intervention



Strategies for treatment of obesity

- Diet
- Exercise
- Behavior therapy
- Medications
- Surgery

Clinically Relevant Weight Loss Effects



1. Knowler et al. *N Engl J Med*. 2002;346:393-403. 2. Li et al. *Lancet Diabetes Endocrinol*. 2014;2:474-480. 3. Datillo et al. *Am J Clin Nutr*. 1992;56:320-328. 4. Wing et al. *Diabetes Care*. 2011;34:1481-1486. 5. Foster et al. *Arch Intern Med*. 2009;169:1619-1626.
6. Kuna et al. *Sleep*. 2013;36:641-649. 7. Warkentin et al. *Obes Rev*. 2014;15:169-182. 8. Wright et al. *J Health Psychol*. 2013;18:574-586.

Estimated metabolic and vascular benefits of losing 10% weight? Haslam D, et al. BMJ 2006;333:640-2

Blood pressure

- Fall of about 10 mm Hg in systolic and diastolic blood pressure in hypertensive patients

Diabetes

- Fall of up to 50% in fasting glucose for newly diagnosed patients

People at risk for diabetes, such as those with impaired glucose tolerance

- > 30% fall in fasting or two hour insulins
- > 30% increase in insulin sensitivity
- 40-60% fall in incidence of diabetes

Lipids

- Fall of 10% in total cholesterol
- Fall of 15% in low density lipoprotein cholesterol
- Fall of 30% in triglycerides
- Rise of 8% in high density lipoprotein cholesterol

Mortality

- > 20% fall in all cause mortality
- > 30% fall in deaths related to diabetes
- > 40% fall in deaths related to obesity

- Patients with severe obesity should be treated initially in a medical program that focus on
  - Diet
  - Activity
  - Lifestyle changes
  - Behavior modification, and
  - Specialized psychosocial assessment and support

Individualizing Treatment

Patient-specific factors to consider

- Body mass index
- Waist circumference
- Comorbidities
- Previous weight loss attempts
- Patient concerns, needs, and expectations

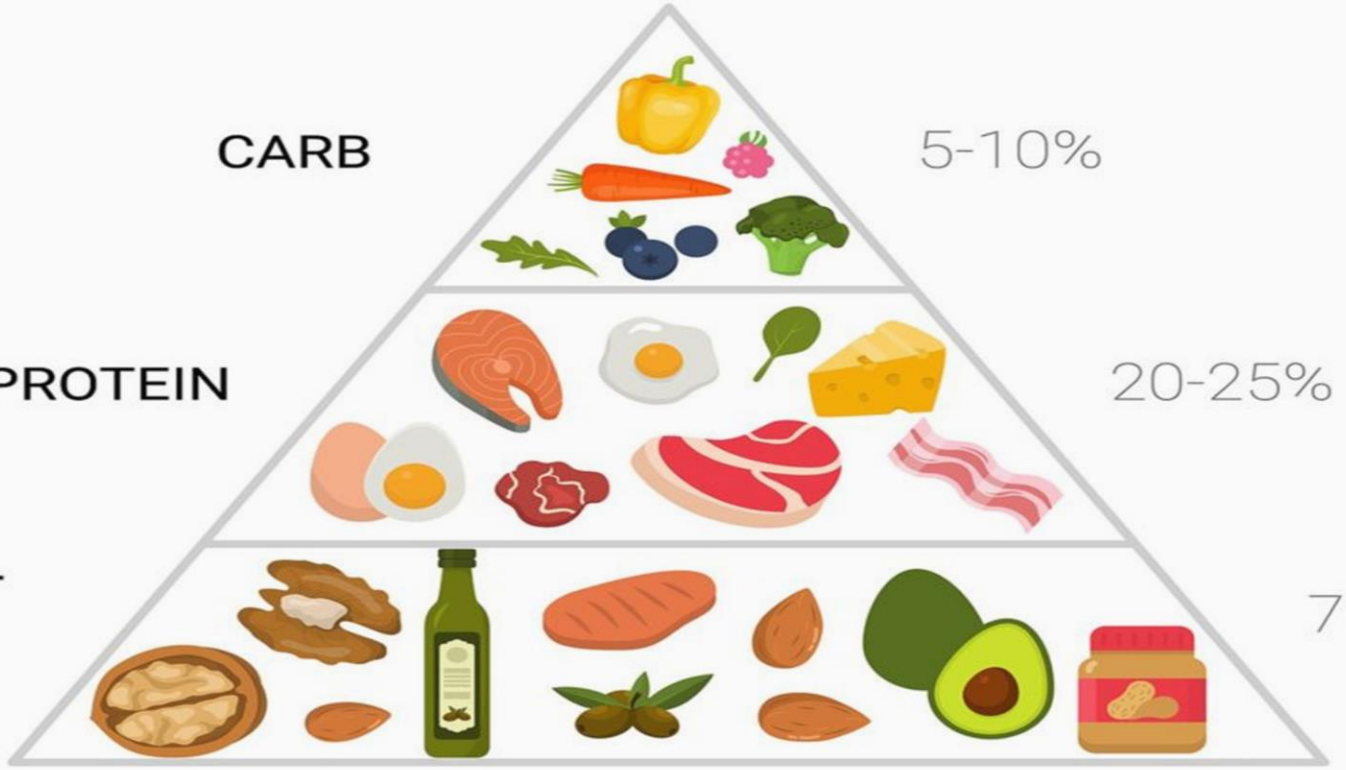
Weight Loss

- This is usually the first option or treatment. It can include a combination of regular exercise and a healthy diet. This can help to lower the body's overall fat levels and also liver fat.
- It's good to decrease body weight by 10%. They include various diet programs including:

- Keto/Atkins
- Intermittent Fasting (IF)
- Paleo
- Mediterranean diet
- Vegetarian/Vegan

A KETO DIET

WHAT CAN I EAT



AVOID:

Dangers of the Keto Diet

- **The 'Keto Flu'**

  The body does take some time to get adjusted to the diet. However, many dieters feel that the transition period is an unpleasant one. As the body enters ketosis, some of the reported **symptoms** are **fatigue, lethargy, dizziness, nausea, poor sleep**, etc. This is termed the 'keto flu'.

- **Gastrointestinal Issues**

  In the keto diet, the consumption of vegetables and fruits is minimal.

- **The lack of fiber in the keto diet** can lead to gastrointestinal issues like diarrhea or constipation.

- **Can Lead to Weight Regain**

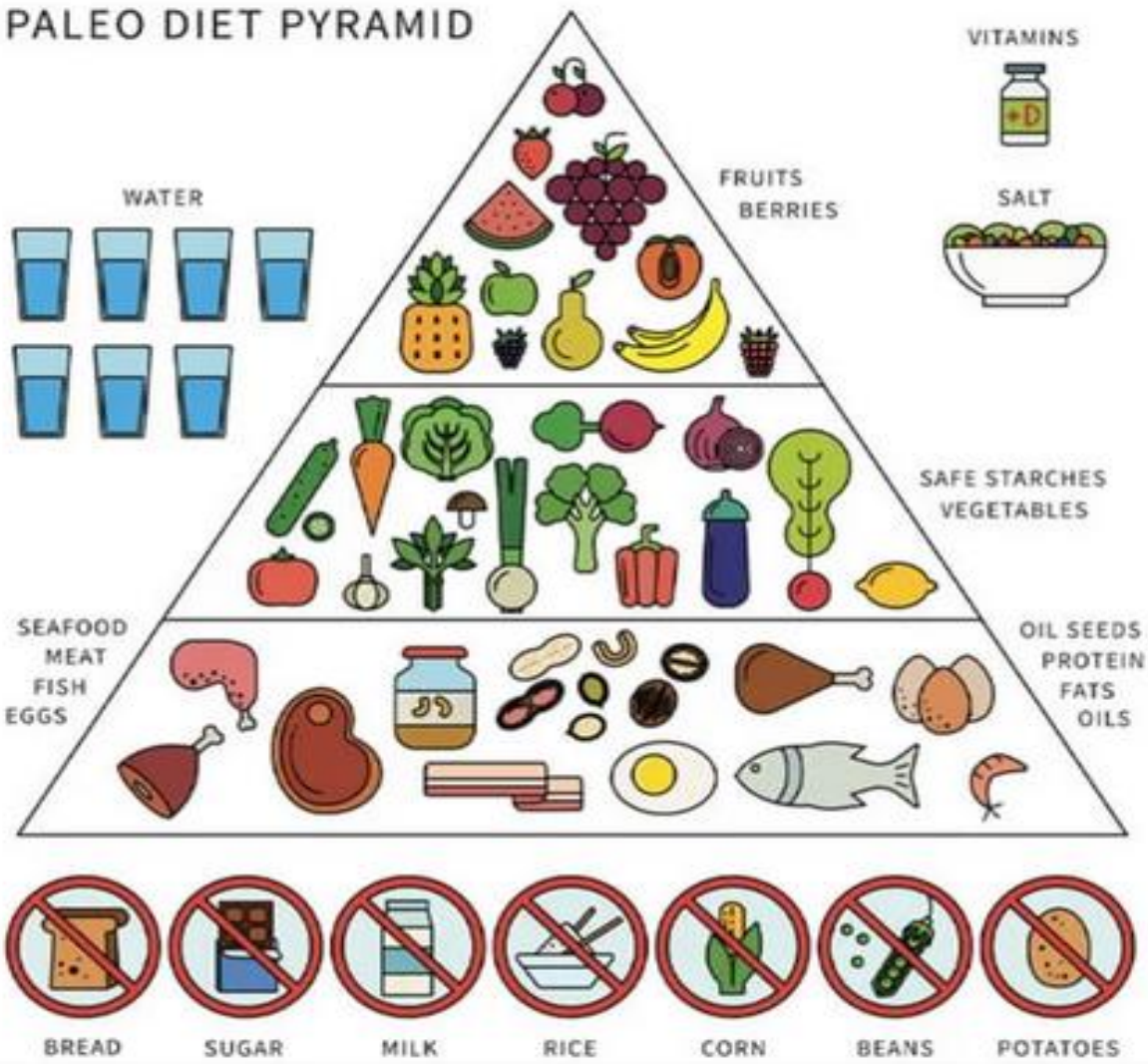
5–10% carbs | 20–25% protein | 60–75% fat

15–30% carbs | 15–30% protein | 40–70% fat

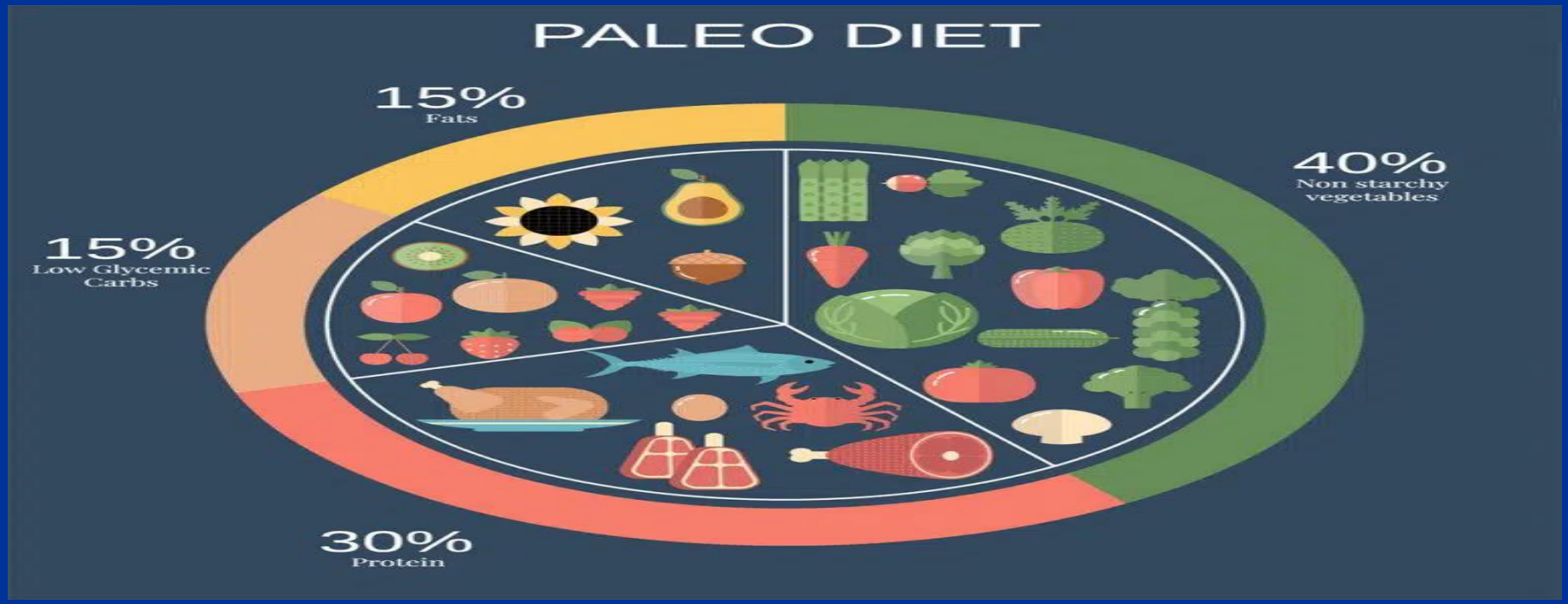
WHAT TO EAT:

- Healthy Fats
- Eggs
- Meat
- Poultry
- Seafood

- Full-fat Dairy
- Nuts & Seeds
- Leafy Greens
- Low Carb Veggies
- Berries



The paleo diet pyramid includes wholesome ingredients and excludes processed foods.



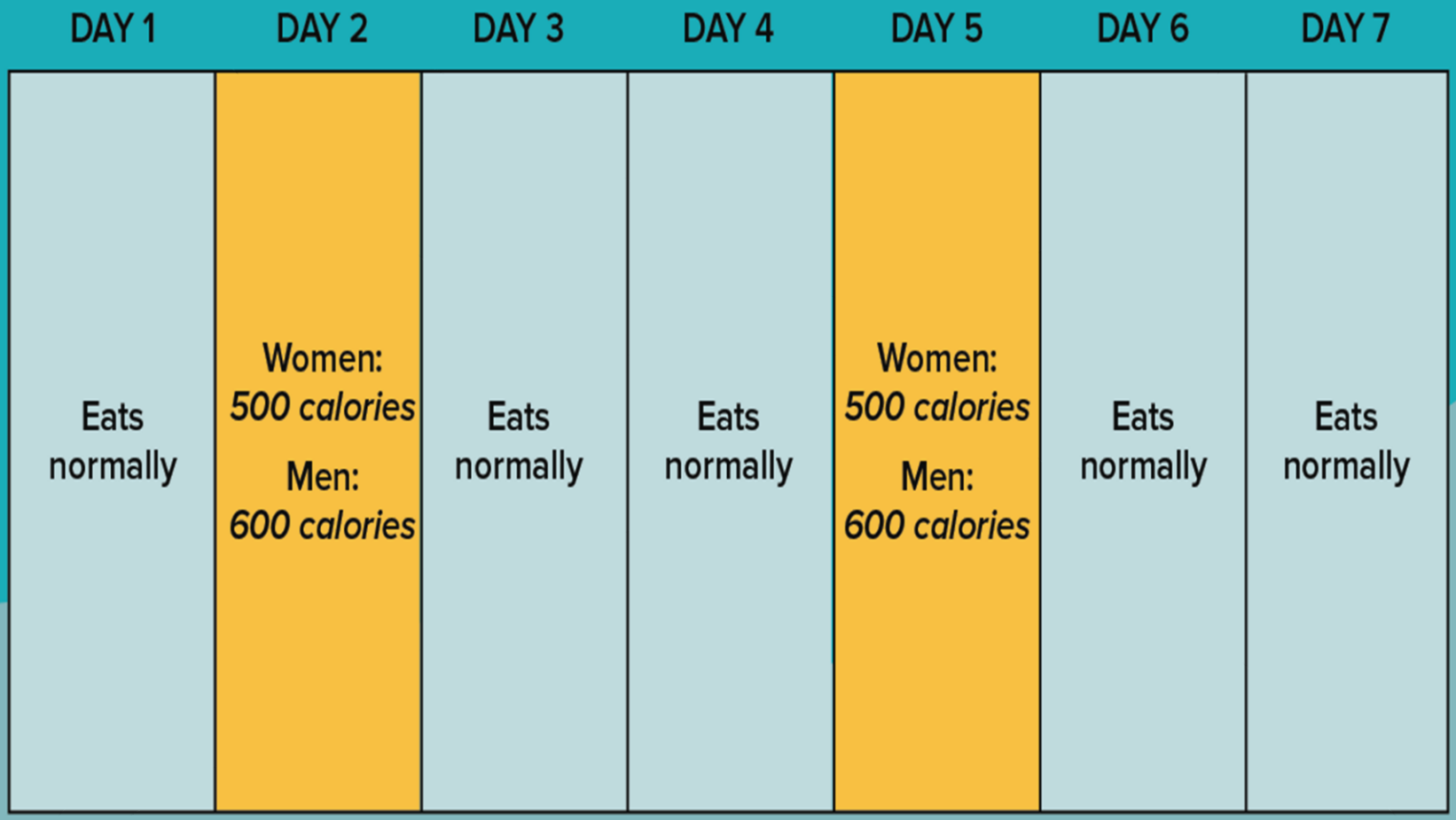
What to eat?

- **Fruits**
- **Vegetables**
- **Nuts and seeds**
- **Lean meats, especially grass-fed animals or wild game**
- **Fish, especially those rich in omega-3 fatty acids, such as salmon, mackerel and albacore tuna**
- **Oils from fruits and nuts, such as olive oil or walnut oil**

What to avoid?

- Grains, such as wheat, oats and barley
- Legumes, such as beans, lentils, peanuts and peas
- Dairy products
- Refined sugar
- Salt
- Potatoes
- Highly processed foods in general

THE 5:2 DIET


DAY 1
DAY 2
DAY 3
DAY 4
DAY 5
DAY 6
DAY 7
Eats normally
Women: 500 calories
Men: 600 calories
Eats normally
Eats normally
Women: 500 calories
Men: 600 calories
Eats normally
Eats normally

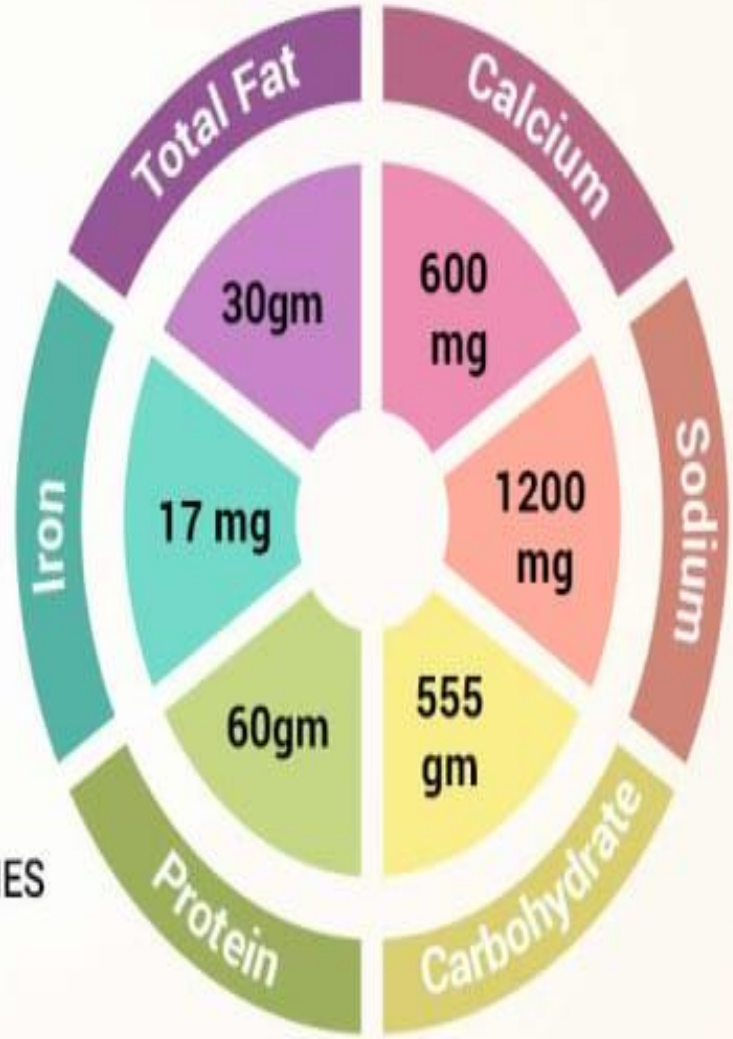
Types of Intermittent fasting

- Fast for 12 hours a day
- Fasting for 16 hours
- Fasting for 2 days a week
- Alternate day fasting
- A weekly 24 hours fast
- Meal skipping
- The warrior diet

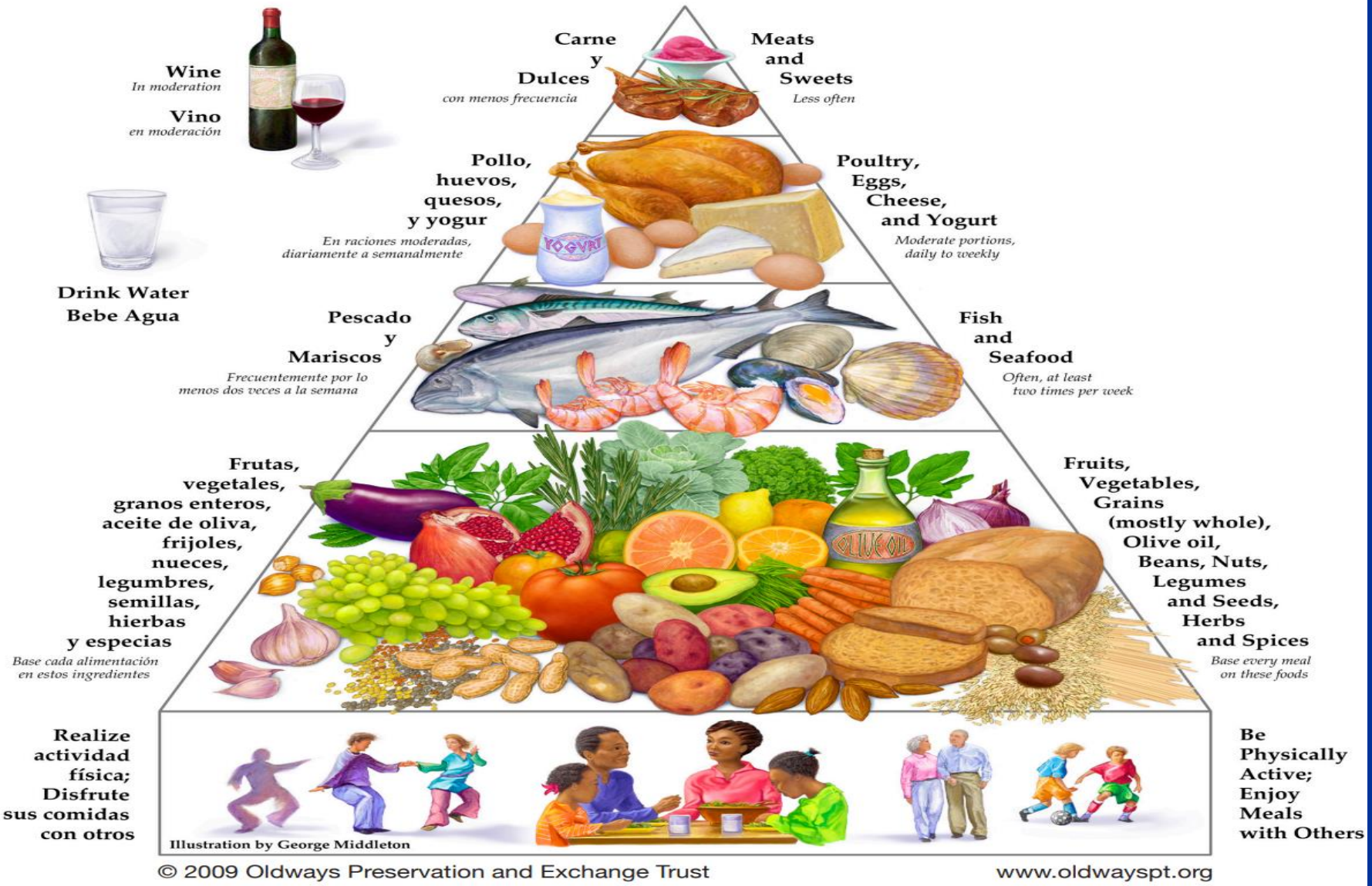
Paleo Diet Chart

TOTAL CALORIES
(kcals/Day)

2730



Mediterranean Diet Pyramid
La Pirámide de la Dieta Mediterránea



www.oldwayspt.org

7 Day GM Diet Plan

Day 1		All fruits except bananas
Day 2		All vegetables except potatoes
Day 3		All fruits and vegetables except bananas and potatoes
Day 4		8 bananas & 3 cups of low fat milk
Day 5		300g of chicken breast or beef & 6 tomatoes
Day 6		300g of chicken breast or beef & vegetables
Day 7		Brown rice & vegetables & fruits juice

general motors diet

Drug (full dose and administration)	Company	Approval	Weight loss (placebo/drug)	Side effects	Refs
Mitochondrial uncoupler					
DNP	Stanford University	1933–1938 (USA)	No data for controlled treatment ≥52 weeks	Hyperthermia, tachycardia, fever, tachypnoea, death	34
Sympathicomimetic					
Diethylpropion/afepramone	Merrell National Drug	1959–present (EU)	No controlled treatment ≥52 weeks	Nausea, constipation, insomnia, headache, tension and irritation, seizures	34
Methamphetamine	Abbott Laboratories	1947–1979 (USA)		Nigh risk for abusiveness and addiction	34
Phenmetrazine	Ciba-Geigy Corp	1956–present (USA)		Nausea, diarrhoea, dry mouth	34
Phendimetrazine	Carnick Laboratories	1959–present (USA)		Nausea, diarrhoea, dry mouth	34
Phenylpropanolamine	Thompson Medical	1960–2000 (USA)		Haemorrhagic stroke	
Fenfluramine and dexfenfluramine	Wyeth Ayerst	1973–1997 (USA)	−2.8%/−5.4%	Cardiac valvular insufficiency and pulmonary hypertension	285
Cathine (nor-pseudoephedrine) (53.3 mg, OD, oral)	Riemser Pharma	1975–present (EU, only for short-term use)	−2.4%/−6.6% to 9.9% (dose-dependent, short-term use only)	Tachycardia, increase in blood pressure, restlessness, sleep disorder, depression	32
Sibutramine (10 mg, OD)	Abbott Laboratories	1997–2010 (USA, EU)	+0.7%/−1.7%	Non-fatal myocardial infarction and stroke (in individuals with pre-existing CVD)	154
Phentermine (15–30 mg, OD, oral)	Teva Pharmaceuticals	1959–present (USA, only for short-term use)	−1.7%/−6.6% to −7.4% (dose-dependent)	Palpitations, elevated blood pressure	286
Polypharmacy					
Rainbow pills	Clark & Clark and others	1961–1968 (USA)	No controlled treatment ≥52 weeks	Insomnia, palpitations, anxiety, increase in heart rate and blood pressure, death	287

Drug (full dose and administration)	Company	Approval	Weight loss (placebo/drug)	Side effects	Refs
CB1 receptor blocker					
Rimonabant (20 mg, OD)	Sanofi SA	2006–2009 (EU)	−1.6%/−6.4%	Depression, suicidal ideation	288
Pancreatic lipase inhibitor					
Orlistat (120 mg TID, oral)	Roche Pharmaceuticals	1999–present (USA, EU)	−6.1%/−10.2%	Liver injury, gastrointestinal symptoms	289
5-HT_{2C} serotonin agonist					
Lorcaserin (10 mg, BID, oral)	Arena Pharmaceuticals, Eisai	2012–2020 (USA)	−2.2%/−5.8%	Depression, suicidal ideation, palpitations, gastrointestinal symptoms, increased cancer risk	65

Sympathomimetic/anticonvulsant					
Phentermine/topiramate ER (with titration) (15 mg/92 mg, OD, oral)	Vivus	2012–present (USA)	−1.2%/−7.8% to 9.3% (dose-dependent)	Depression, suicidal ideation, cardiovascular events, memory loss, birth defects	290,291
Opioid receptor antagonist/dopamine and noradrenaline reuptake inhibitor					
Naltrexone SR/bupropion SR (with titration) (32 mg/360 mg, BID, oral)	Orexigen Therapeutics Inc.	2014–present (USA, EU)	−1.3%/−5.0% to −6.1% (dose-dependent)	Seizures, palpitations, transient blood pressure elevations	292
GLP1R agonists					
Liraglutide (with titration) (3.0 mg, OD, subcutaneous injection)	Novo Nordisk	2014–present (USA, EU)	−2.6%/−8%	Nausea/vomiting, diarrhoea, constipation, pancreatitis, gallstones	176
Semaglutide (2.4 mg, once weekly, subcutaneous injection)	Novo Nordisk	2021 (USA)	−2.4%/−14.9%	Nausea/vomiting, diarrhoea, constipation	38

How Obesity Drugs Work !

Suppress Appetite

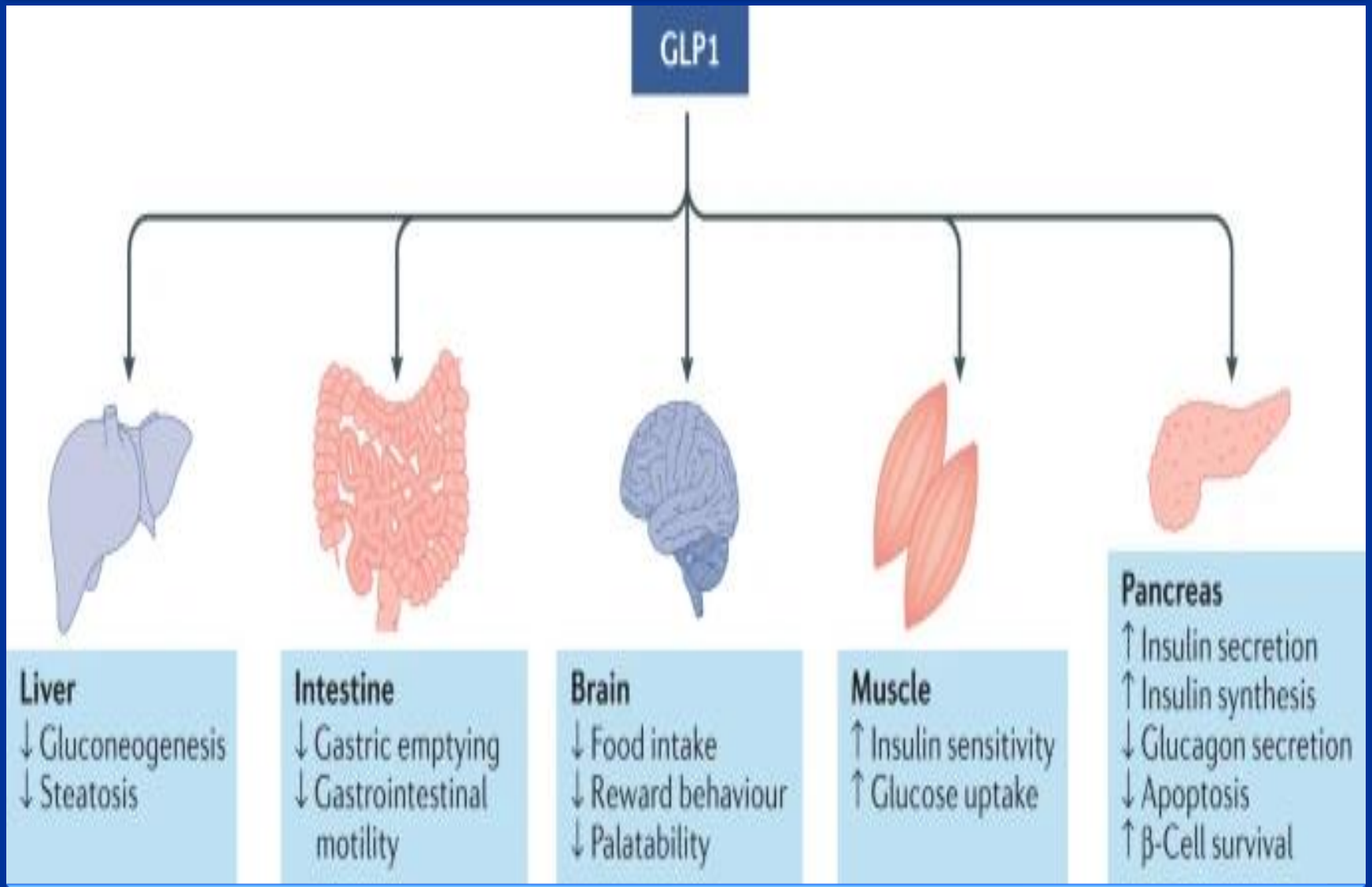
Early Satiety

Alter Fat Digestion

Potential Strategies for Anti-Obesity Drug Action

- **Reducing food intake.** Either amplify effects of signals/factors that inhibit food intake or block signals/factors that augment food intake
- **Blocking nutrient absorption** (especially fat or carbohydrates) in the intestine.
- **Increasing thermogenesis.** Either increase metabolism and dissipate food energy as heat or increase energy expenditure through the enhancement of physical activity.
- **Modulating fat metabolism/storage.** Regulate fat synthesis/breakdown by making appropriate adjustments to food intake or energy expenditure.
- **Modulating the central regulation of body weight.** Either alter the internal set point or modulate the signals presented regarding fat stores.

Regulation of body weight and glucose metabolism by GLP1R agonism



Glucagon-like peptide 1 receptor (GLP1R) agonism exerts both direct and indirect effects on energy and glucose metabolism in key peripheral organs as well as the brain.

Weight loss drugs in clinical development

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID/ref.[a]
GLP1/glucagon dual agonists				
Cotadutide (MEDI0382)	AstraZeneca	Phase II	T2D, NASH	NCT04019561 NCT03235050
BI 456906	Boehringer Ingelheim	Phase II	Obesity, T2D	NCT04153929
Efinopegdutide (^{LAPS}GLP/GCG)	Hanmi Pharmaceutical	Phase II	NASH	NCT03486392
OXM	Eli Lilly	Phase I	T2D	See Related links

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID/ref.[a]
GIP/GLP1 dual agonists				
Tirzepatide	Eli Lilly	Phase III	Obesity, T2D	NCT04657003
GIP/GLP peptide I	Eli Lilly	Phase I	T2D	See Related links
GIP/GLP peptide II	Eli Lilly	Phase I	T2D	See Related links
NN9709	Novo Nordisk	Discontinued	Obesity, T2D	See Related links

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID/ref.[a]
GIP/GLP1/glucagon tri-agonists				
HM15211 (^{LAPS}Triple Agonist)	Hanmi Pharmaceutical	Phase II	NASH	NCT04505436
GGG tri-agonist	Eli Lilly	Phase I	T2D	See Related links
NN9423	Novo Nordisk	Discontinued	Obesity, T2D	See Related links
GIPR agonists				
GIPR agonist long acting	Eli Lilly	Phase I	T2D	See Related links
ZP 6590	Zealand Pharma	Preclinical	Obesity	See Related links

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID/ref.[a]
GLP1R agonists				
Efpeglenatide (^{LAPS}Exd4 Analog)	Hanmi Pharmaceutical	Phase III	T2D	NCT03353350 NCT03496298
Rybelsus	Novo Nordisk	Phase III	Obesity	NCT03919929
Danuglipron (PF-06882961)	Pfizer	Phase II	Obesity, T2D	NCT04707313 NCT03985293
GLPR-NPA	Eli Lilly	Phase I	T2D	See Related links
PF-07081532	Pfizer	Phase I	T2D	NCT04305587
Glucagon analogue				
HM15136 (^{LAPS}Glucagon Analog)	Hanmi Pharmaceutical	Phase I	Obesity	See Related links

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID/ref.[a]
Leptin sensitizers				
Withaferin A	Academic, non-commercial	Phase I	Obesity, T2D	293
Celastrol	Academic, non-commercial	Preclinical	Obesity, T2D	294
Leptin/amylin	Amylin Pharmaceuticals	Discontinued	Obesity, T2D	See Related links

Y2R agonists				
PYY analogue	Eli Lilly	Phase I	T2D	See Related links
NN9748 (NN9747)	Novo Nordisk	Phase I	Obesity, T2D	NCT03574584
NNC0165-1875 + semaglutide	Novo Nordisk	Phase II	Obesity, T2D	NCT04969939

Amylin/calcitonin dual agonists				
KBP-089	Nordic Biosciences	Phase I	T2D	NCT03907202
KBP-042	Nordic Biosciences	Discontinued	T2D	NCT03230786
Davalintide	Amylin Pharmaceuticals	Discontinued	Obesity, T2D	See Related links

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID/ref.[a]
Drugs targeting the ghrelin pathway				
CYT009-GhrQb	Cytos Biotechnology	Phase I	Obesity	See Related links
Nox-B11	Noxxon Pharma	Preclinical	Obesity	See Related links
AZP-531	Millendo Therapeutics SAS	Discontinued	Hyperphagia in patients with Prader–Willi syndrome	NCT03790865

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID/ref.[a]
Mitochondrial uncoupler				
BAM15	Continuum Biosciences	Preclinical	Obesity, NASH	See Related links
Other appetite suppressants				
GDF15 (LA-GFD15)	Novo Nordisk	Phase I	Obesity	See Related links
LY-3463251 (GDF15 agonist)	Lilly	Phase I	T2D, obesity	NCT03764774
JNJ-9090/CIN-109 (GDF15 agonist)	Jansenn/CinFina Pharma	Phase I	Obesity	NA

Cardiovascular Benefits of Anti-Obesity Meds

Medication	T2DM	Dyslipidemia	Hypertension	CVD outcomes	Notable trials
Orlistat[1,2]	↓BG; ↓ A1c	↓TG; ↓LDL ↓total chol.	↓SBP ↓DBP		XENDOS
Phentermine/ topiramate[3,4]	↓BG; ↓ annual incid. of T2DM	↓TG; ↓LDL ↑HDL	↓SBP ↓DBP		CONQUER SEQUEL
Bupropion/ naltrexone[5,6]	↓ A1c 0.6%	↓TG ↓LDL ↑HDL	↑SBP ↑DBP (both minimal)		COR-I COR-II COR-Diabetes
Liraglutide[7,8]	↓ cumulative incid. of T2DM ↓A1c 0.3%	↓TG; ↓LDL ↑HDL	↓SBP ↓DBP	↓MACE by 13% (1.8mg dose)	SCALE LEADER
Semaglutide[9,10]	↓ A1c 1.6%	↓TG	↓SBP ↓DBP	↓MACE by 26% (1mg dose)	STEP 1 SELECT SUSTAIN 6

BG, blood glucose; CVD, Cardiovascular Disease; DBP, diastolic blood pressure; HDL, high density lipoproteins; TG, LDL, low density lipoproteins; MACE, major adverse cardiovascular event; SBP, systolic blood pressure; T2DM, Type II Diabetes Mellitus; TG, triglycerides;

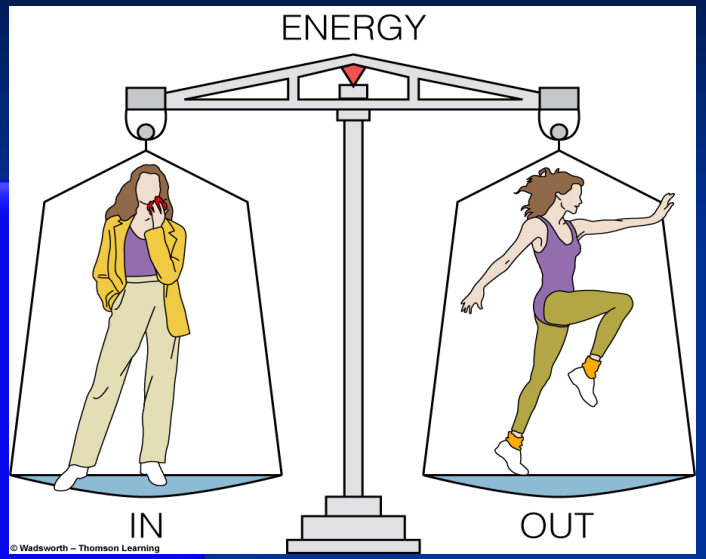
1.Hollander PA, et al. *Diabetes Care*. 1998;21(8):1288–1294. 2.Sahebkar A, et al. *J Am Soc Hypertens*. 2018;12(2):80-96. 3. Garvey WT, et al. *Am J Clin Nutr*. 2012;95(2):297-308. 4.Gadde K, et al. *Lancet*. 2011;377(9774):1341-1352. 5.Hollander P, et al. *Diabetes Care*. 2013;36(12):4022-4029. 6. Apovian C, et al. *Obesity (Silver Spring)*. 2013;21(5):935-943. 7.Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22. 8. Victoza™ [package insert]. Novo Nordisk. 9.Wilding J, et al. *N Engl J Med*. 2021; 384:989-1002. 10.Marso SP, et al. *N Engl J Med*. 2016;375(19):1834-1844.

Energy Balance

- Excess energy whether from
  - Fat
  - Carbohydrate
  - Protein

can be converted into fat and stored in fat cells

Energy Balance



- If energy in = energy out
  - Maintain weight
- If energy in > energy out
  - Gain weight
  - Stored as fat
- If energy in < energy out
  - Lose weight
  - Body pulls on fat stores and lean tissue

Why Treat Obesity?

- Contributes to approximately 300,000 deaths a year, making it 2nd only to smoking as a cause of death
- Contributes or causes to many other health problems including:
  - Type 2 Diabetes Mellitus
  - Coronary Artery Disease
  - Degenerative Joint Disease
  - Certain Types of Cancer
  - Nonalcoholic Steatohepatitis

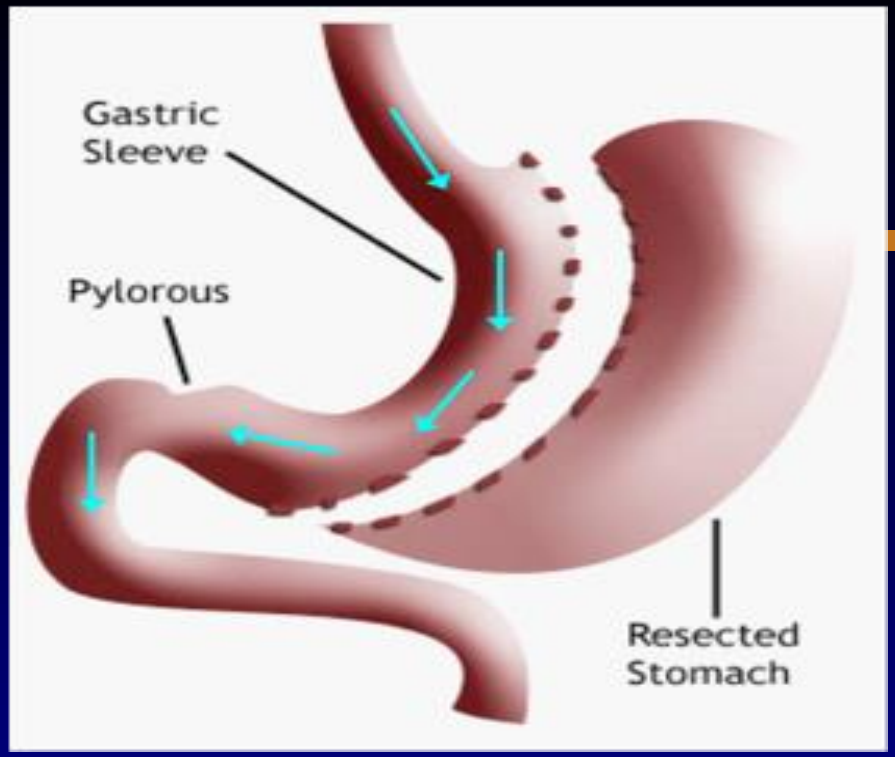
تنظیم دارویی

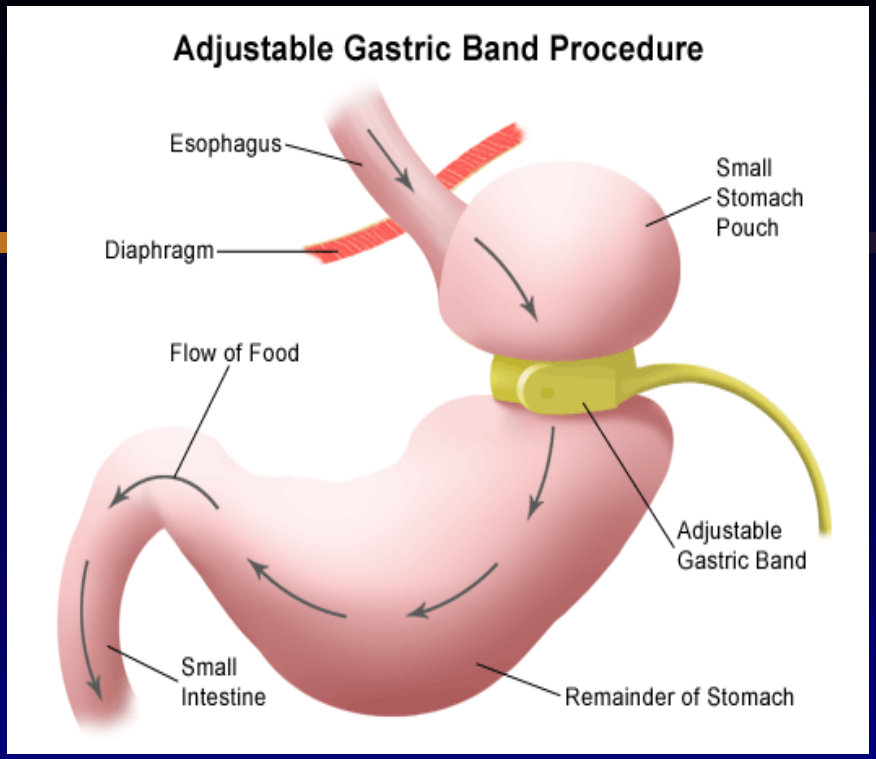
- داروهای موثر بر CNSخود در سه دسته قرار می گیرند

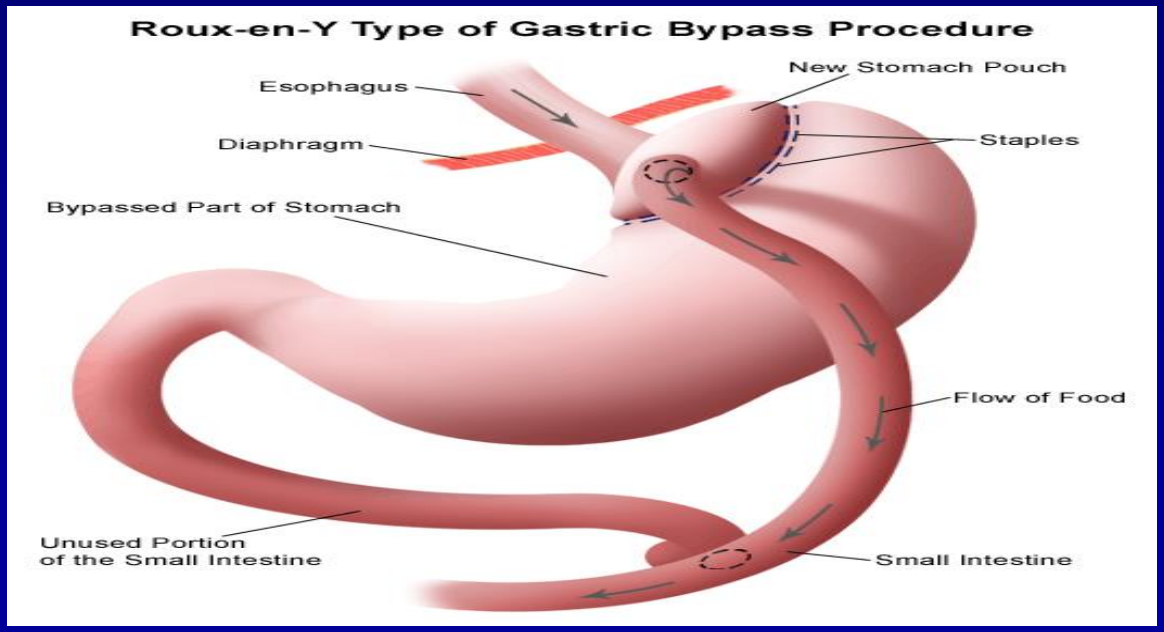
- داروهاي كاتكولامينرژيک كه داروهاي سروتونينرژيک و داروهاي كاتكولامينرژيک-سروتونينرژيک.

- عوارض جانبي داروهاي مؤثر بر CNS شامل خشكي دهان، سردرد، بي خوابي و يبوست مي گردد.

- **CRF- كاهش اشتها**


Gastric
Sleeve
Pylorous
Resected
Stomach


Adjustable Gastric Band Procedure
Esophagus
Small
Stomach
Pouch
Diaphragm
Flow of Food
Adjustable
Gastric Band
Small
Intestine
Remainder of Stomach


Roux-en-Y Type of Gastric Bypass Procedure
New Stomach Pouch
Esophagus
Diaphragm
Staples
Bypassed Part of Stomach
Flow of Food
Unused Portion
of the Small Intestine
Small Intestine

Side Effects & Complications

1 in 200-300 patients in the US die from bariatric surgery

- Iron deficiency
- Vitamin B_{12} deficiency
- Folic Acid deficiency
- Dehydration
- Vitamin A deficiency
- Electrolyte deficiency
- Protein deficiency
- Hyperparathyroidism
- Follow up of nutritional and metabolic problems after bariatric surgery

- Diabetes Care 28:481-484,2005

- Nausea
- Vomiting
- Abdominal pain
- Constipation
- Marginal ulceration
- Gallstones
- Bleeding ulcer
- Obstruction of the stomach outlet

Shikora SA. *Nutrition in Clinical Practice*. 2000;15:13.
www.mayoclinic.com. Surgery for obesity: What is it and is it for you?. Accessed February 15, 2005.

Indications for Drug Therapy in Obesity

BMI > 30 kg/m2 (failed diet and exercise alone)

BMI 27 – 29.9 (with comorbidities)

- **No contraindications to drug therapy**
  - **Medication interactions**
  - **Medical conditions that may be adversely affected by the obesity drug**

Snow, et al , Ann Intern Med, 2005.

Side Effects & Complications

1 in 200-300 patients in the US die from bariatric surgery

- Iron deficiency
- Vitamin B_{12} deficiency
- Folic Acid deficiency
- Dehydration
- Vitamin A deficiency
- Electrolyte deficiency
- Protein deficiency
- Hyperparathyroidism
- Follow up of nutritional and metabolic problems after bariatric surgery

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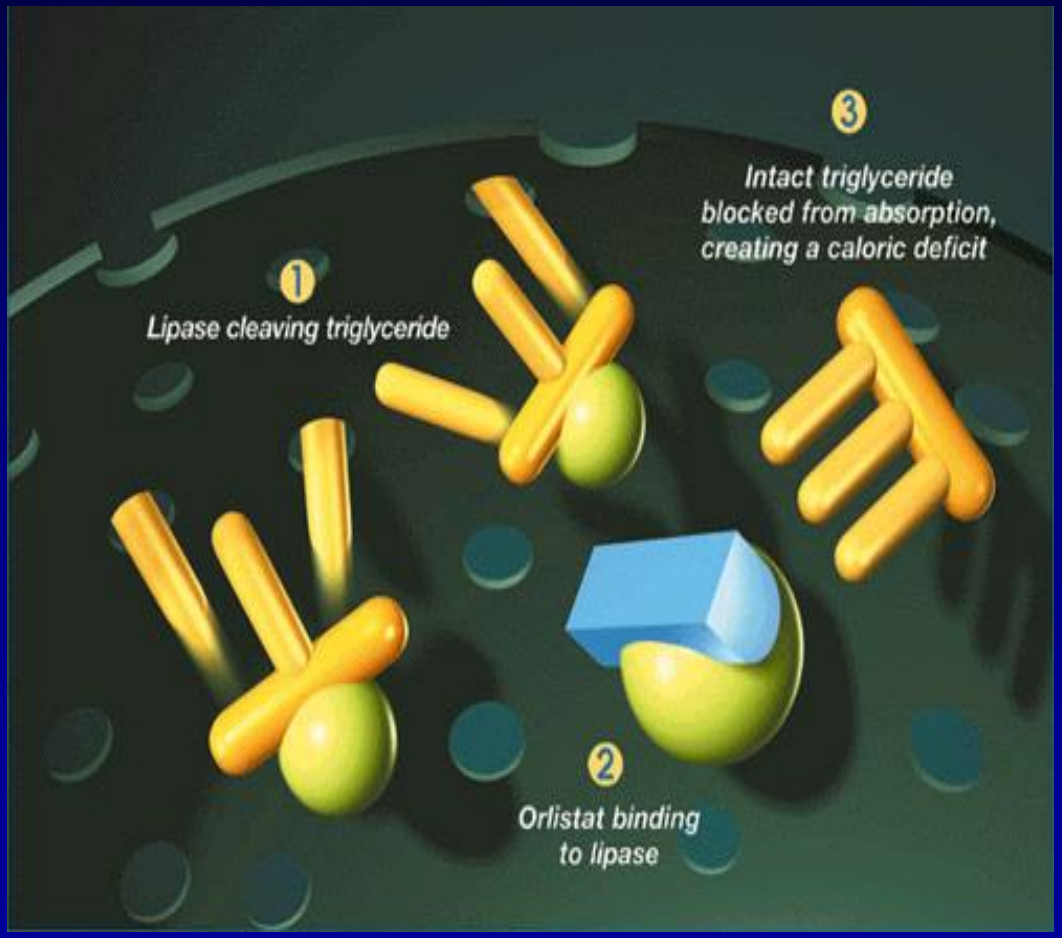
Shikora SA. *Nutrition in Clinical Practice*. 2000;15:13.
www.mayoclinic.com. Surgery for obesity: What is it and is it for you?. Accessed February 15, 2005.

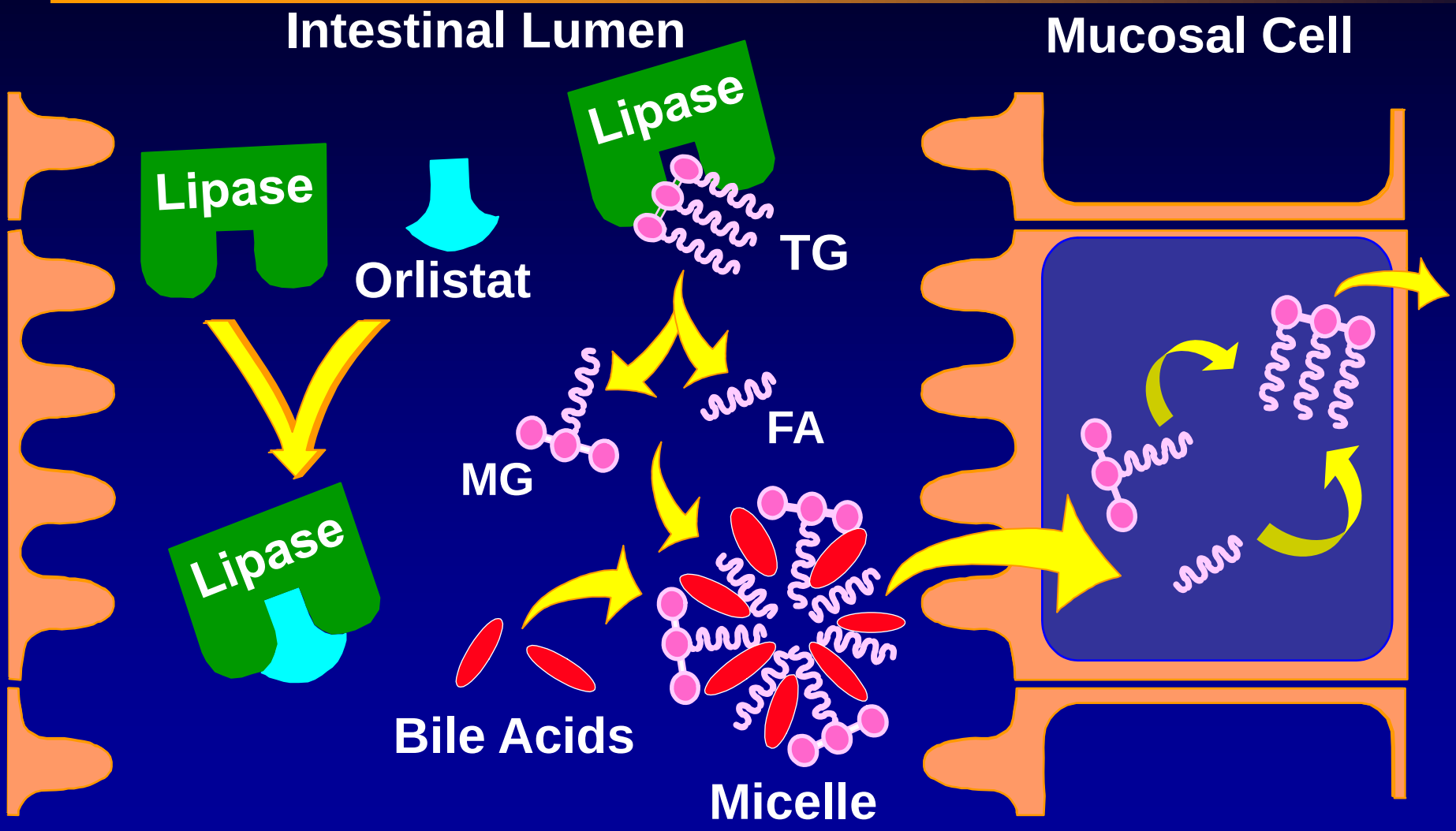
Orlistat


3
Intact triglyceride
blocked from absorption,
creating a caloric deficit
1
Lipase cleaving triglyceride
2
Orlistat binding
to lipase

Orlistat (Xenical)

- Gastrointestinal lipase inhibitor that blocks the absorption of up to one third of ingested fat.
- In addition to helping reduce weight, orlistat has been shown to also:
  - lower plasma low-density lipoprotein cholesterol (LDL) cholesterol levels.
  - The decline in LDL cholesterol is greater than that expected due to weight loss alone.
  - Lower HgbA1C in diabetic patients

Orlistat Prevents Fat Digestion by Binding to Gastrointestinal Lipases



TG=triglyceride; MG=monoglyceride; FA=fatty acid

Gastrointestinal Side Effects of Orlistat Therapy

	Year 1		Year 2	
	Placebo	Orlistat	Placebo	Orlistat
Fatty/oily stool	5	31	1	8
Increased defecation	7	20	2	2
Liquid stools	10	13	5	8
Fecal urgency	3	10	2	3
Flatulence	3	7	2	3
Flatus with discharge	0	7	0	1
Fecal incontinence	0	7	0	2
Oily evacuation	1	6	0	5
Low plasma vitamin conc:				
Vitamin A	0.6	0.3	0.8	0
Vitamin D	0.6	5.1	0.8	3.1
Vitamin E	0.9	4.6	0	1.6

Values are percentage of subjects.

Sjostrom et al. *Lancet* 1998;352:167.

Summary

- Weight loss with obesity medicines is modest
- Obesity medicines are not a substitute for diet and exercise
- Weight loss is often not maintained after drug is discontinued
- Most obesity medicines are not covered by insurance

Drug	Wt loss
Sibutramine	4-5 kg
Phentermine	3-4 kg
Orlistat	2-3 kg
Metformin	2 kg
Exenatide	2-3 kg
Bupropion	2-3 kg
Fluoxetine	Mixed
Topamax	6-7 kg
Rimonabant	6-7 kg

Herbal/Natural Wt Loss Comments

- Positives
  - It's not all bad
  - Food is natural and a great place to make modifications for both weight & overall health
  - Support, accountability and commitment
    - Useful
  - There are some amazing stories…

Weight Loss Supplements

Weight Loss Supplements

- Increase energy expenditure
- Modulate carbohydrate metabolism
- Increase satiety
- Increase fat oxidation or reduce fat synthesis

- Block dietary fat absorption
- Increase water elimination
- Enhance mood
- Other miscellaneous or unspecified

Weight Loss Supplements

Chromium and Ginseng

- Modulate carbohydrate metabolism
  - Chromium
  - Ginseng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En cas de fatigue, de difficultés de concentration, d'états de faiblesse et d'épuisement
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Weight Loss Supplements

Chromium and Ginseng

- Chromium is thought to play a role in carbohydrate and lipid metabolism
- Chromium deficiency is associated with hyperglycemia, hyper-insulinemia, hypertriglyceridemia and low HDL
- Three (small) RCTs of chromium supplements showed no difference in weight loss when compared to placebo

Weight Loss Supplements

Chromium and Ginseng

- No adverse events at recommended dose of chromium, but rhabdomyolysis and renal failure have been reported at super-therapeutic doses (1000mcg vs 200 to 400mcg)

Weight Loss Supplements

Chromium and Ginseng

- Ginseng has preliminary data suggesting that it may improve glucose tolerance
- No RCTs in humans have shown greater weight loss with ginseng when compared to placebo

Weight Loss Supplements

Chromium and Ginseng

- The Good:
  - They may be safe
- The Bad:
  - No good RCTs to show efficacy
- The Ugly:
  - Potential renal failure

Weight Loss Supplements

Glucomannan, Psyllium, and Guar Gum

- Increases satiety
  - Guar gum
  - Glucomannan
  - Psyllium

Weight Loss Supplements

Glucomannan, Psyllium, and Guar Gum

- Action: soluble fiber that absorbs water within the gut causing a fullness sensation

- May improve control of diabetes and hyperlipidemia (fiber affect)

Weight Loss Supplements

Glucomannan, Psyllium, and Guar Gum

- Glucomannan: 3 (small) RCTs showed dosages of 3 to 4g per day were tolerated and yielded modest weight loss
- Psyllium: Showed no difference in weight loss in patients with Type 2 Diabetes (but did improve glucose and lipid parameters)
- Guar gum: 11 RCTs showed no benefit over placebo

Weight Loss Supplements

Glucomannan, Psyllium, and Guar Gum

- The Good:
  - They may be safe
- The Bad:
  - No good RCTs to show efficacy, save modest weight loss with Glucomannan
- The Ugly:
  -

Weight Loss Supplements

Act on Fat Oxidation or Synthesis

- Increase fat oxidation or reduce fat synthesis
  - L-carnitine
  - Hydroxycitric acid (Garcinia Cambogia)
  - Green tea
  - Green Coffee
  - Vitamin B_5
  - Licorice
  - Conjugated linoleic acid
  - Pyruvate

Weight Loss Supplements

Act on Fat Oxidation or Synthesis

- Hydroxycitric Acid:
  - Inhibits mitochondrial citrate lyase, leading to decreased acetyl coenzyme A production and decreased fatty acid synthesis
  - 12-week RCT of mildly overweight women showed nearly 1.5 kg weight loss at 750mg
  - However, a larger study of men and women showed no difference at 1,500mg dose

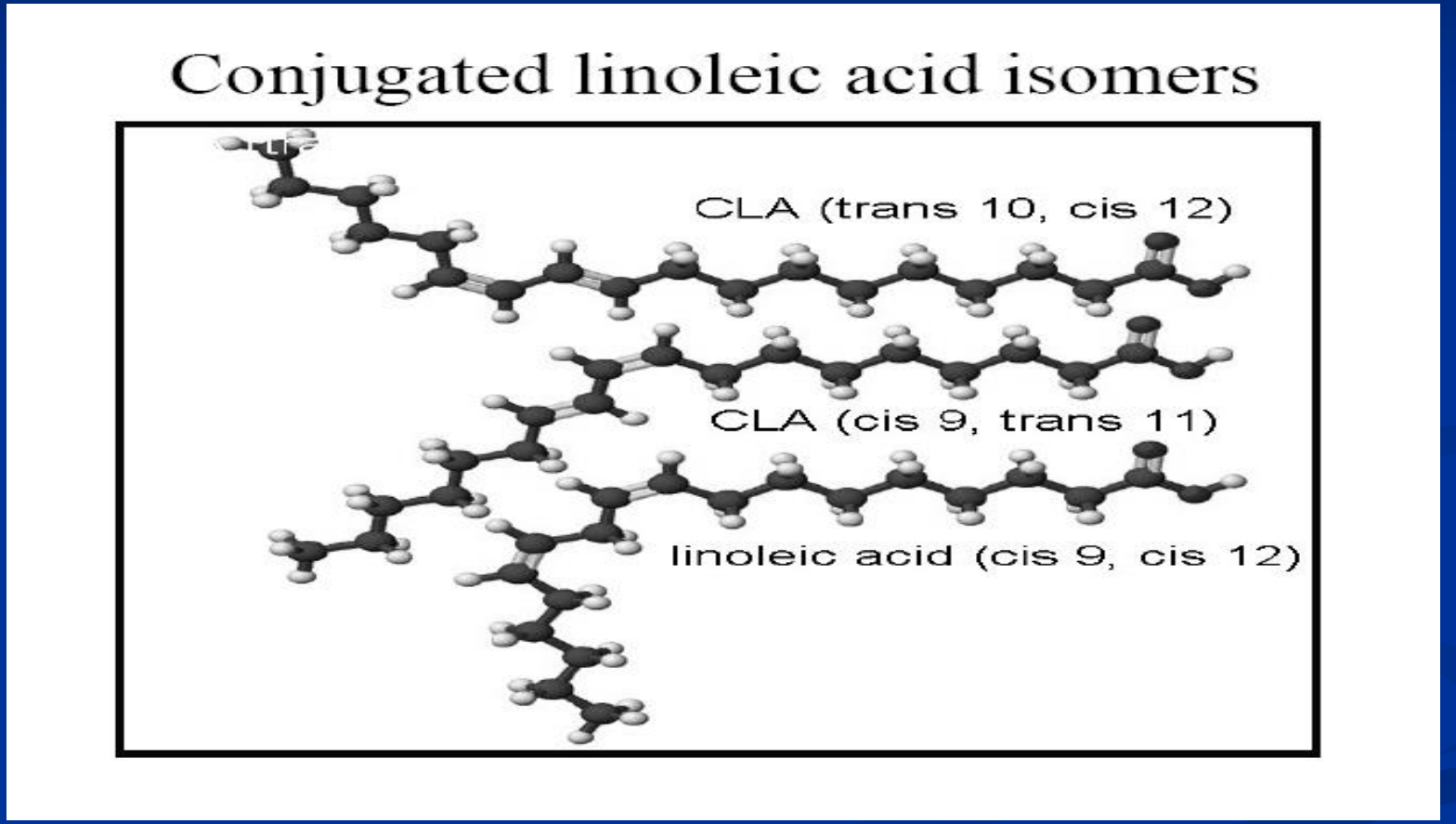
Weight Loss Supplements

Act on Fat Oxidation or Synthesis

- Conjugated linoleic acid:
  - In mice, reduces fat deposition postulated to be through increased fat oxidation and decreased triglyceride uptake in adipose tissue
  - 12-week RCT of 3.4 to 6.8 g/day showed no change in BMI and mild to moderate GI symptoms
  - May increase insulin resistance

Weight Loss Supplements

CLA= Conjugated Linoleic Acid



Both the cis-9, trans-11 and trans-10, cis-12 CLA isomers

Nutri FIT

Conjugated Linoleic Acid 1000 mg

Helps Reduction of Body Fat*

Nutri Century

60 SOFTGELS

DIETARY SUPPLEMENT

Supplement Facts

Serving Size 1 Softgel

Amount Per Serving		% Daily Value
Calories	10	
Calories from Fat	10	
Total Fat	1 g	2%
Saturated Fat	1 g	6%
Conjugated Linoleic Acid (80%)	1000 mg	**

** Daily value not established

Other Ingredients: Gelatin, glycerin and purified water. No preservatives, artificial flavour or colour, wheat, dairy, soy, gluten, yeast or sugar.

Directions: Take 1-2 softgels daily before meals or as directed by a healthcare practitioner.

Warnings: KEEP OUT OF REACH OF CHILDREN. Do not use if you are pregnant or breastfeeding. Consult a healthcare practitioner prior to use if you have any medical condition(s) including liver and/or heart disease, metabolic syndrome and if you are diabetic. Discontinue use and consult a healthcare practitioner if you experience any abdominal discomfort.

DO NOT USE IF SECURITY SEAL IS BROKEN OR MISSING.

Storage: Store at room temperature in a dry, dark place tightly closed.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any diseases.

مکمل رژیمی- غذایی نوتری فیت

۶۰ عدد کپسول ژلاتینی نرم

شماره ثبت فراورده: ۷۰۰۶۷۰۰۶۷۱۰۰۱۱

کد GS1: ۶۲۶۰۶۱۲۶۰۳۰۰٤

موارد مصرف: کمک به کاهش چربی در بدن

منع مصرف: خانم های باردار وشیرده

هشدارها: دور از دسترس کودکان نگهداری شود. در صورت هرگونه بیماری از جمله بیماری های قلبی – عروقی، کبدی، دیابت و سندروم متابولیک و یا مصرف هرگونه دارو قبل از مصرف با پزشک مشورت شود. در صورت بروز مشکل گوارشی، مصرف فرآورده را قطع و با پزشک مشورت نمایید. در صورت هر گونه آسیب دیدگی درپوش ایمنی استفاده نشود.

مقدار مصرف: روزی ۲-۱ عدد قبل از غذا یا طبق دستور پزشک

شرایط نگهداری: در جای خشک و خنک دور از نور و رطوبت در دمای کمتر از ۲۵ درجه سانتیگراد نگهداری شود .

تاریخ انقضاء و شماره سری ساخت روی بسته بندی درج شده است.

مکمل های رژیمی- غذایی، جایگزین دارو در تشخیص، پیشگیری و یا درمان بیماری ها نمی باشند.

ساخت کانادا

بسته بندی شده تحت لیسانس شرکت Nutri Century Corporation

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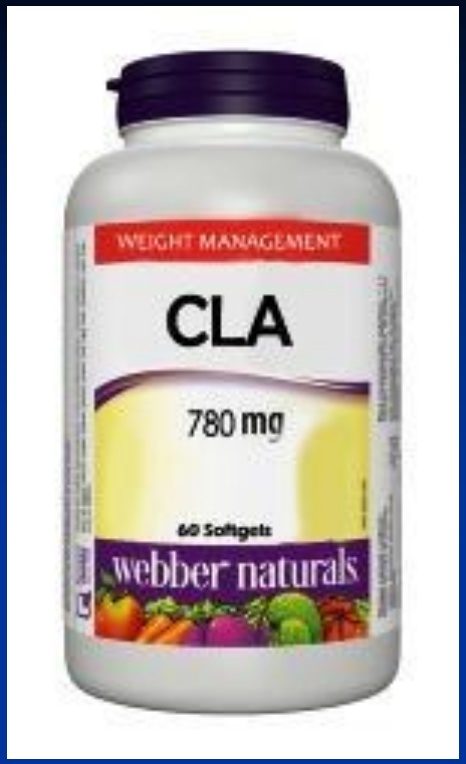
WEIGHT MANAGEMENT
CLA
780 mg
60 Softgels
webber naturals


SUPPLEMENT FACTS
Serving Size: 1 softgel
Servings Per Container: 180
REAL ATHLETES. REAL SCIENCE.


CLA CORE
CONJUGATED LINOLEIC ACID
CORE SERIES
SUPPORTS HEALTHY BODY COMPOSITION*
- AIDS IN WEIGHT LOSS*
- INCREASES METABOLIC RATE*
- REDUCES BODY FAT*
180 SOFTGELS

Weight Loss Supplements

Act on Fat Oxidation or Synthesis

- Green tea in one study increased fat oxidation and thermogenesis; however, study not designed to assess weight loss

- Licorice reduced body fat mass without change BMI; however, shown to also have adverse outcomes of pseudoaldosteronism, hypertension and hypokalemia

Weight Loss Supplements

Act on Fat Oxidation or Synthesis

- Pyruvate at 6g per day had a 1.2 kg weight loss compared to placebo over six weeks

- Vitamin B_5 and L-carnitine have not had any trial to support claims of causing weight loss

Weight Loss Supplements

Act on Fat Oxidation or Synthesis

- The Good:
  - They may be safe
  - Pyruvate may have weight loss
- The Bad:
  - Minimal and sometimes conflicting data to support weight loss
- The Ugly:
  - Conjugated linoleic acid may increase insulin resistance

Weight Loss Supplements

Chitosan

- Block dietary fat absorption
  - Chitosan

Weight Loss Supplements

Chitosan

- Blocks fat absorption by binding to negatively charged fat molecules within the intestinal lumen
- Five RCTs (all by the same investigators) showed effective weight loss
- However, three other well-designed RCTs (by different investigators) showed no differences in weight loss
- No proof of increased fecal fat excretion in healthy individuals taking Chitosan

Weight Loss Supplements

Chitosan

- The Good:
  - They appear be safe
- The Bad:
  - Some investigators show effectiveness in poorly designed studies
  - Should note be taken by those allergic to shellfish
- The Ugly:
  - Different investigators show no effect of Chitosan on weight loss

Weight Loss Supplements

Miscellaneous Other Supplements

- Miscellaneous or unspecified
  - Laminaria
  - Spirulina (blue-green algae)
  - Guggul
  - Apple cider vinegar

Weight Loss Supplements

Miscellaneous Other Supplements

- Spirulina contains phenylalanine, which is reported to inhibit appetite
- However, in 1981, the FDA declared it to be ineffective for weight loss and no studies have since looked at it for weight loss
- Other substances here have also never been studied for weight loss

Nonprescription Weight Loss Products

Product	Claim	Effectiveness	Safety
Alli: OTC version of prescription drug orlistat (Xenical)	Decreases absorption of dietary fat	Effective; weight-loss amounts typically less for OTC versus prescription	FDA investigating reports of liver injury, pancreatitis
Bitter orange	Increases calories burned	Insufficient reliable evidence to rate	Possibly unsafe
Chitosan	Blocks absorption of dietary fat	Insufficient reliable evidence to rate	Possibly safe
Chromium	Increases calories burned, decreases appetite, and builds muscle	Insufficient reliable evidence to rate	Likely safe
CLA	Reduces body fat and builds muscle	Possibly effective	Possibly safe
Country mallow (heartleaf)	Decreases appetite and increases calories burned	Insufficient reliable evidence to rate	Likely unsafe and banned by FDA
Ephedra (Ma Huang)	Decreases appetite	Possibly effective	Likely unsafe and banned by FDA
Green tea extract	Increases calorie and fat metabolism and decreases appetite	Insufficient reliable evidence to rate	Possibly safe
Guar gum	Blocks absorption of dietary fat and increases feeling of fullness	Possibly ineffective	Likely safe
Hoodia	Decreases appetite	Insufficient reliable evidence to rate	Insufficient information
Senna	Cathartic; causes diarrhea	Insufficient reliable evidence	Likely unsafe

Data from Natural Medicines in the Clinical Management of Obesity, Natural Medicines Comprehensive Database, http://naturaldatabase.therapeuticresearch.com:80/ce/ceCourse.aspx?s=ND&cs=&pc=09%2D32&cec=1&pm=5, Accessed on April 19, 2011.

CLA, Conjugated linoleic acid; *FDA*, Food and Drug Administration; *OTC*, over the counter.

The End