Metabolic Syndrome

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Metabolic Syndrome Outline - Part 1

- Background
- Definition
- Pathophysiology
- Associated conditions
- Summary

Background

- Metabolic syndrome (MetS) describes a group of risk factors that increase the risks for cardiovascular disease (CAD, PVD, CVD) and type 2 diabetes mellitus (T2DM).
- MetS takes into account central obesity, lipid profile, blood pressure and blood glucose.
- Management focuses on lifestyle changes and medical treatment of the individual risk components.

Background: The impact of MetS is profound

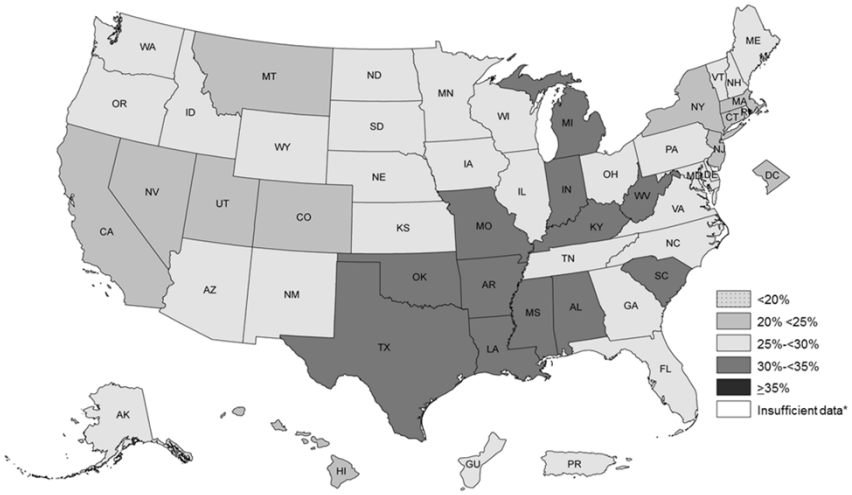
- Those with MetS have a two fold increased chance of death from CVD and three fold increased chance of a CVD event.
- Those with metabolic syndrome have five fold increased risk of developing T2DM.
- The incidence of MetS rises with the rates of obesity on the rise.
- The incidence of MetS rises as the world's population ages.
- MetS will overtake smoking as the driving risk for CVD.
- Estimates are that 20-25% of the world's adult population and up to 1/3 of the US adult population have MetS.

Background: The impact of MetS is profound

- NHANES data 2003-2004 vs 2011-2012 → prevalence is increasing
  - Up 18.3% in ages 20-39
  - Up 46.7% in those > 60 years
- Age > 60, 50% of women and Hispanics had MetS

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2011

¶ Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



***Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.**

Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2020

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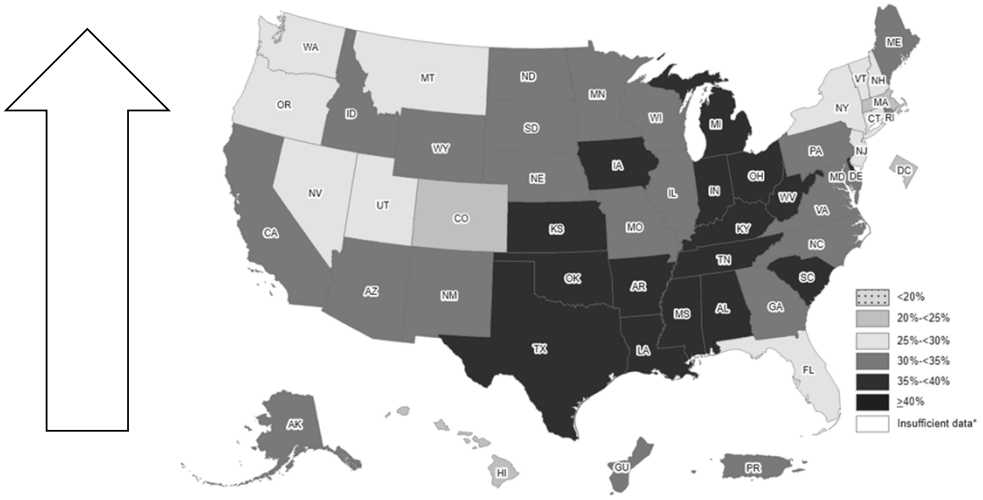


→ Ohio: 35.5% prevalence

2020:
→ No state with an obesity rate < 20%
→ 36 states have obesity rates > 30%

→ *In 1990, no states had a prevalence > 15%*

***Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.**

Background: Other names of MetS

- Dysmetabolic syndrome
- Hypertriglyceridemic waist
- Insulin resistance syndrome
- Obesity syndrome
- Syndrome X

Definition

Described in 1988

Banting Lecture 1988

Role of Insulin Resistance in Human Disease
By Gerald M. Reaven

Diabetes, December 1988

- Reduced insulin mediated glucose uptake
- Inability to suppress free fatty acids (FFA)
- Elevated glucoses develop in those who cannot maintain β-cell compensation

Credited with first describing metabolic syndrome (Syndrome X)

Definitions

- WHO 1998: insulin resistance + 2 other criteria (obesity, dyslipidemia, HTN, microalbuminuria
- European Group for the Study of Insulin Resistance (EGIR) 1999: insulin resistance + 2 additional criteria (WC, HTN, lipids)
- National Cholesterol Education Program (NCEP) ATP III 2001 with AHA 2005 update: 3 or more criteria (WC, HTN, ↑triglycerides, ↓HDL, glucose)
- International Diabetes Foundation (IDF) 2005: obesity (vs IR) + 2 other criteria; recognizes variance in different populations

NCEP ATP III definition

No absolute criteria** Any 3 of following factors:	
Waist circumference	Males ≥ 102 cm = 40 in Females ≥ 80 cm (≥ 88 cm =35 in
High triglycerides	≥ 150 mg/dL (1.7 mmol/L) Or specific treatment for this lipid abnormality
Low HDL	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females Or specific treatment for this lipid abnormality
Elevated blood pressure	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg Or treatment of diagnosed hypertension
Elevated fasting glucose	Fasting plasma glucose ≥ 100 mg/dL (5.6 mmol/L) Or previous diagnosis of type 2 diabetes

NCEP ATP III

- Does not require any specific criterion be met
- May reduce bias by not building on pre-existing recognition of obesity or insulin resistance

Definition: International Diabetes Federation, 2006

Central obesity Plus any of the **two** following factors:	**- waist circumference with ethnicity specific values OR** **- BMI > 30 kg/m2**
High triglycerides	≥ 150 mg/dL (1.7 mmol/L) Or specific treatment for this lipid abnormality
Low HDL	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females Or specific treatment for this lipid abnormality
Elevated blood pressure	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg Or treatment of diagnosed hypertension
Elevated fasting glucose	Fasting plasma glucose ≥ 100 mg/dL (5.6 mmol/L) Or previous diagnosis of type 2 diabetes

IDF 2006

- Requires obesity but not insulin resistance – this has been a criticism
- Acknowledges difference between populations with regards to CV and T2DM risk

Definition: Measurement of central obesity

- Waist circumference

- Body mass index

BMI classification	
Underweight	< 18.5
Normal range	18.5 - 24.9
Overweight	⩾ 25.0
Preobese	25.0 - 29.9
Obese	⩾ 30.0
Obese class I	30.0 - 34.9
Obese class II	35.0 - 39.9
Obese class III	⩾ 40.0

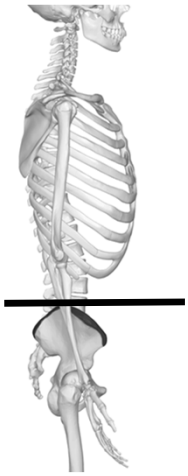
Definition: Waist circumference

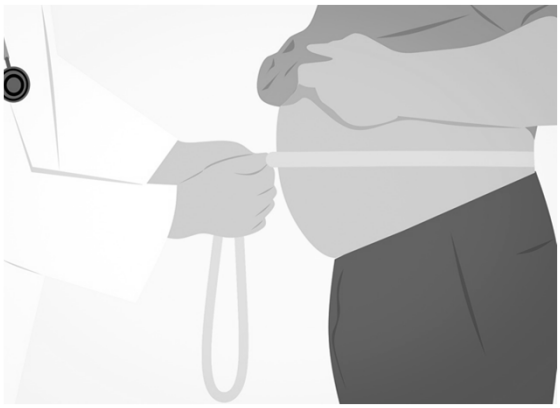
- correlates with cardiometabolic risk but has limitations
  - varied by ethnic group origin
  - Does not differentiate subcutaneous from visceral adiposity
  - Inter-observer variability
- WHO and IDF – Measure in the horizontal plane midway between the lowest ribs and the iliac crest
- National Cholesterol Education Program ATP III - Measure in the horizontal plane of the superior border of the iliac crest
- Should we measure in different locations based on sex and ethnicity?

Definition: Waist circumference (NHANES/ATP III/CDC)

- Examiners stands in front of the standing patient and palpates the right iliac crest. Just above this border, a horizontal mark is drawn and crossed with a vertical mark in the mid axillary line.
- Hold the tape measure horizontally around the abdomen at this mark and parallel to the floor.
- Keep the tape measure sung but not compressing the skin.
- Read the measurement to the nearest 0.1 cm at the end of the participant's normal expiration with minimal inspiration.

Waist circumference





Definition: Waist circumference by ethnicity

Ethnicity/Country		Waist Circumference
Europoids (North America/Europe)	Male Female	≥ 94 cm (≥ 102 cm = 40 in ATP III, USA) ≥ 80 cm (≥ 88 cm =35 in ATP III, USA)
South Asians	Male Female	≥ 90 cm ≥ 80 cm
Chinese	Male Female	≥ 90 cm ≥ 80 cm
Japanese	Male Female	≥ 90 cm ≥ 80 cm
Ethnic South and Central Americans	Use South Asian data	
Sub-Saharan Africans	Use European data	
Eastern Mediterranean & Middle East populations	Use European data	

Definition: BMI

- BMI – easy clinical way to access obesity by taking into account body weight and height but has limitations
  - Does not account for fat and lean tissue
  - Cannot distinguish the location of fat distribution
- Traditionally, overweight is defined as BMI ≥25 kg/m^2 and obese as BMI ≥30 kg/m^2
- This does not account for racial or ethnic specificity

Definition: BMI in the Asian population

- The traditional cut offs for based on BMI resulted in a disconnect between lower obesity rates in Asians (in Asia and Asian Americans) yet higher type 2 diabetes with a lower BMI.
  - The relationship between BMI and type 2 diabetes is shifted to a lower threshold in this population.
- There is a higher percent body fat in Asians at the same BMI in comparison to non-Hispanic whites.
  - Potential propensity to develop visceral adiposity as compared to peripheral adiposity
- Varied cut offs due to heterogeneity in the Asian population (23-27.5) but data suggests that using a cut off of > 23 kg/m^2 is useful in diabetes screening purpose (ADA recommendation)

Definition: additional metabolic parameters to consider….

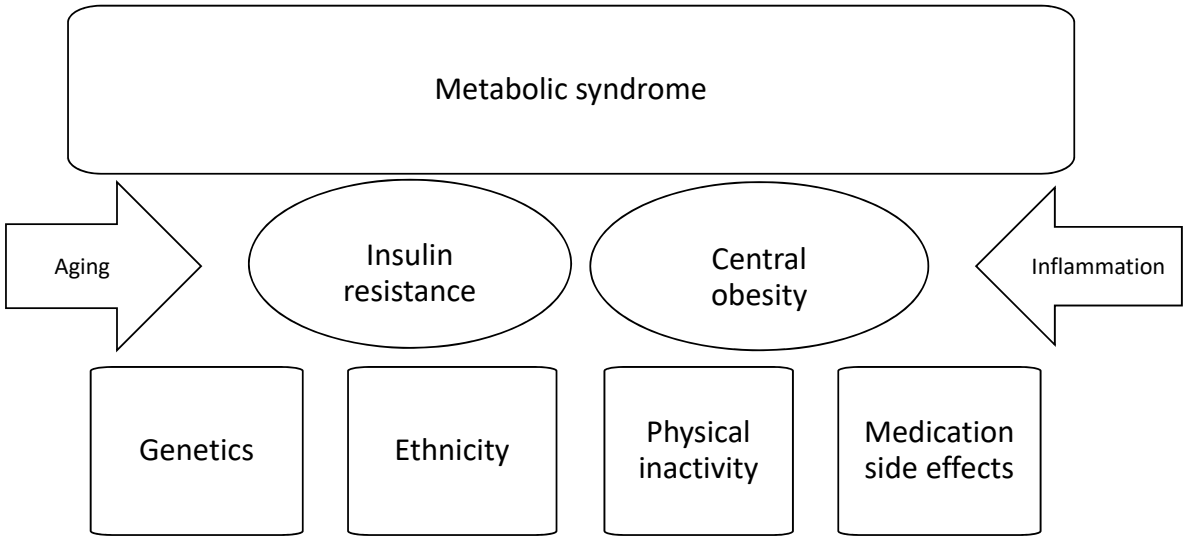
- Visceral adiposity – DXA, CT/MRI, biomarkers (leptin, adiponectin), liver steatosis
- Atherogenic dyslipidemia - Elevated apolipoprotein B (Apo B) and small LDL particles
- Insulin resistance – fasting insulin/proinsulin, HOMA-IR, elevated free fatty acids, insulin/glucose clamp models
- Vascular dysregulation – endothelial dysfunction, microalbuminuria
- Prothrombotic state – fibrinolytic markers, clotting factors
- Hormonal factors – pituitary adrenal axis?

Definition of Metabolic Syndrome

- Help in identifying those at risk for CVD/T2DM but do not account for other important risk factors:
  - Family history
  - Risk based on sex (other than WC measurement)
  - Smoking
  - Total or LDL cholesterol levels
- More likely helps in grouping patients into a shared pathophysiology
- Motivate patients and physicians to implement risk reduction strategies

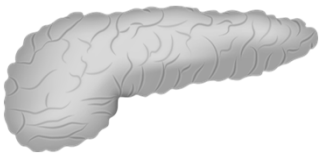
Pathophysiology

Pathophysiology: Influencers of MetS



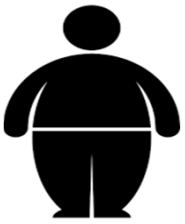
Pathophysiology: Insulin resistance

- Insulin targets become less responsive to action of insulin
- Pancreatic beta cells attempt to compensate by making more insulin
- Over time, the beta cell cannot compensate sufficiently and the measured glucose is above normal levels.
- The environment also promotes a pro-inflammatory state.
- Elevated free fatty acids/triglycerides are also seen with insulin resistance due to impaired lipoprotein lipase activity and impaired inhibition of lipolysis.
- Not as easy to measure in routine clinical practice, at least not until the glucose is elevated.



Pathophysiology: Central obesity

- Obesity is considered to be a worldwide epidemic.
- Obesity is correlated with reduced quality of life, shortened life span and increased healthcare costs.
- Central obesity correlates with visceral adiposity.
- Visceral adiposity is associated with insulin resistance.
- Obesity is correlated with higher CVD risk.



Pathophysiology: Central obesity

- White adipose tissue is a deposit for fat and is an endocrine organ and immune system organ that secretes adipokines and cytokines.
  - Adipokines influence insulin signaling, glucose uptake, fatty acid oxidation, etc.
  - Cytokines are involved with inflammation and angiogenesis
- Weight gain causes white adipose tissue hypertrophy and phenotypic change to a pro-inflammatory/insulin resistant state and there is stromal tissue invasion by immune cells.
- Obesity = chronic inflammatory disease.

Kawai, et al. Am J Physiol Cell Physiol 2021 Mar 1;320:3, C375-C391.

Pathophysiology: Central obesity & Insulin resistance

- Visceral adipose tissue is most affected in obesity and immune cell infiltration and inflammation **impairs lipid storage**.
- This results in **ectopic lipid deposition** such as in muscle and liver.
- Ectopic lipid deposition impairs insulin signaling in these tissues.
- Inflammatory cytokine actions also result in insulin resistance.

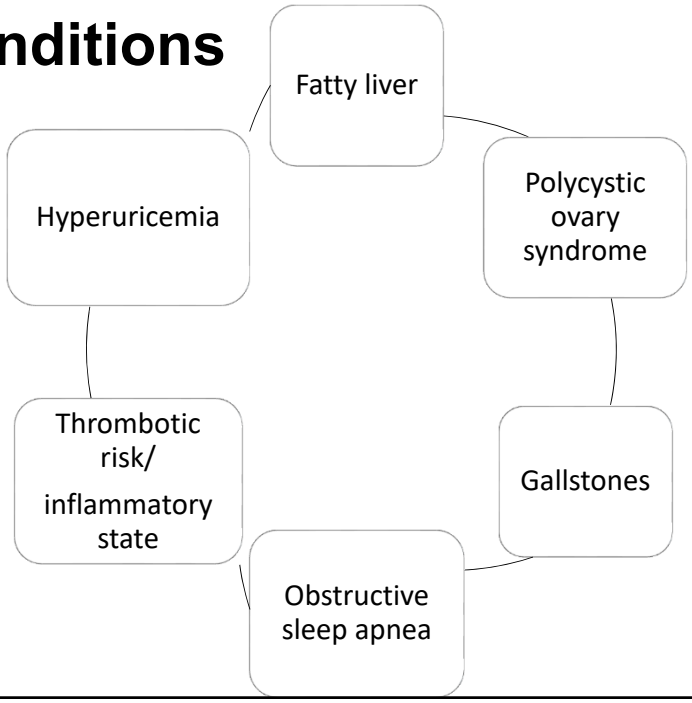
Kawai, et al. Am J Physiol Cell Physiol 2021 Mar 1;320:3, C375-C391.

Pathophysiology: Aging

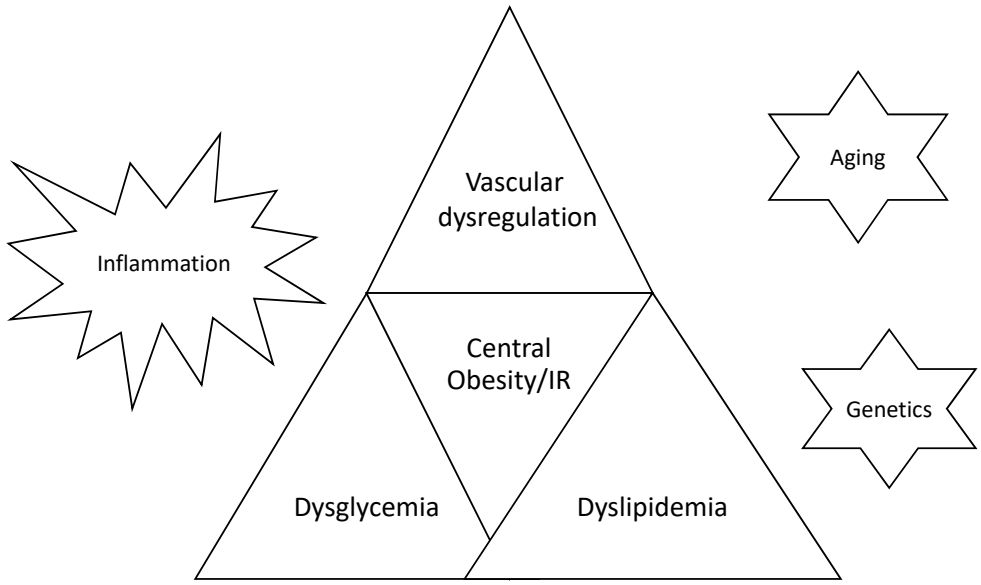
- Sarcopenia: decreased muscle mass, strength and quality
- Reduction in functional status and increased inactivity
- Increased fat mass – intrabdominal, skeletal muscle, liver
- "Sarcopenic obesity" describes the loss of muscle mass/quality with the progression of obesity
- Aging is also associated with reduced mitochondrial function with ectopic fat distribution and this is linked to insulin resistance
- "Inflammaging" – chronic state of inflammation in aging
- mTOR, telemore shortening, hypothalamic changes, changes in circadian rhythm also may play roles

Dominguez LJ et al. Curr Opin Clin Nutr Metab Care. 2016 Jan;19(1):5-11.

Associated conditions



Summary: Metabolic Syndrome



Management of Metabolic Syndrome

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Management

- Lifestyle modification
  - Nutrition
  - Physical activity
- Pharmacotherapy
- Surgery/endoscopic therapies
- Emerging Topics
  - Microbiome

Nutrition


Nutrition Facts
8 servings per container
Serving size 2/3 cup (55g)
Amount per serving
Calories 230
% Daily Value*
Total Fat 8g 10%
Saturated Fat 1g 5%
Trans Fat 0g
Cholesterol 0mg 0%
Sodium 160mg 7%
Total Carbohydrate 37g 13%
Dietary Fiber 4g 14%
Total Sugars 12g
Includes 10g Added Sugars 20%
Protein 3g
Vitamin D 2mcg 10%
Calcium 260mg 20%
Iron 8mg 45%
Potassium 235mg 6%
* The % Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

- Low calorie diet
  - Men 1500-1800 kcal/day
  - Women 1200-1500 kcal/day
- 500 kcal/day deficit should produce roughly 1 lbs per week of weight loss
- No one diet is most effective – go with patient preferences
- Maintain appropriate balance of nutrients
- Dietary intake should not be lower than 800 calories per day
- Initial goal of 10% decrease in body weight

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. [No authors listed]. Obes Res. 1998 Sep;6 Suppl 2:51S-209S. Review. Erratum in: Obes Res 1998 Nov;6(6):464.

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Nutrition

- Does macronutrient content matter?
  - "Low carb" = reduce processed carbs in diet in favor of more complex carbs + fiber
  - "Low fat" = lower *saturated fat* content
  - Lower sodium intake overall

- Does timing of meals really matter?
  - Some data suggest that timing of meals does matter - humans have an internal clock (circadian) built on day/night even though we have altered our lifestyles in modern times to include night shifts & bright light.

Cornier *et al*. The Metabolic Syndrome. Endocrine Reviews, December 2008, 29(7):777–822

Physical Activity

- Overall risk of MetS is doubled in adults who report no moderate or vigorous activity vs those who engage in 150 min/wk
- Aerobic activity and resistance activity are both beneficial
- Aerobic exercise has been shown to reduce abdominal adiposity in the absence of overall weight loss.

Cornier *et al*. The Metabolic Syndrome. Endocrine Reviews, December 2008, 29(7):777–822

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. [No authors listed]. Obes Res. 1998 Sep;6 Suppl 2:51S-209S. Review. Erratum in: Obes Res 1998 Nov;6(6):464.

Activity

TABLE IV-5:

DURATION OF VARIOUS ACTIVITIES TO EXPEND 150 KILOCALORIES FOR AN AVERAGE 70 KG (154 LB) ADULT

Intensity	Activity	Approximate duration in minutes
Moderate	Volleyball, noncompetitive	43
Moderate	Walking, moderate pace (3mph, 20 min/mile)	37
Moderate	Walking, brisk pace (4mph, 15 min/mile)	32
Moderate	Table tennis	32
Moderate	Raking leaves	32
Moderate	Social dancing	29
Moderate	Lawn mowing (powered push mower)	29
Hard	Jogging (5 mph, 12 min/mile)	18
Hard	Field hockey	16
Very Hard	Running (6 mph, 10 min/mile)	13

Source: Surgeon General's Report on Physical Activity and Health

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. [No authors listed]. Obes Res. 1998 Sep;6 Suppl 2:51S-209S. Review. Erratum in: Obes Res 1998 Nov;6(6):464.

Activity – a caveat

- Exercise (especially at higher intensity) leads to calorie expenditure
- As the body perceives the calorie loss, hunger signals increase
- It is possible for people to gain weight while increasing exercise due to overeating in response to hunger[1]

- A survey-study performed in 1997 of 784 people who were able to maintain 30 lbs of weight loss for > 1 year, only 1% achieved this with exercise alone[2]

1. Church TS, Martin CK, Thompson AM, Earnest CP, Mikus CR, et al. (2009) Changes in Weight, Waist Circumference and Compensatory Responses with Different Doses of Exercise among Sedentary, Overweight Postmenopausal Women. PLoS ONE 4(2): e4515.

2. Mary Klem et al. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr* 1997;66:239-46.

Pharmacotherapy

- Treating hypertension
  - Goal of < 130/80 in patients with high CV risk
  - Goal of < 140/90 in patients with average CV risk
  - ACEinh/ARB preferred, CCB, thiazide diuretics next agent
- Treating dyslipidemia
  - Reduce saturated fats in the diet, increase unsaturated, especially omega-3
  - Lipid lowering agents indicated based on CV risk score

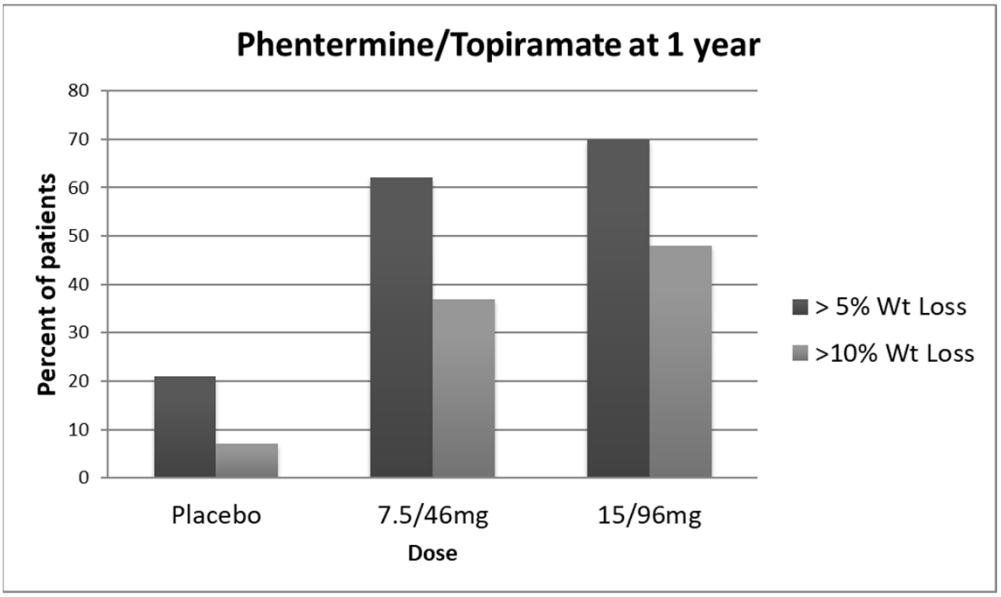
Pharmacotherapy for Obesity

Drug	Weight loss above placebo	Pluses	Minuses
Phentermine	7.9 lbs in *24* wks	Inexpensive	No long term data, side effects
Orlistat	6.5-7.5 lbs 52 wks	No systemic effect, OTC, long term data	Side effects, less weight loss
Phentermine-Topiramate	14.5 lbs (7.5mg) 18.9 lbs (15mg) at 52 wks	Robust weight loss, long term data	Teratogenic, cost
Bupropion-Naltrexon	~13 lbs at 52 wks	Use for food addiction (?)	Side effects, cost
Liraglutide	12.3 lbs at *56* wks	Side effect profile, CVOT data, long term data	Significant cost
Semaglutide	27.3 lbs at *68* wks	Best weight loss	Significant cost

J Clin Endocrinol Metab, February 2015, 100(2):342–362

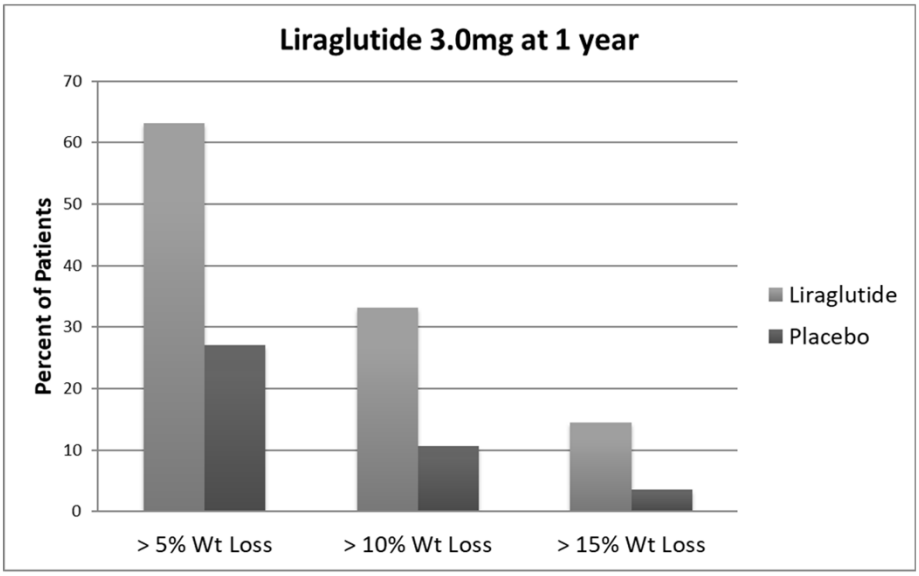
N Engl J Med 2021;384:989-1002. DOI: 10.1056/NEJMoa2032183

Pharmacotherapy Comparison



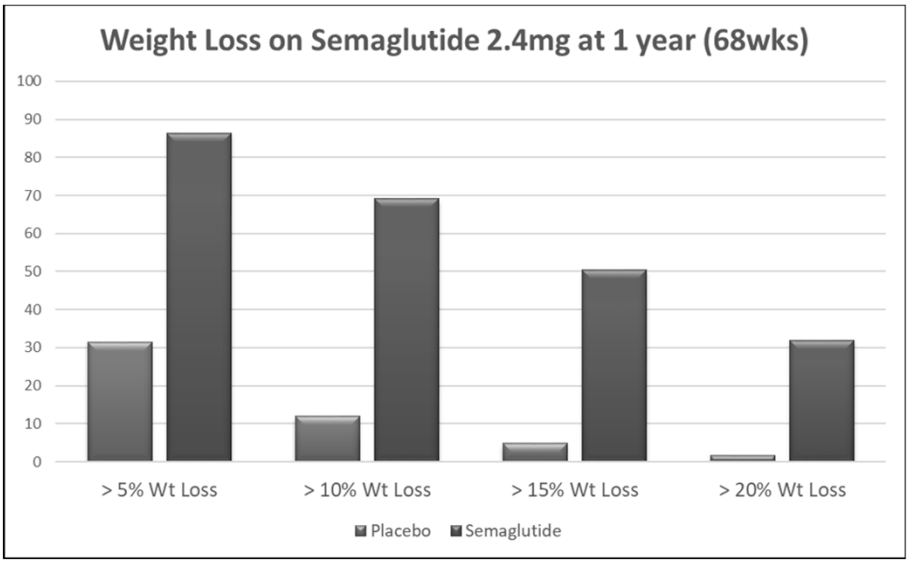
Lancet 2011; 377: 1341–52

Pharmacotherapy Comparison



N Engl J Med 2015;373:11-22.

Pharmacotherapy Comparison



N Engl J Med 2021;384:989-1002.

Endoscopic Therapies Intragastric Balloons

- Approved for use in patients with **BMI 30-40**
- Orbera – in two RCT (66 & 128 enrollees), patients using the IGB for **6 months** achieved weight loss of 14.2% vs. 4.8% in the control (18.2 kg vs 6 kg in the control). In long term follow-up, mean weight regain was about half of the initial weight lost.
- ReShape Duo (dual balloon system) – REDUCE trial enrolled 326 subjects, of those eventually 264 opted for balloon placement. Early retrieval occurred in 9.1%. Those with IGB lost 7.6% vs 3.6% in the control group. Approved for use up to **6 months**.
- Obalon (ingestible) – can place up to 3 balloons prior to removal (**3-6 months** later). Initial study with 17 subjects with a mean BMI of 31 (44 attempted balloons), treated for 12 weeks – lost median 5kg (no control).

Hurt, et al. Novel Nonsurgical Endoscopic Approaches for the Treatment of Obesity. Nutrition in Clinical Practice. Volume 32 Number 4, August 2017 493–501

Bariatric Surgery

- Indicated for BMI ≥ 35kg/m^2 with comorbidities, or ≥ 40kg/m^2
- Highly effective in achieving meaningful and durable weight loss
  - RNY gastric bypass = avg 35-40% wt loss
  - Sleeve gastrectomy = avg 30-35% wt loss
- Swedish Obese Subjects Study reduced the incidence of type 2 diabetes by nearly 80% in subjects who underwent bariatric surgery

N Engl J Med 2012;367:695-704

Bariatric Surgery

- Stampede trial – comparison of diabetes remission rates based on type of surgery vs intensive medical therapy

5 year Outcome	Sleeve Gastrectomy (n=47)	RNY Gastric Bypass (n=49)	Intensive Medical Therapy (n=38)
# of pts with A1C <6% (on no medicine)	11 (23.4%)	14 (28.5%)	2 (5.3%)
A1C change from baseline	-2.1 +/- 2.3% P=0.003	-2.1 +/- 1.8% P=0.003	-0.3 +/-2%
Weight change from baseline (kg)	-18.6 +/- 7.5 P=0.003	-23.2 +/- 9.6 P=0.003	-5.3 +/- 10.8

N Engl J Med 2017;376:641-51

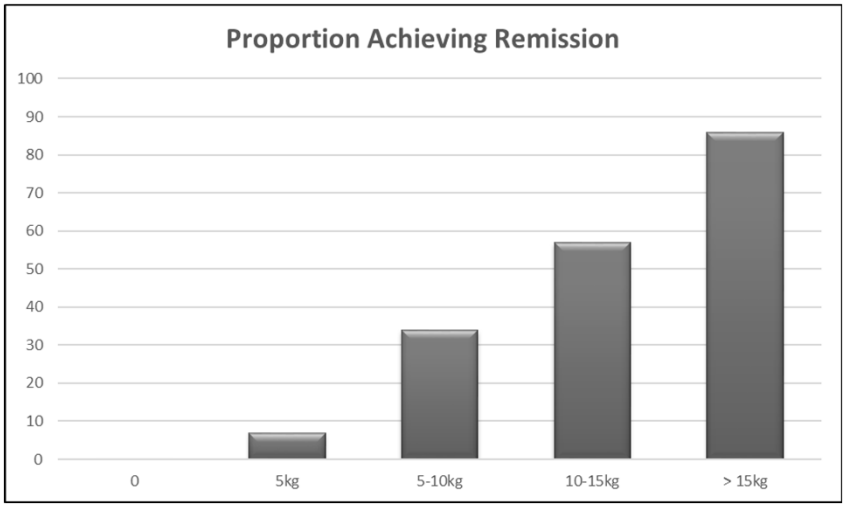
Intensive Lifestyle Therapy

- DiRECT Trial conducted in the UK within primary care offices, roughly 300 participants
- Enrolled patients with known DM2 (essentially MetS by waist circ, SBP, and A1C)
- 3 months of meal replacement (60% carb based, 13% fat, 26% protein) followed by 2-8 weeks of food reintroduction, then monthly visits
- 15,000 step goal after food reintroduction
- Goal of at least 15kg weight reduction and maintenance by majority of participants

Lancet 2018; 391: 541–5

Intensive Lifestyle Therapy

- 24% of participants met the 15kg wt loss goal at 12 months
- 46% had remission of diabetes



Lancet 2018; 391: 541–5

Gut Microbiome

- Emerging area of research – thus far most data provide associations of certain gut bacteria with either favorable (Akkermansia) or unfavorable (Bacteroides) phenotypes
- Short chain fatty acids (SCFAs) are end products of bacterial fermentation, some like butyrate and propionate are associated with less inflammation and reduced appetite
- Short term results of oral supplementation of certain gut bacteria have shown improvements in insulin sensitivity and reductions of insulinemia.

J Clin Invest. 2019;129(10):4050–4057

Conclusions

- Metabolic syndrome is a constellation of findings that increases the risk of development of T2DM and CVD
- Addressing risks by lifestyle modification is essential
- Diet changes to encourage low saturated fats, increased complex carbohydrates, and reducing sodium
- Weight loss goal to achieve 10% TBW, which can include medications, endoscopic, or surgical procedures