

Update on the Metabolic Syndrome

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Disclosure

Advisory Board: Biophytis; Eli Lilly; Keros; Pfizer
Pharmaceuticals; Wave; Zyversa

Consultant: AstraZeneca

Data Safety Monitory Board: Advarra

Research Grant: Amgen; Cleerly; Ionis
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Objectives

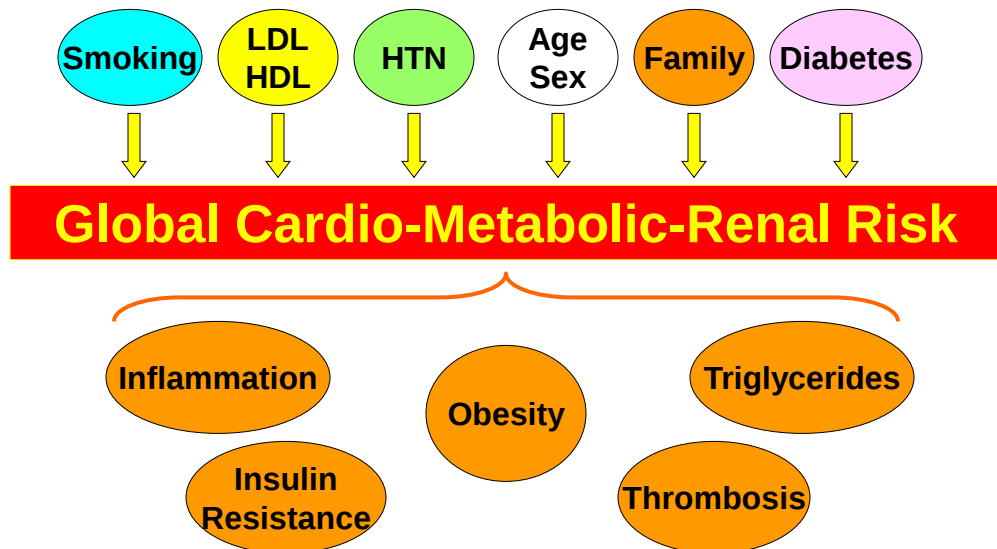
- Define the Metabolic Syndrome and the 'newer' Cardiovascular-Kidney-Metabolic Syndrome
- Examine the impact of the Metabolic Syndrome on disease risk and morbidity
- Review the treatment and management options for patients with the Metabolic Syndrome

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The Metabolic Syndrome: Overview

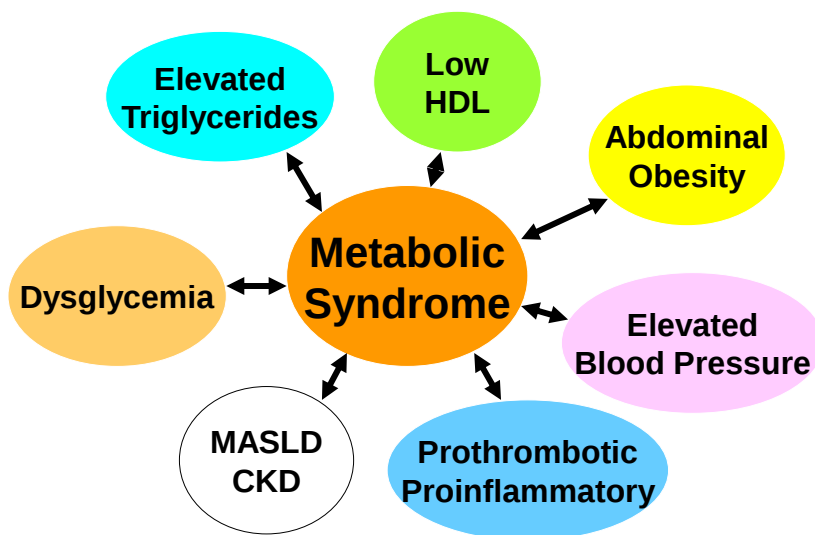
- What is it?
- Why do we care?
- How do we define it?
- How should we manage it?
- Is there a controversy?

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The Metabolic Syndrome: General "Clustering" of Features



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The Metabolic Syndrome: General “Clustering” of Features

- Abdominal obesity
- Atherogenic dyslipidemia
 - Elevated Triglycerides
 - Low HDL-Cholesterol
 - Small dense LDL particles
- Raised blood pressure → HTN
- Insulin resistance → IFG, IGT, GDM, T2DM
- Prothrombotic state
- Proinflammatory state
- Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)
- Others?

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The Metabolic Syndrome: *A Little History*

• HTN-Hyperglycemia-Gout - Kylin	1923
• Insulin Insensitivity – Himsworth	1936
• “Diabetogenic Obesity” – Vague	1947
• “Syndrome X” – Reaven	1988
• WHO - Metabolic Syndrome	1998
• NCEP - Metabolic Syndrome	2001
• Dysmetabolic Syndrome (277.7)	2003
• Metabolic Syndrome “Controversy”	2005
• “Consensus” Definition	2009
• Endocrine Society Guideline	2019
• Cardiovascular-Kidney-Metabolic Syndrome	2023

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AHA Consensus Definition: *The Metabolic Syndrome*

Diagnosis Established When ≥ 3 are Present:

- Elevated Waist Circumference
 - Men: > 40 in (102 cm); Women: > 35 in (88 cm)
 - Population and country specific
- Elevated Triglycerides: ≥ 150 mg/dl*
- Low HDL Cholesterol*
 - Men: < 40 mg/dl
 - Women: < 50 mg/dl
- Elevated Blood Pressure: $\geq 130/85^*$
- Elevated Fasting Glucose: ≥ 100 mg/dl*

Circulation 120:1640-1645, 2009

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Population Specific Waist Circumference Thresholds

Population	Waist Circumference (cm)	
	Men	Women
Caucasian	102	88
Asian	90	80
Middle East	94	80
Sub-Saharan African	94	80
Central/South America	90	80

Circulation 120:1640-1645, 2009

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Patients at Metabolic Risk

Endocrine Society Clinical Practice Guideline

Diagnosis Established When 3 or more are Present:

- Elevated Waist Circumference
 - Men: > 40 in (103 cm); Women: > 35 in (88 cm)
 - Population and country specific
- Elevated Triglycerides: ≥ 150 mg/dl*
- Low HDL Cholesterol*
 - Men: < 40 mg/dl
 - Women: < 50 mg/dl
- Elevated Blood Pressure: $\geq 130/85$ *
- **Elevated Glycemia:**
 - Fasting Glucose: ≥ 100 mg/dl*
 - 2-hr OGTT: ≥ 140 mg/dl*
 - HbA1c: $\geq 5.7\%$ *

JCEM 104:3939–3985, 2019

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Cardiovascular-Kidney-Metabolic Syndrome

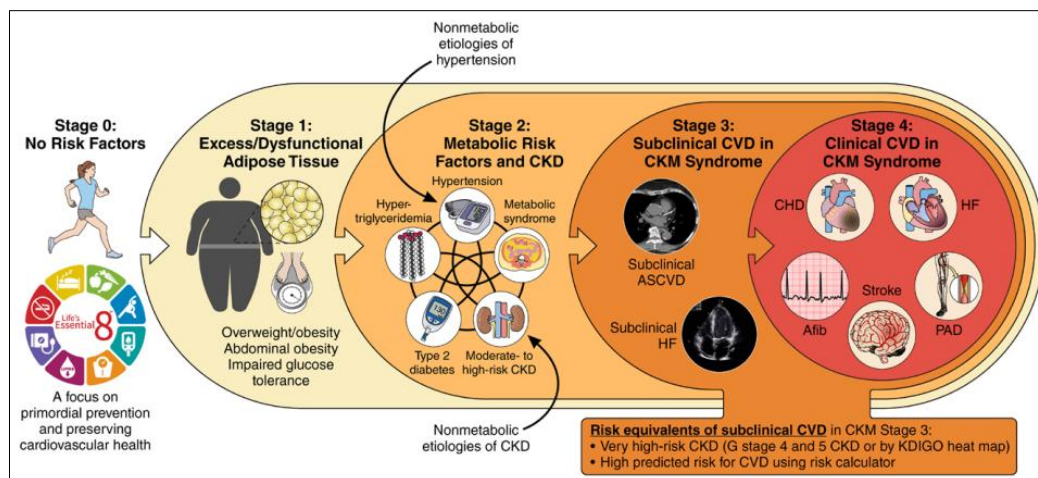
AHA Presidential Advisory and Scientific Statement

Circulation 148:1606–1635, 2023
Circulation 148:1636–1664, 2023

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Cardiovascular-Kidney-Metabolic Syndrome

AHA Presidential Advisory and Scientific Statement



Circulation 148:1606–1635, 2023
Circulation 148:1636–1664, 2023

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Definition of CKM Syndrome Stages

CKM Stage	Definition
Stage 0	No CKM risk factors
Stage 1	Excess or Dysfunctional Adiposity: - BMI ≥ 25 kg/m² (or ≥ 23 kg/m² if Asian ancestry), - WC $\geq 88/102$ cm in women/men (or if Asian ancestry $\geq 80/90$ cm in women/men) - Fasting Blood Glucose ≥ 100-123 mg/dL or HbA1c 5.7-6.4%
Stage 2	Metabolic Risk Factors and CKD: - Hypertriglyceridemia (≥ 135 mg/dL) - Hypertension (stages 1 and 2) - Metabolic Syndrome - Diabetes - CKD
Stage 3	Subclinical CVD in CKM: - Subclinical ASCVD (coronary artery calcification or by angiography) - Subclinical HF (NT-proBNP ≥ 125 pg/mL, hs-troponin I ≥ 14 ng/L for women and ≥ 12 for men) or by echocardiographic parameters - Risk equivalents (high risk by KDIGO classification or high 10-y CVD risk)
Stage 4	Clinical CVD in CKM - Stage 4a: no kidney failure - Stage 4b: kidney failure present

Circulation 148:1606–1635, 2023
Circulation 148:1636–1664, 2023

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Problems with These Definitions

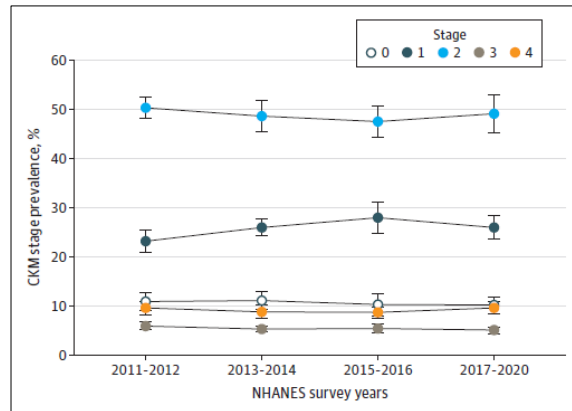
- Should all factors be given the same weight?
- Thresholds are ill-defined
- Who measures waist circumference?
- Are the cutoffs for “prediabetes” sensitive enough – should we be identifying “insulin resistance” before hyperglycemia occurs?
- Is the CVD risk of the syndrome greater than the sum of its parts?
- Treatment of the “*syndrome*” no different than treatment of components

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So, Why Should We Care About
The Metabolic Syndrome?

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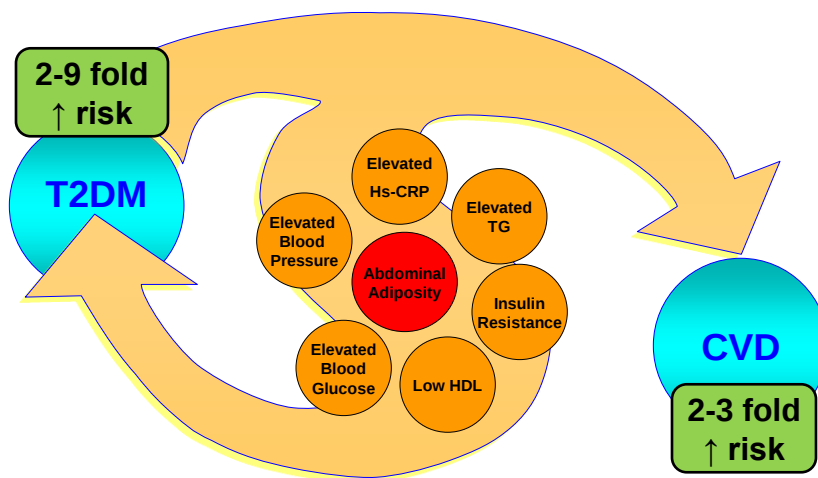
Prevalence of the Cardiovascular-Kidney-Metabolic Syndrome in US Adults



JAMA 331:1858–1860, 2024

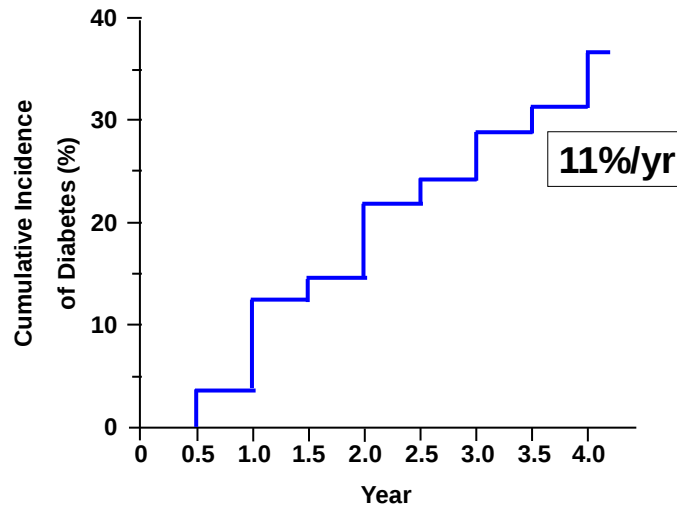
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Abdominal Adiposity as a Component of Cardiometabolic Risk



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Diabetes Prevention Program Progression to Diabetes



N Engl J Med 2002;346:393-403.

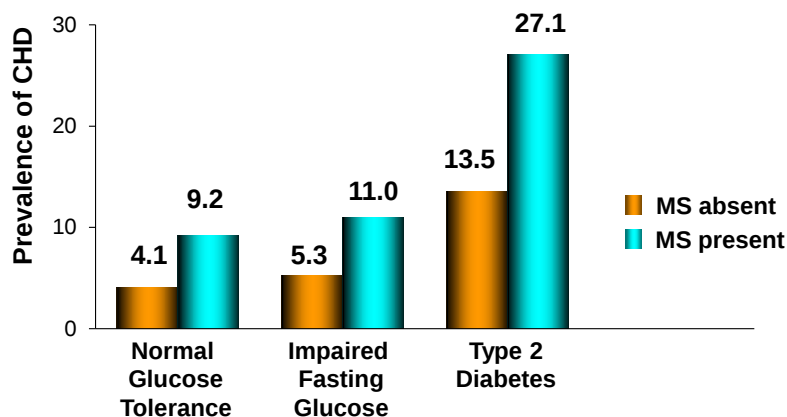
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The Metabolic Syndrome Type 2 Diabetes Incidence

- | | | |
|------------|----------------------|-----------------------------------|
| • 3-fold | Kokalainen P et al | <i>Diabetes Care</i> , 1999 |
| • 4-fold | Park PJ et al | <i>Diabetes Care</i> , 2002 |
| • 2,3-fold | Hanson RL et al | <i>Diabetes</i> , 2002 |
| • 5,9-fold | Laaksonen DE et al | <i>Am J Epid</i> , 2002 |
| • 3-fold | Lorenzo C et al | <i>Diabetes Care</i> , 2003 |
| • 6-fold | Nakanishi N et al | <i>Diab Res Clin Pract</i> , 2004 |
| • 2,4-fold | Wang JJ et al | <i>Horm Metab Res</i> , 2004 |
| • 6-fold | Wilson PW et al | <i>Circulation</i> , 2005 |
| • 2,3-fold | Wannamethee SG et al | <i>Arch Int Med</i> , 2005 |
| • 2,3-fold | Wang JJ et al | <i>Atherosclerosis</i> , 2006 |
| • 4-fold | Meigs JB et al | <i>JCEM</i> , 2006 |
| • 6,7-fold | Lorenzo C et al | <i>Diabetes Care</i> , 2007 |

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Association of the Metabolic Syndrome with CHD

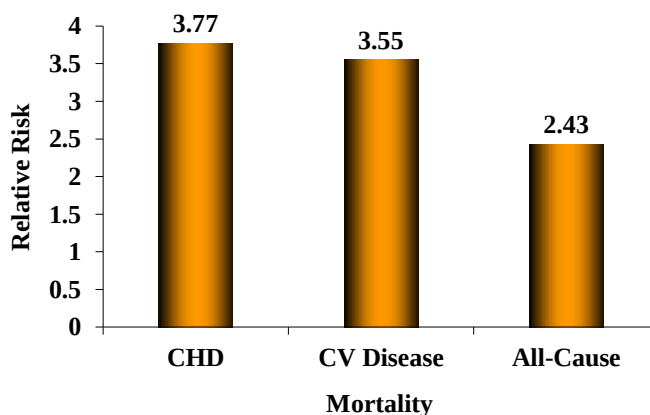


Diabetes Care 24:683, 2001

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Metabolic Syndrome and CVD Mortality

Middle-Aged Men – Median Follow Up 11.6 y



JAMA 288:2709, 2002

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The Metabolic Syndrome Other Associated Conditions

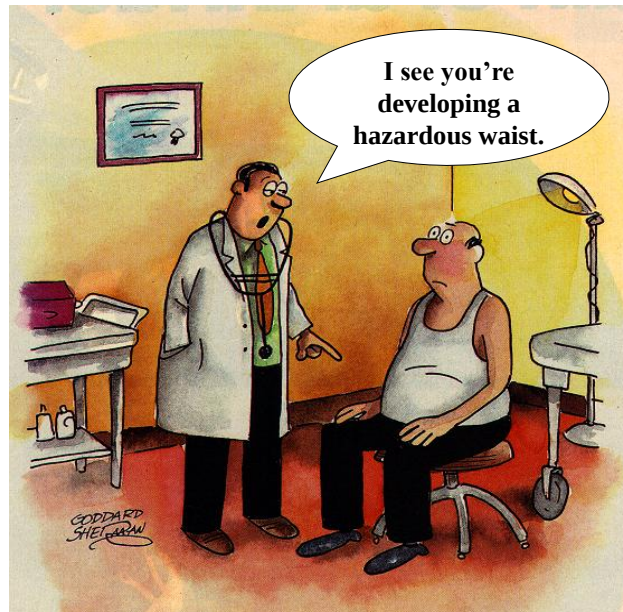
- Metabolic Associated Steatotic Liver Disease
- Sleep Disorders: Obstructive Sleep Apnea
- PCOS, adverse pregnancy outcomes
- Hypogonadism
- Lipodystrophies
- Microvascular Disease
- Chronic inflammatory conditions
- Others

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Is There a Unifying Pathophysiologic Cause of the Metabolic Syndrome?

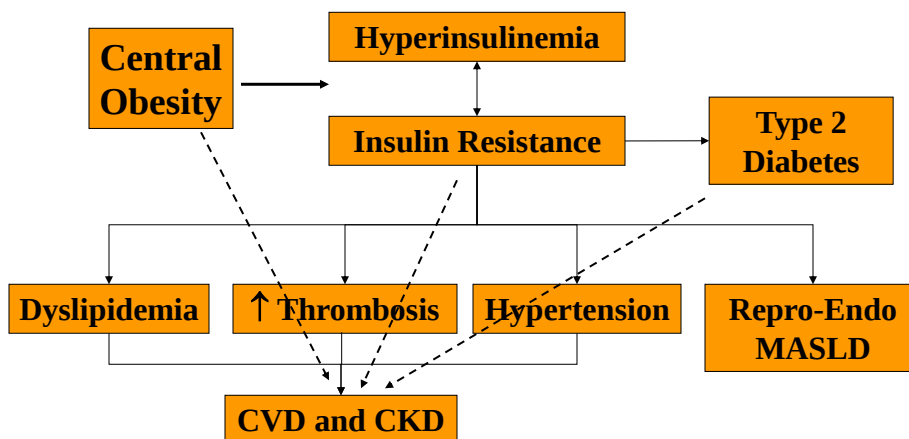
- Maybe – Maybe Not
- Abdominal adiposity and Insulin Resistance appear to be at core of pathophysiology of the Metabolic Syndrome AND its individual components

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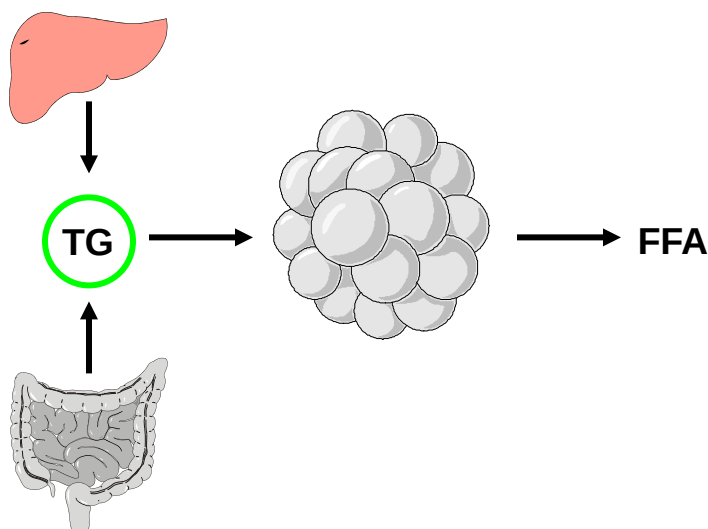
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The Consequences of the Metabolic Syndrome



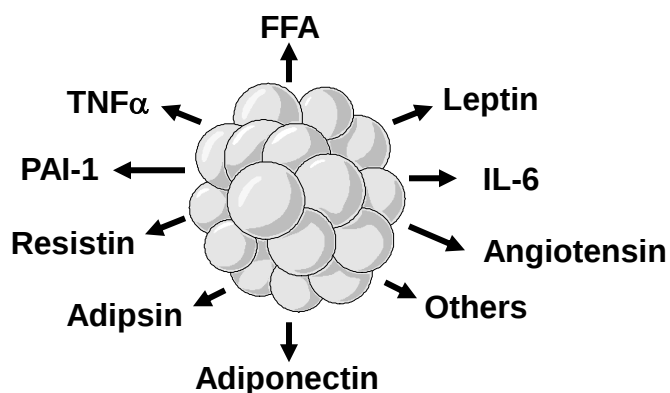
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Adipose Tissue: Storage Function



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Adipose Tissue: Secretory Function

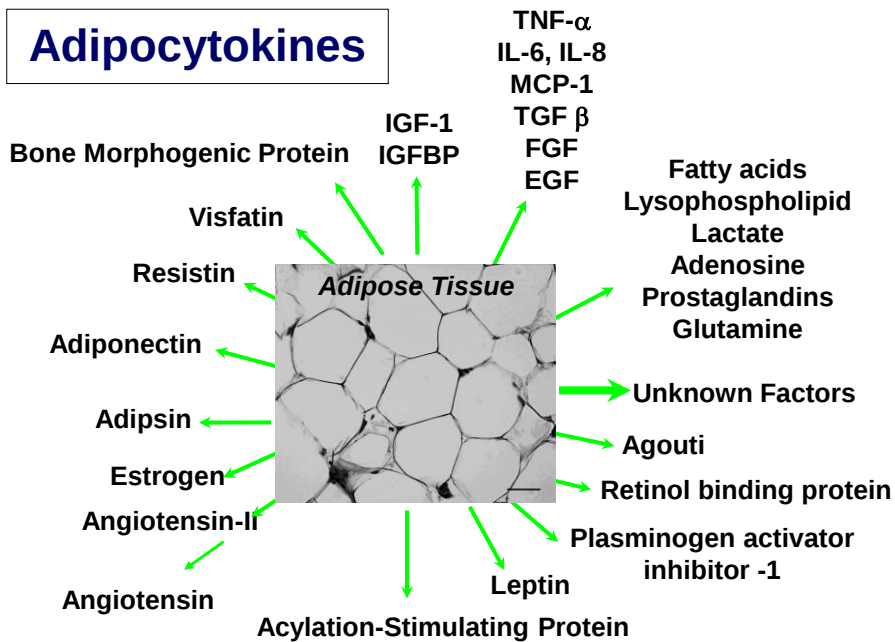


Adipo- or Lipocytokines

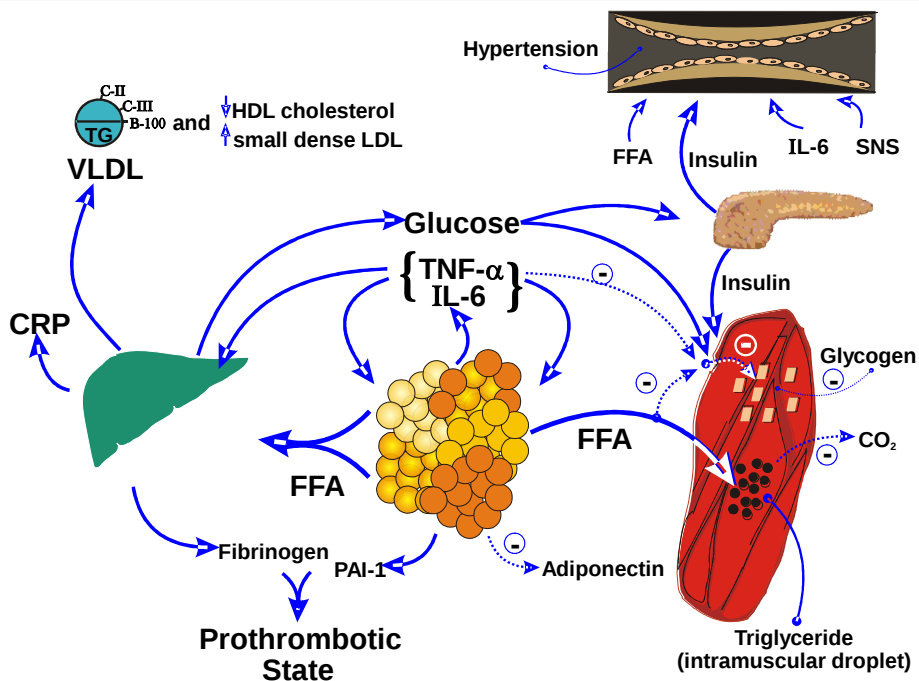
Pittas et al, *J Clin Endocrinol Metab* 2004; 89:447-52

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Adipocytokines



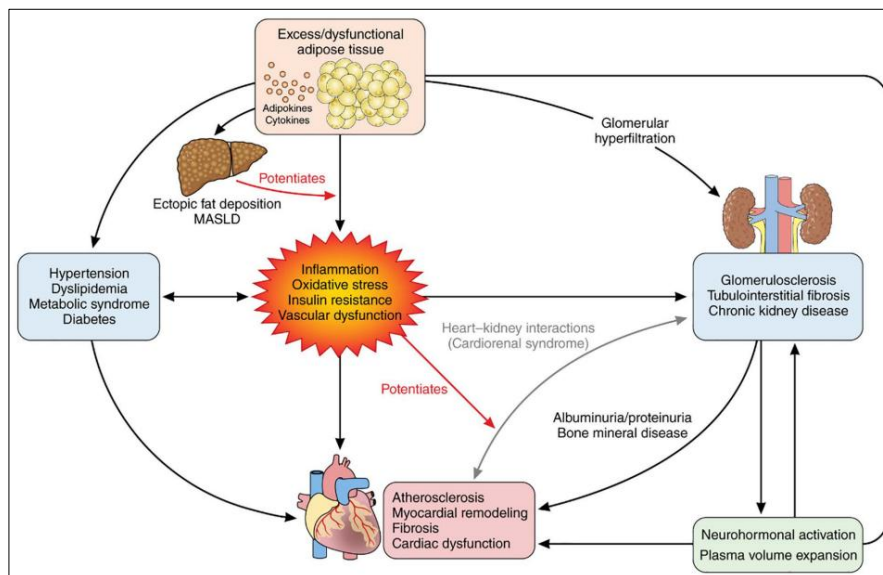
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Eckel et al, *Lancet*, 2005

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Pathophysiology Underlying the CKM Syndrome



Circulation 148:1606–1635, 2023
Circulation 148:1636–1664, 2023

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Visceral Adiposity, Insulin Resistance and the Metabolic Syndrome

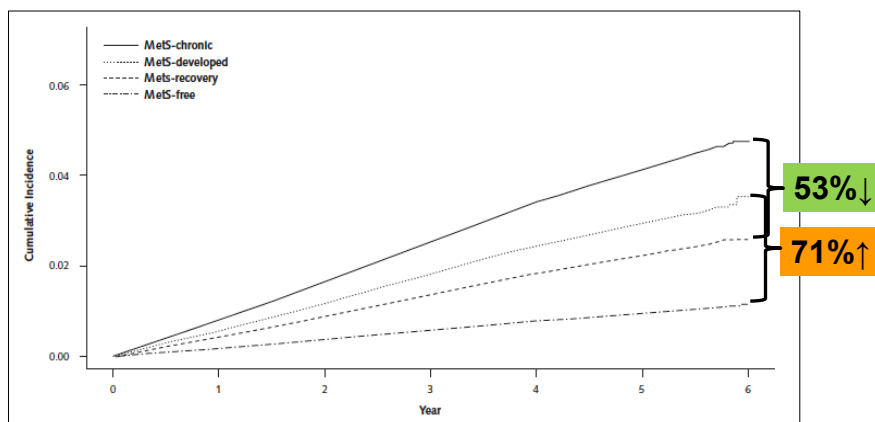
- Insulin resistance may or may not be unifying pathophysiologic cause of the Metabolic Syndrome
- Nevertheless, targeting visceral adiposity and insulin resistance should be central to the management of the Metabolic Syndrome patient
- All of the components of the Metabolic Syndrome improved when adiposity and insulin resistance are targeted

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Clinical Management of The Metabolic Syndrome

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Altered Risk for CV Events with Changes in the Metabolic Syndrome Status

Park et al. *Annals Int Med* 2019

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Who Should We Screen?

- If one feature is present, look for the others!
- Start screening in everyone even in early life
- Screen everyone with overweight and obesity
- Look for *the pattern*
- Pay attention to social determinants of health

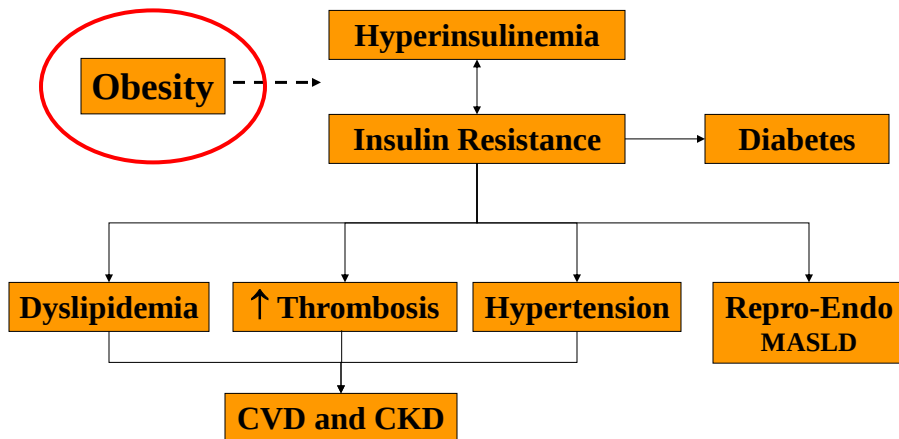
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The Metabolic Syndrome: How Should We Screen?

- Vital signs
 - Body Weight and Height – BMI
 - Waist Circumference
 - Blood Pressure
- Lab work:
 - Fasting Lipid Panel
 - Glycemia: FPG vs OGTT vs HbA1c
 - Complete Metabolic Panel: ALT/AST, creatinine
 - CBC: platelet count
 - Urine: albumin to creatinine ratio
- Other:
 - Coronary Artery Calcium
 - Echocardiogram and/or cardiac biomarkers
 - FIB-4 index

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The Metabolic Syndrome: Treatment Goals



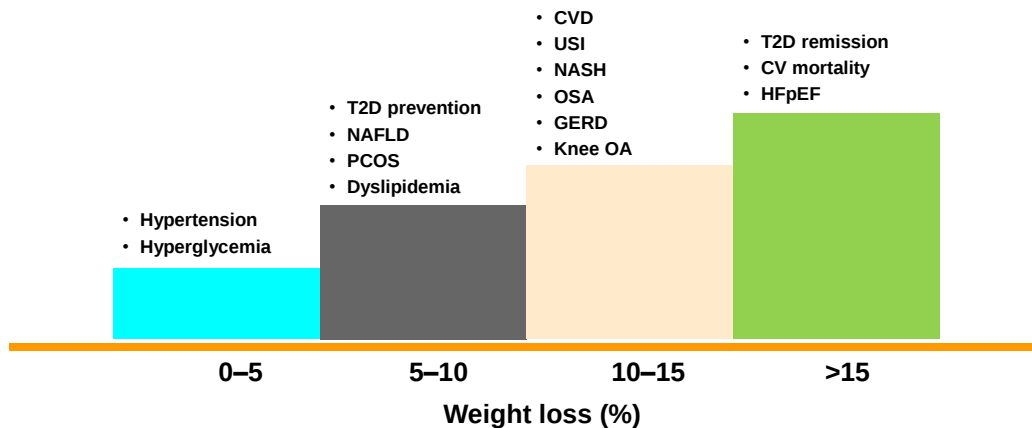
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Weight Loss Interventions: Guide to Selecting Treatment

Treatment	BMI				
	25-26.9	27-29.9	30-35	35-40	>40
Diet, Exercise	+	+	+	+	+
Pharmacology		w/ co-morbidities	+	+	+
Surgery				w/ co-morbidities	+

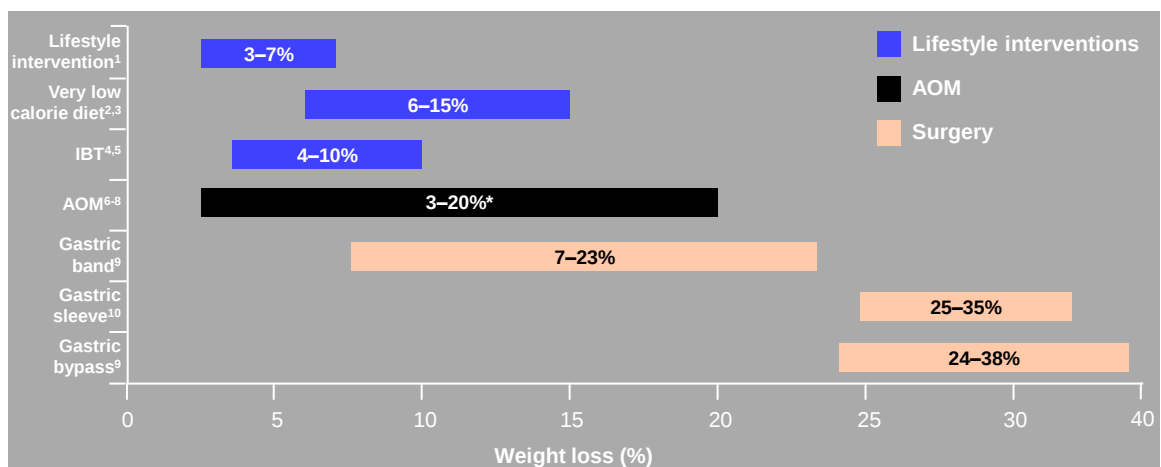
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Greater Weight Loss Improves More Obesity-Related Complications



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Efficacy of Existing Weight Loss Interventions



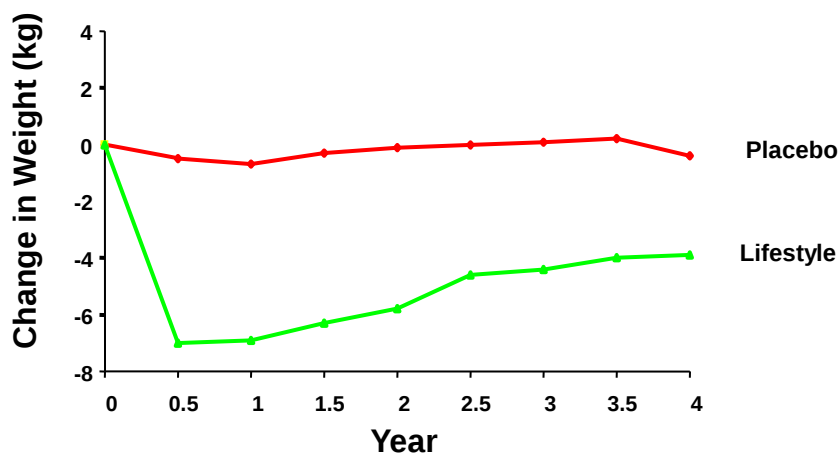
*Based on mean weight loss achieved by the completer populations in the largest phase 3 clinical trial of each respective product's clinical development program as reported in the AACE Guidelines (2016).

AACE, American Association of Clinical Endocrinology; AOM, anti-obesity medications; IBT, intensive behavioral therapy.

1. le Roux CW et al. Lancet 2017;389:1399-409; 2. Lean ME et al. Lancet 2018;391:541-51; 3. Tsai AG and Wadden TA. Obesity 2006;14:1283-93; 4. Wadden TA et al. Obesity 2011;19:1987-98; 5. Wadden TA et al. Obesity 2019;27:75-86; 6. Garvey WT et al. Endocr Pract 2016;22(Suppl 3):1-203; 7. Tak YJ and Lee SY. Curr Obes Rep 2021;10:14-30; 8. 10. Novo Nordisk. Wegovy (semaglutide). Package Insert. Available at: <https://www.novo-pl.com/wegovy.pdf>. Accessed August 2022; 9. Courcoulas AP et al. JAMA 2013;310:2416-25; 10. IFSO Sleeve Gastrectomy. Available at: <https://ifso.com/patient-sleeve-gastrectomy/>. Accessed August 2022;

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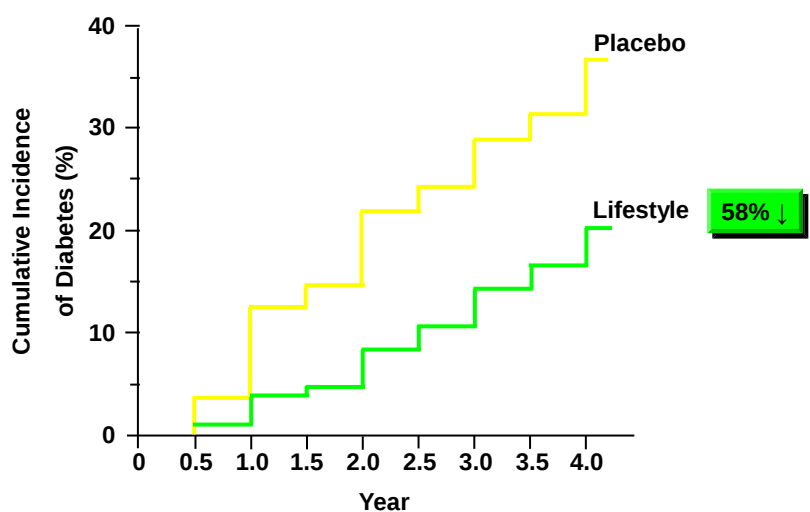
Diabetes Prevention Program



Knowler et al. N Engl J Med 2002;346:393-403.

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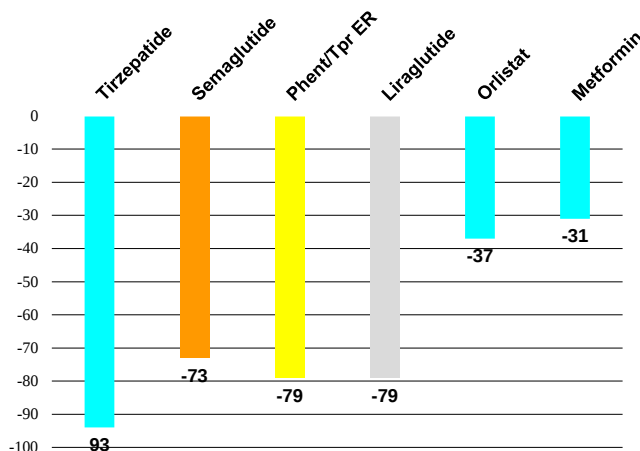
Diabetes Prevention Program



Knowler et al. N Engl J Med 2002;346:393-403.

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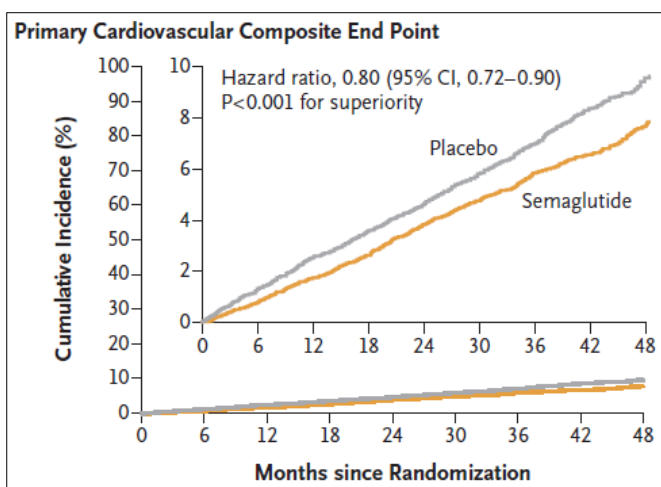
Incidence of Diabetes with Obesity Medication Induced Weight Loss



Lincoff et al. NEJM 2023; Garvey et al. Diabetes Care 2014; Le Roux et al. Lancet 2017; Torgerson et al. Diabetes Care 2004; Knowler et al. N Engl J Med 2002; Jasterboff et al. NEJM 2024.

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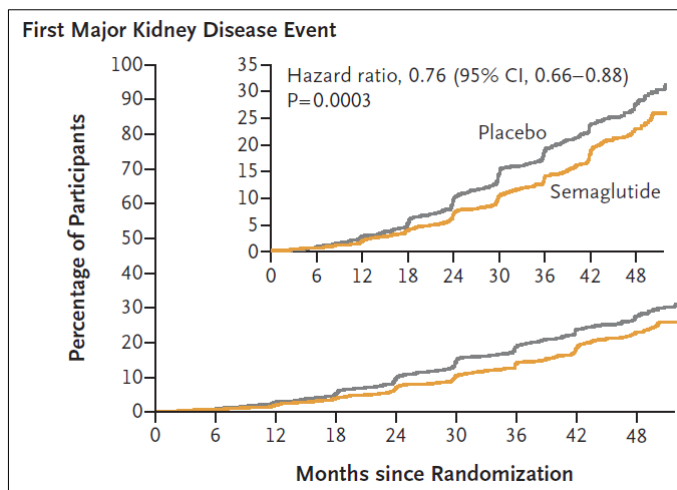
SELECT Trial: Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes



Lincoff et al. NEJM 2023.

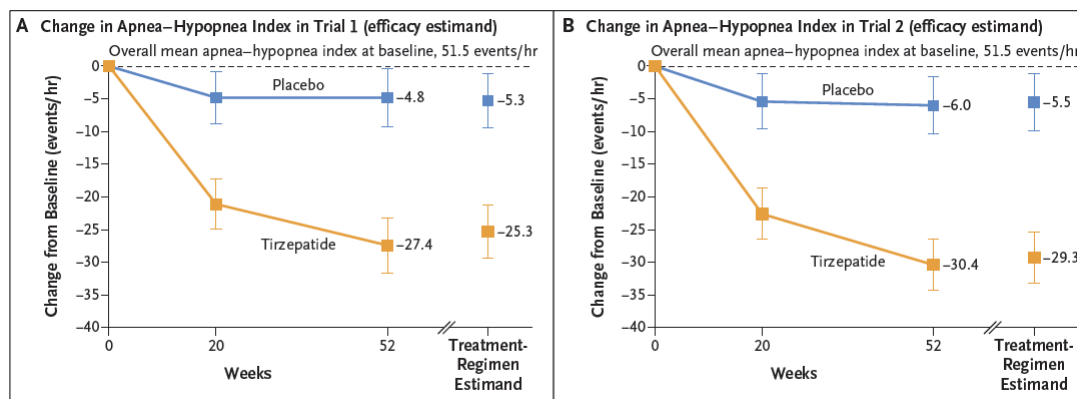
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FLOW Trial: Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Perkovic et al. *NEJM* 2024.

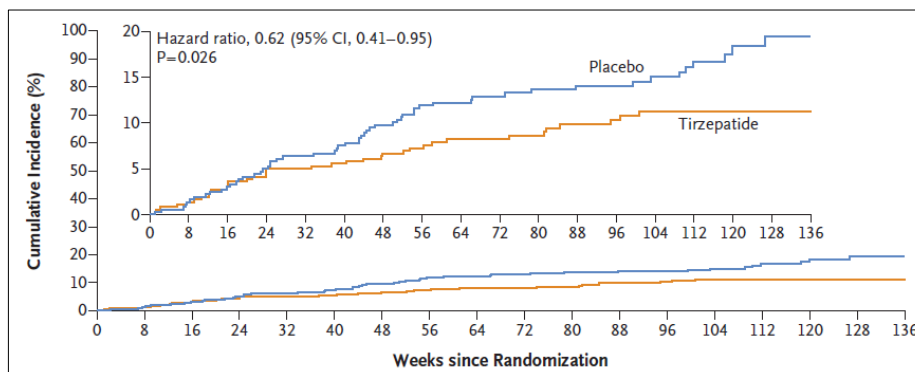
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SURMOUNT-OSA Trial: Tirzepatide for the Treatment of OSA and Obesity

Malhotra et al. *New Engl J Med*. 2024.

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SUMMIT Trial: Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity



Packer et al. *New Engl J Med.* 2024.

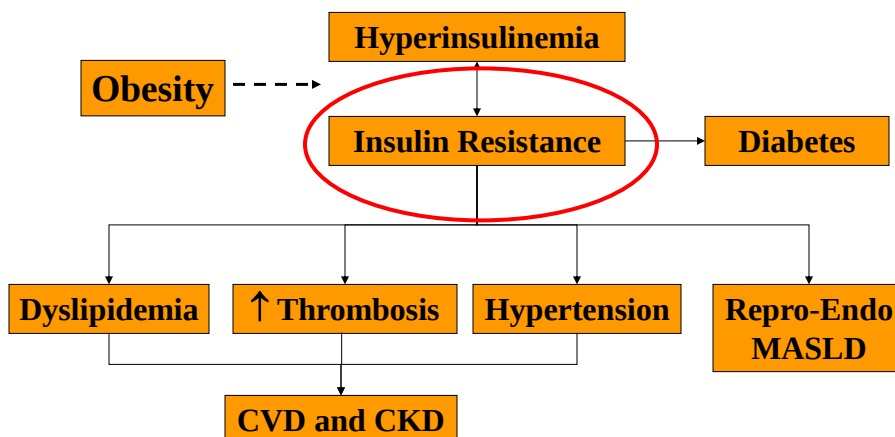
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“Treating” Abdominal Adiposity

- Diet:
 - Hypocaloric diet and weight loss improve insulin sensitivity
 - No best or ideal diet
 - Inexpensive and effective
 - But will it happen?
- Physical Activity
 - ↓ visceral adiposity
 - Improves insulin sensitivity
 - ↑ Fitness → ↓ CVD, diabetes, and Mortality
- Weight Loss Pharmacotherapy – Obesity Medications
 - Effective!
 - Lack of “buy in” by providers and patients?
 - Cost?
- Metabolic-Bariatric Surgery

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The Metabolic Syndrome: Treatment Goals



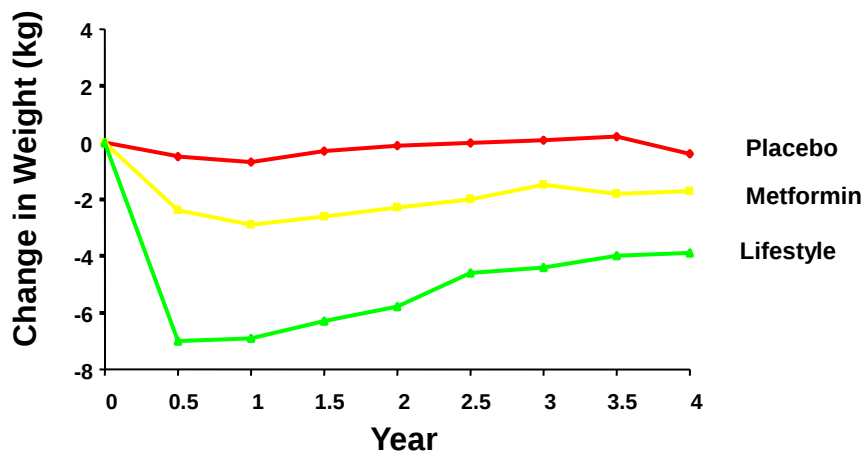
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“Treating” Insulin Resistance

- Weight loss
 - Lifestyle
 - Obesity Medications
 - Metabolic Surgery
- Diet
- Physical Activity
- Pharmacotherapy – Insulin Sensitizers
- What are the goals?

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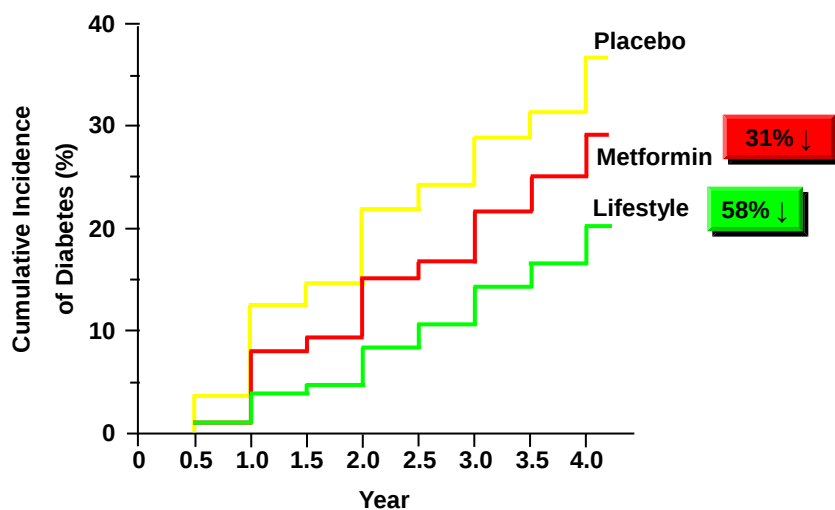
Diabetes Prevention Program



Knowler et al. N Engl J Med 2002;346:393-403.

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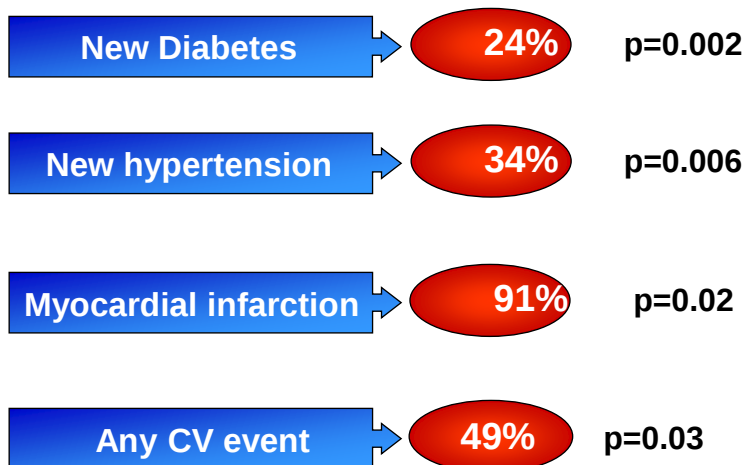
Diabetes Prevention Program



Knowler et al. N Engl J Med 2002;346:393-403.

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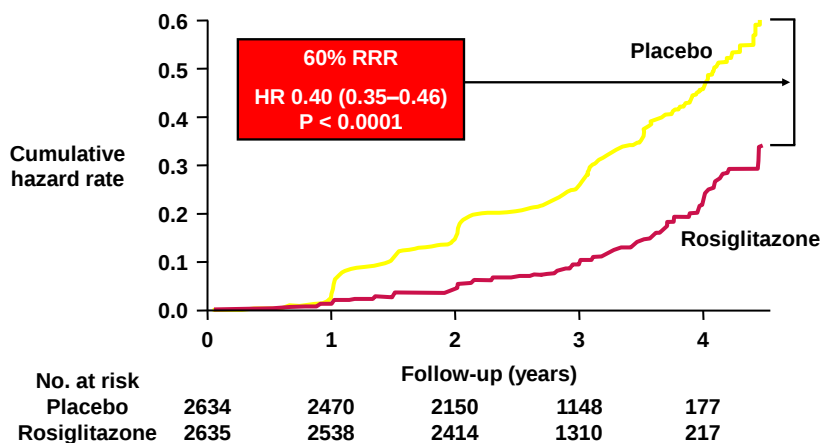
STOP NIDDM: Risk Reduction with Acarbose



Chiasson JL et al. JAMA 2003;290:486–94.

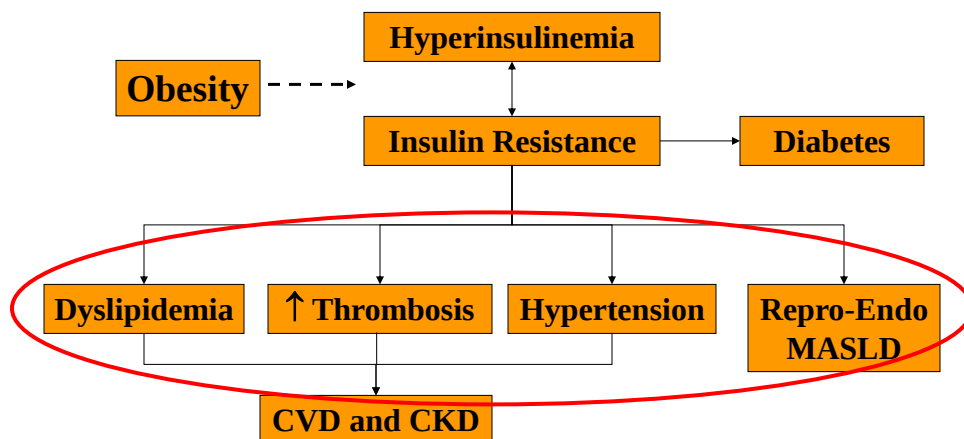
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DREAM Study: The Effects of Rosiglitazone on Diabetes Progression



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The Metabolic Syndrome: Treatment Goals



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Treating the Comorbidities

- Dyslipidemia:
 - Primary goal should be LDL-C lowering (statin therapy)
 - Secondary goals should be Non-HDL-C lowering or TG lowering
- Elevated BP:
 - ACE inhibitors or ARBs should be first line?
- Diabetes:
 - consider SGLT2i and GLP-1 RA
- CKD: consider SGLT2i and GLP-1 RA and ACEi/ARB
- MASLD/MASH:
 - weight loss
 - Consider TZD, GLP-1 +/- GIP RA, SGLT2i, Resmetirom
- Pro-Thrombotic State
- Others?

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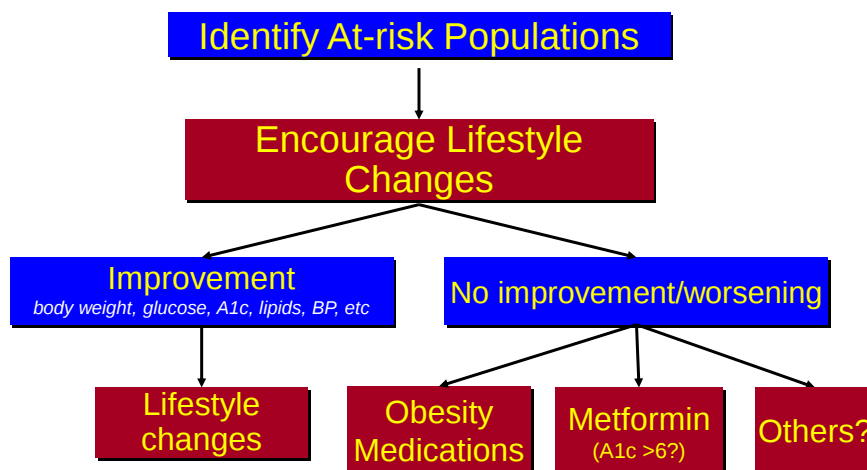
The Metabolic Syndrome: Treatment

- No 'right answer'
- Lifestyle Modification: diet and exercise
 - Minimal risk, relatively low cost, proven efficacy
 - Preferred approach especially in low-risk individuals?
- Pharmacologic Therapy
 - Be clear in your own mind about what you are treating
 - Obesity: obesity medications
 - Insulin resistance: metformin, TZD, obesity medications
 - Dyslipidemia: statins, fibrates, fish oil?
 - Hypertension: ACEi, ARB
 - Diabetes: GLP-1 RA, SGT2i, TZD
 - Hypercoagulable State: aspirin?
 - Others?

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So, What Should We Do?

Proposed Clinical Approach



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Case

- AC is a 57-year-old woman with a history of hypertension, hyperlipidemia and prediabetes. She gained weight especially in her 'mid-section' after she went through menopause at age 49. She has tried watching her diet and being more active but has not lost much weight. She wonders if her health problems are related to each other and how these might be impacting her risk for other health issues.
- She is currently on lisinopril, estradiol patch (s/p hysterectomy), atorvastatin
- Family History: mother has diabetes and father died after a heart attack in his late 60's.
- She tries to eat a Mediterranean style diet, walks her dog ~30 min daily
- Her BMI is currently up to 32.4 kg/m²
- Labs are notable for: A1c 6.0%, TG 230, HDL 38, LDL 96, Cr 0.8, AST 28



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Which of the Following Are True Regarding Her Health Issues?

- A. Her current medical problems are unrelated and should be treated as separate diseases.
- B. Weight gain and obesity are likely contributing to the cause of and/or worsening her health issues.
- C. Weight loss through lifestyle change is not likely to be sustainable and is not associated with clinical benefits such as preventing the progression to diabetes or improvements in cardiovascular risk
- D. Obesity medications are not indicated and would not likely lead to long-term health benefits.
- E. Statins cause diabetes and should not be used in patients with pre-diabetes, as such a fibrate would be a better treatment option for her hyperlipidemia.

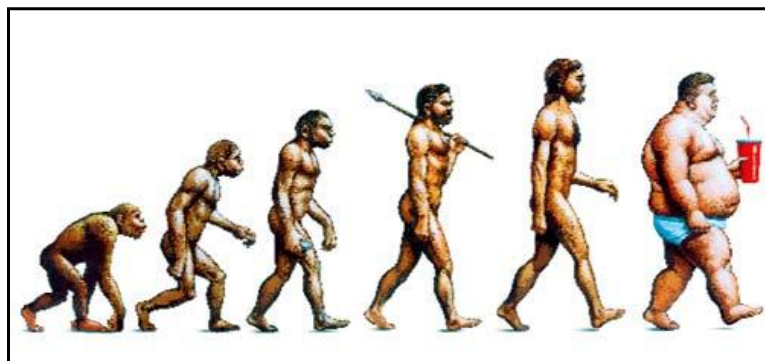


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Which of the Following Would You Recommend as the Best Next Treatment Option for This Patient?

- A. Counsel on lifestyle changes and behavior modification with an initial goal of 5-10% weight loss.
- B. Consider starting her on an obesity medication.
- C. Consider adding metformin for her pre-diabetes.
- D. Screen her for CKD and MASLD.
- E. All of the above

The Metabolic Syndrome



An Evolutionary Process?