Rethinking Metabolic Syndrome

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Disclosures

- None

Educational Objectives

- Have a better understanding of the common underlying mechanisms of CKM Syndrome and their multisystem manifestations
- Describe the individual features and manifestation of specific end organ involvement in CKM
- Be able to classify at risk patients for CKM Syndrome and list risk factors
- Understand and apply evidence based treatment and early intervention to prevent or attenuate the systemic damage

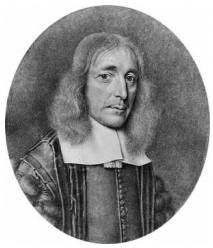
Suggested Readings

- Chiadi E. Ndumele. Circulation. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association, Volume: 148, Issue: 20, Pages: 1606-1635, DOI: (10.1161/CIR.0000000000001184)
- 2023 ADA Standards: Volume 46 Issue Supplement_1 | Diabetes Care | American Diabetes Association (diabetesjournals.org)
- Winkelmayer_KDIGO-Arrhythmia-NKF-NOLA-2020.pdf
- Blood Pressure in CKD – KDIGO
- Diabetes in CKD – KDIGO

History of Diabetes Mellitus

- Hesy-Ra ~1,552 B.C.E.
- 1st described treatments for the "passage of too much urine" which attracted ants and was linked to a state of progressive emaciation ants
- First link of kidney to diabetes

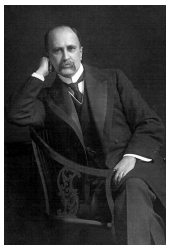
Thomas Willis 1621-1675



- Best know for his brain anatomical work-Circle of Willis
- First to number the cranial nerves (much to the chagrin of 1st year med students)
- Willis 1st used the term *diabetes mellitus,* which he associated with melancholy (depression)
  - Willis's disease is an archaic term for DM

Sir William Osler 1848-1919

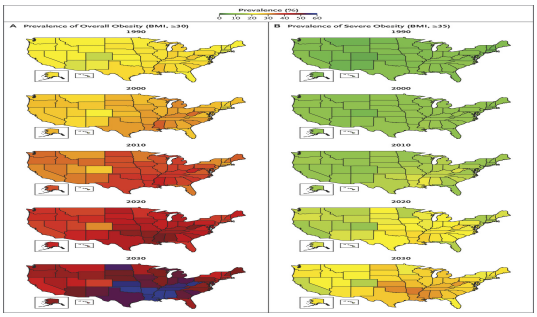
- The platter kills more than the sword



Typical Inpatient Problem circa 1979: 10 Plus Conditions

- 1. Obesity
- 2. Type-DM
  - Retinopathy, peripheral neuropathy, kidney disease
- 3. Hypertension
  - Hypertensive kidney and heart disease
- 4. Hyperlipidemia
- 5. Obstructive sleep apnea
- 6. Cerebral vascular disease
  - Hx TIA, stroke
- 7. Coronary heart disease
  - s/p MI
- 8. Peripheral vascular disease
  - s/p below the knee amputation
  - Foot ulcer
- 9. Chronic kidney disease
  - Secondary to DM and HTN
- 10. Congestive heart failure

Estimated Prevalence of Overall Obesity and Severe Obesity by State 1990-2023



ZJ Ward et al. *N Engl J Med* 2019;381:2440-2450

Presidential Advisory Cardiovascular-Kidney Metabolic Syndrome (CKM)


Circulation

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Home > Circulation > Ahead of Print > Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association

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REVIEW ARTICLE

Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association

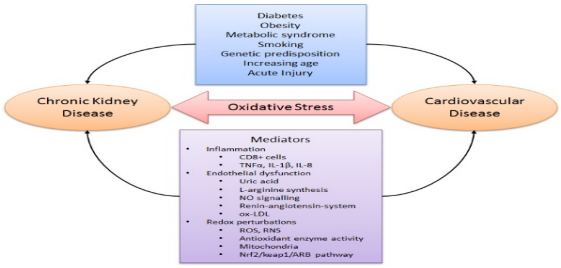
Significance: The first comprehensive incorporation of risk factors, staging, and interventions which include addressing the Social Determinants of Health (SODH). The treatment recommendations are evidence based and incorporate current guidelines from multiple societies.

Definition

- CKM syndrome is a systemic disorder characterized by pathophysiological interactions among metabolic risk factors, CKD, and the cardiovascular system leading to multiorgan dysfunction and a high rate of adverse cardiovascular outcomes.
- CKM syndrome includes both individuals at risk for CVD due to the presence of metabolic risk factors, CKD, or both and individuals with existing CVD that is potentially related to or complicates metabolic risk factors or CKD.
- Encompassing multisystem metabolic derangement leading to generation of neuroendocrine and inflammatory mediators leading to endothelial damage.
- Instead of 10 individual conditions; 1 condition with multiple manifestations

- *Circulation.* 2023;148:4.

Kidney Disease = Cardiovascular Disease



Pathophysiology of Metabolic Syndrome/T2DM
Alteration of Multiple Neuroendocrine Systems
A Perfect Storm of Genetics and Environment

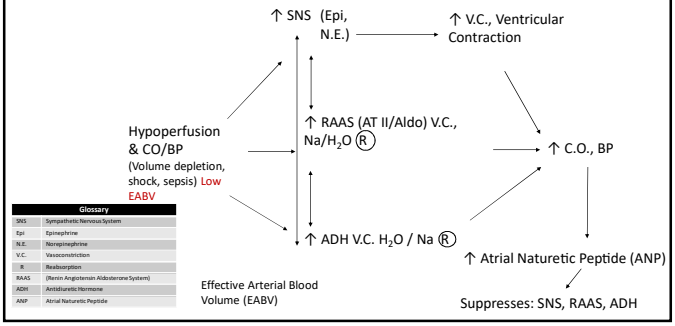
Neuroendocrine mediators

- Renin-angiotensin-aldosterone
- Insulin-glucose-glucagon-cortisol-growth hormone
- Catecholamines
- Glucocorticoids
- Endothelin-1
- Growth hormone
- Endocannabinoids
- Low level of adiponectin

Inflammatory Mediators

- Adipokines
- Leptin
- IL-6
- TNF-α
- Monocyte chemoattractant protein-1 (MCP-1)
- Resistin

How the Body Responds to Volume Depletion & Metabolic Syndrome



Glossary	
SNS	Sympathetic Nervous System
Epi	Epinephrine
N.E.	Norepinephrine
V.C.	Vasoconstriction
R	Reabsorption
RAAS	(Renin Angiotensin Aldosterone System)
ADH	Antidiuretic Hormone
ANP	Atrial Naturetic Peptide

White Adipose Tissue As an Endocrine Organ

- **Adipose tissue** is a source of **inflammatory mediators** leading to **insulin resistance (IR)** and other features of **metabolic syndrome**
- Increased adipose tissue outstrips vasculature leading to local tissue **hypoxia** with **subsequent inflammation** and **angiogenesis**
- The **net effect** is **ACCELERATED** arthrosclerosis and increased **CV risk**

British J Nutrition. 2004;92:347

Insulin Resistance (IR)

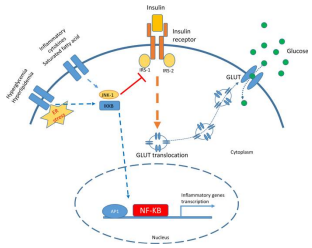
- **Definition**:
  - **Inability** of **insulin** levels (endogenous or exogenous) to increase **glucose uptake**, **metabolism**, and **utilization** by muscle, adipose, and liver tissues
- **Types of IR**:
  - Pre-receptor
  - Receptor
  - Post-receptor
  - Defective insulin signaling:
    - Decrease GLUT-4 receptor

Insulin Resistance (IR)

- **Acquired**:
  - Excess dysfunctional adipose tissues*
  - Physical inactivity
  - Nutritional imbalance, irregular eating/fructose
  - Aging
  - High sodium diets
  - Glucotoxicity (end organ)
  - Lipotoxicity
  - Medications
- **Genetic**:
  - Myotonic dystrophy
  - PCOS
  - Type A insulin resistance
  - Ataxia-telangiectasia
  - Alstom syndrome
  - Rabson-Mendenhall syndrome
  - Werner syndrome
  - Lipodystrophy

* Most common cause

Inflammation and Insulin Resistance



Type 2 Diabetes and its Impact on the Immune System - PMC (nih.gov)

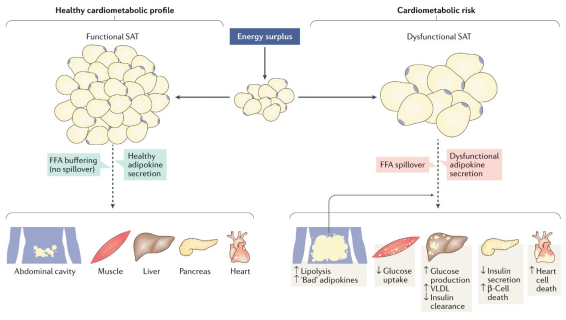
Lipotoxicty

- **Excess/ dysfunctional adipose tissue** secrete **proinflammatory** and **prooxidative factors** and **neuroendocrine mediators** that **promote injury** to **endothelial, cardiac, renal, and hepatic tissues**. These factors also **decrease sensitivity** to the actions of **insulin** leading to **impaired glucose tolerance**

Lipotoxicity

- **Dysfunctional adipose tissue/lipotoxicity**:
  - **Excess dietary glucose/fructose** induced **de novo lipogenesis***
    - Truncal obesity
    - Fatty infiltration of liver, mesentery, heart, liver, etc.
    - NAFLD/MAFLD
  - **Fatty acid induced IR**:
    - De novo lipogenesis
  - **Lipid deposition** in **muscle** tissues (all **3** types)
  - **Lipo**-and **glucotoxicity** induced **inflammation**:
    - Promotes insulin resistance
  - **Low grade SIRS**:
    - Elevated CRP, Il-6, TNF, etc.

*Schwartz JM, Clearfield M, Mulligan K, *J Osteopathic Medicine* 2017;117:520-527



Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol* **16**, 177–189 (2020). https://doi.org/10.1038/s41574-019-0310-7

Glucotoxicity

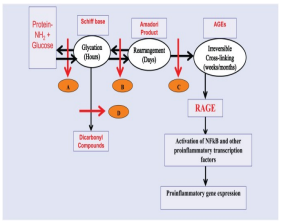
- **Definition**:
  - Impaired β-cell function/response during states of elevated glucose
  - Mitochondrial stress
  - Advanced glycosylated end-products (AGEs)
  - End organ damage

Effects of Chronically Elevated Glucose Levels

- **Long term effects**:
  - Worsening insulin resistance **IR**
  - Inflammation, oxidative stress
  - Excess glucose leads to de novo fatty acid production and deposition into tissues
  - **Genesis of end organ damage**:
    - Glucotoxicity
    - Insulin resistance
    - Lipotoxicity
    - AGEs
  - **Hyperfiltration of the kidney**:
    - RAAS activation
    - Subsequent activation of SNS, ADH

Effects of Hyperglycemia: Advanced Glycation/Glycosylation End Products (AGE)

- **Elevated glucose levels (glucotoxicity) lead to:**
  - Metabolic interactions with proteins to form **AGE** leading to **tissues injury** and **inflammatory** state



AGEs: Coming to an End Organ Near You Soon

- Kidney
- Retina
- Nerves
- Vasculature

Increased Sympathetic Activity

- Elevated **epinephrine** (Epi) and **norepinephrine** (NE) levels are frequently seen in Type 1 and 2 DM renal disease
- **Epi** and **NE** add to **hyperfiltration** by actions on the nephron, peripheral vessels, and positive inotropic and chronotropic effect leading to **elevated BP** and **increased** glomerular capillary pressure (**P_{GC}**)
- Epi and NE **activate** the **RAAS**
- **Increased** all-cause CV risk in part due to increased SNS tone

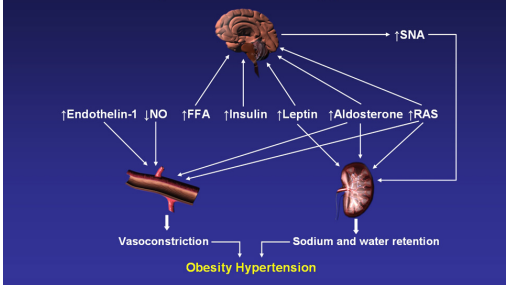
Neumann *Kidney Int* 2004 (65); 1568-1576.

Aldosterone in Diabetes

- Increased activity of the **renin-angiotensin-aldosterone system** (**RAAS**) of seen in and contributes to the pathogenesis of many conditions
  - DM, HTN, cardiovascular, hepatic and kidney diseases
  - Inhibition, blockade are key therapeutic targets
- Patient with **primary hyperaldosteronism** (Conn's syndrome) have a higher incidence of CV events, insulin resistance, and impaired glucose tolerance
- Elevated or upper limit of normal levels of serum aldosterone is strongly associated with **glucose intolerance** (pre-diabetes), **insulin resistance**, and **Type 2 DM**

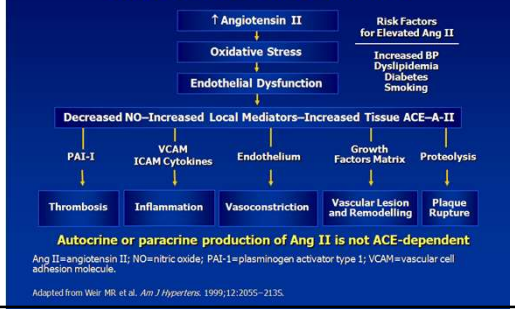
Stas et al *J Clin HTN* 2008; Feb;10(2) 94-96.

Mechanisms and Hormonal Systems Involved in Obesity-Associated Hypertension



NO=nitric oxide; FFA=free fatty acids; RAS=renin-angiotensin system; SNA=sympathetic nerve activity.
Rahmouni K et al. *Hypertension*. 2005;45:9–14.

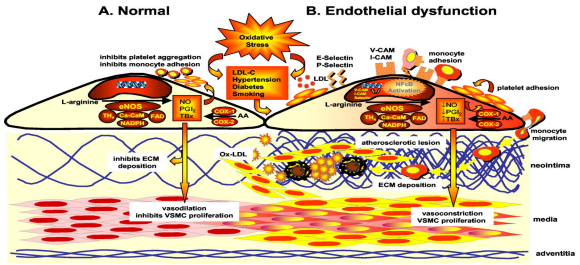
Effect of Tissue-Specific Angiotensin II Upregulation



Ang II=angiotensin II; NO=nitric oxide; PAI-1=plasminogen activator type 1; VCAM=vascular cell adhesion molecule.

Adapted from Weir MR et al. *Am J Hypertens*. 1999;12:205S–213S.

Key Target: Endothelial cells

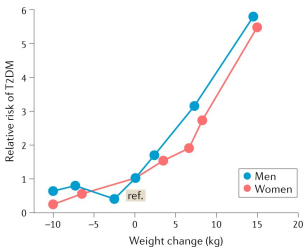


Melo LG. Arteriosclerosis, Thrombosis, and Vascular Biology. Endothelium-Targeted Gene and Cell-Based Therapies for Cardiovascular Disease, Volume: 24, Issue: 10, Pages: 1761-1774, DOI: (10.1161/01.ATV.0000142363.15113.88)

Obesity to Metabolic Syndrome to T2DM

- Increased **caloric** intake:
  - **Simple sugars (fructose),** refined, highly processed foods, added antibiotics/ steroids all lead to **increased insulin requirement**
  - Alteration of **glucose stimulated insulin secretion** (GSIS)
  - Increased renal reabsorption of glucose
  - B-cell exhaustion
- Lower intracellular glucose levels (from decreased insulin level or resistance) lead to increased counter regulatory hormones and RAAS
  - **Systemic effects**: Cardiorenal disease, vascular, neuropathic disease, etc.

Role of Weight Gain and Loss of Risk of T2DM



Magkos F, *Nature Reviews Endocrinology* 2020;16:545-555

Key Players in CKM Syndrome

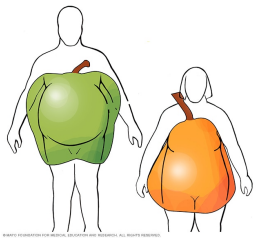
- Body mass index (BMI):
  - Metabolic risk factors
- Waist circumference:
  - Metabolic risk factor
  - Circumference should be an independent vital sign 1
- Fasting blood glucose/ HbA1c Metabolic risk factor
- Lipids (LDL, HDL, Triglycerides)
- Blood pressure:
- Chronic kidney disease of any cause (elevated creatinine and/or albuminuria)
- Hepatic steatosis, inflammation, fibrosis/cirrhosis
- Sleep duration/quality:
- Address mental health challenges/stressors
- Address Social Determinants of Heath (SODH) which may be impacting the patient's life

Staging of CKM

- Stage 0: Normal weight, glucose, lipids, BP, no CKD or subclinical CVD
- Stage 1: Excess/Dysfunctional Adiposity
- Stage 2: Metabolic Risk Factors and/or CKD
- Stage 3: Subclinical CVD or CKD
- Stage 4: Clinical CVD in CKM

Stage 1: Excess/Dysfunctional Adiposity

- **Overweight, abdominal or dysfunctional obesity**
- **Waist circumference** should be considered as an **independent vital sign**[1]
- No other metabolic, CKD, or CVD risk factors
  - Normal BP, glucose, albuminuria, lipids, non-tobacco use



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Metabolic Syndrome/Obesity (3 or more) Cardiovascular-Kidney-Metabolic Risk Factors

- **BMI:**
  - Ideal: 18.5kg/m^2 -25 kg/m^2
  - Overweight: 25kg/m^2-29.9 kg/m^2, Asian ≥ 23 kg/ m^2
  - Obese ≥ 30.0 kg/ m^2
  - May not be accurate in all patients
- **Waist circumference:**
  - Women: ≥ 88 cm, ≥ 80 cm in Asians
  - Men: ≥ 102 cm, ≥ 90 in Asians
- **Impaired glucose tolerance:**
  - Fasting blood glucose:
    - ≥100-149 mg/dL
  - HemoglobinA1c:
    - 5.7-6.4%
- **Elevated triglycerides:**
  - >150 mg/dL
  - Or currently treated
- **Low HDL:**
  - Men: <40 mg/dL
  - Women: < 50 mg/dL
- **SBP**: ≥130 mm Hg/**DBP** ≥85 mm Hg
  - Or currently treated

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report - PubMed (nih.gov)

Cardiovascular-Kidney-Metabolic Risk Factors

- Evidence of hepatic steatosis
- Obstructive sleep apnea//sleep issues
- Smoking, alcohol

1. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol* **16**, 177–189 (2020). https://doi.org/10.1038/s41574-019-0310-7

Stage 2: Metabolic Risk Factors and/or CKD

- **Presence of Metabolic syndrome, prediabetes, Type-2 DM**
- **Elevated triglycerides**:
  - **>150 mg/dL**
  - Or **currently treated**
- **Low HDL**:
  - **Men: <40 mg/dL**
  - **Women: < 50 mg/dL**
- **SBP: ≥130 mm Hg/DBP ≥85 mm Hg**
  - Or **currently treated**

Chiadi E. Ndumele. Circulation. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association, Volume: 148, Issue: 20, Pages: 1606-1635, DOI: (10.1161/CIR.0000000000001184)

Stage 2: Metabolic Risk Factors and/or CKD

- **CKD:**
  - Presence of **CKD** significantly **accelerates** the course of **CVDz**
  - **Elevated serum creatinine and/or albuminuria**
    - Serum **creatinine** estimated GFR **(eGFR)** non-race based
  - Spot urine **albumin/urine creatinine ratio (ACR) ≥ 30 mg/dL**
  - **Note: Elevated ACR** is the **earliest indicator** of diabetic and other kidney diseases, CVDz, and other systemic illnesses:
    - HTN
    - Most types of cardiovascular disease: MI, stroke, PVDz
  - **ACR** is an **early** and **significant risk factors** that should be part of a **cardiovascular risk assessment**

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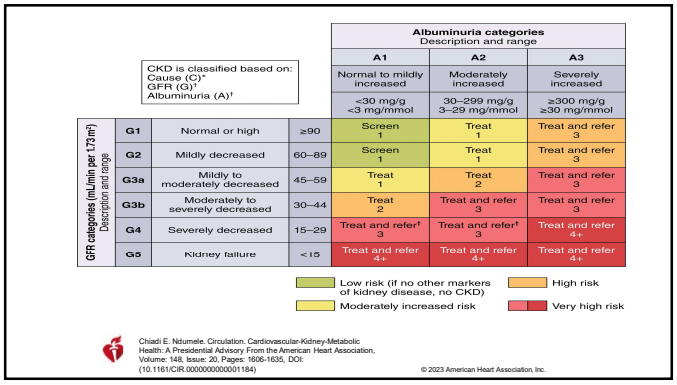

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Stage 3: Subclinical CVD or CKD

- **Subclinical ASCVD** or **subclinical HF** in people with **excess/dysfunctional adiposity:**
- **Subclinical HF:**
- **Subclinical ASCVD Risk Equivalent:**
  - CKD Stages G2 - G3b
  - High risk: G4-G5
  - High predicted all cause CVDz

Chiadi E. Ndumele. Circulation. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association, Volume: 148, Issue: 20, Pages: 1606-1635, DOI: (10.1161/CIR.0000000000001184)

Stage 3: Subclinical CVD or CKD

- **Subclinical ASCVD** or **subclinical HF** in people with **adiposity:**
  - CT coronary calcium score (CAC)
  - CT angiography
- **Subclinical HF:**
  - **Elevated NT-proBNP: >125 pg/mL***
  - **Echocardiographic evidence:**
    - Atrial enlargement(s), impaired relaxation, systolic dysfunction
  - **hs-troponin I:**
    - Women: ≥ 10 ng/mL
    - Men: ≥ 12 ng/mL
  - **hs-troponin T:**
    - Women: ≥ 14 ng/mL
    - Men: ≥ 22 ng/mL Hs-troponin I

***Note:**
•CKD, age, female sex, atrial fibrillation, inflammation, hyperthyroidism, sacubitril/valsartan **overestimate** BNP level.
•Obesity, Early MI, pericardial effusion **underestimate** BNP level
Journal of Cardiology. 2021; 78: 269–274

Stage 4: Clinical CVD in CKM

- **Clinical CVD** in people with **excess/dysfunctional adiposity**
- **Clinical CVD:**
  - Coronary artery disease, HF, stroke, peripheral vascular disease, atrial fibrillation
- **Other CKM risk factors:**
  - **CKM Stage 4a**: no kidney failure
  - **CKM Stage 4b:** kidney failure present (CKD Stage G2-5)

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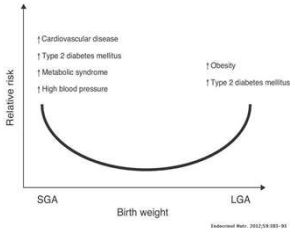
Risk for Type 2 Diabetes Mellitus

- Co-existing **maternal diabetes** (preexisting or gestational)
  - increases risk in child
- **Prematurity**: increased risk
- **SGA**: small for gestational age:
  - <10th percentile for age and weight
- **LGA**: large for gestational age:
  - >4.0 kg



Diabetes Burden: Prevalence by Ethnicity

- **Native American/Alaska Native**: 14.5%
  - Women: 14.8%
- **Black, non-Hispanic**: 12.1%
- **Hispanic**: 11.8 %
  - Mexican 14.4%
  - Puerto Rican: 12.4%
  - Central/South America 8.3%
  - Cuban: 6.5%
- **Asian**: 9.5%
  - Indian subcontinent: 12.6%
  - Filipinos 10.4%
  - Chinese: 5.6%
  - Other Asian: 9.9%
- **White non-Hispanic**: 7.4%
- **Education**:
  - **Less than H.S. education: 13.4%**
  - H.S. education: 9.2%
  - More than H.S. education: 7.1%
- **Family income** (all groups)
  - **Below federal poverty level: 14.1%**

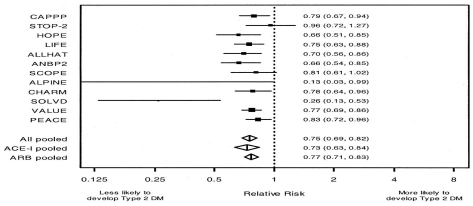
Centers for Disease Control National Diabetes Statistics Report 2022

Do ACE-I or ARBs Prevent Diabetes?

- Meta-analysis of 12 studies involving non-diabetics and the reduction of new onset of T2DM
- 72,333 non-diabetic patients, enrolled in one of 12 trials
  - **ACE-i treated: 27% reduction** in new onset T2DM
  - **ARBs treated: 23% reduction** in new onset T2DM
  - **Pooled: 25% reduction** of new onset T2DM

Abuissa H, 2005 *JACC* ;46:821-826

The Effect of RAAS Blockade on Development of Type 2 Diabetes



Abuissa H 2005 *JACC*;46:821-826

Screening for Prediabetes

- **High risk**:
  - Birthweight
  - Fam hx/maternal/gestational DM, 1st degree relatives
    - Hx GDM: eval minimum q 3 years, weight
  - Age>35
  - BMI ≥25 kg/ m^2
    - Asian American ≥23 kg/ m^2
    - Poor diet, sedentary
  - Obesity, presence of acanthosis nigricans, HTN, hyperlipidemia
  - Polycystic ovary syndrome (PCOS)
  - HIV Hx/Tx
  - **Ethnicity:** Native American, PI, Alaska native, AA, Asian American
  - Role of poverty/education levels
  - Medication associated

2023 ADA Standards: Volume 46 Issue Supplement_1 | Diabetes Care | American Diabetes Association (diabetesjournals.org)

Screening for Prediabetes/ T2DM in Adolescents and Teens

- Onset of puberty or >10 y.o.
  - Younger?
- High risk groups
- **Overweight: BMI ≥ 85th percentile**
- **Obesity: BMI ≥95th percentile**
- FBS, 2 hour post prandial 75 gm, Hb A1c
- Also get Ab to r/o T1DM and r/o MODY

Diabetes Care. 2020 Jan;43(Suppl 1):S163–S82. doi: 10.2337/dc20-S013. PMID: 31862756.

Criteria for Prediabetes

- **Fasting glucose**:
  - 100-124 mg/dL

  or
- **2-hour glucose after 75 gm glucose load**:
  - 140-199 mg/dL

  or
- **HbA1c**:
  - 5.7-6.4%

2023 ADA Standards: Volume 46 Issue Supplement_1 | Diabetes Care | American Diabetes Association (diabetesjournals.org)

MB3

Diagnosis of Type-2 Diabetes Mellitus

- **Fasting plasma glucose: ≥126 mg/dL**
- **2-hour plasma glucose: ≥200 mg/dL** following a **75 gm oral glucose** tolerance test
- **Hemoglobin A1c: ≥ 6.5%**

2023 ADA Standards: Volume 46 Issue Supplement_1 | Diabetes Care | American Diabetes Association (diabetesjournals.org)

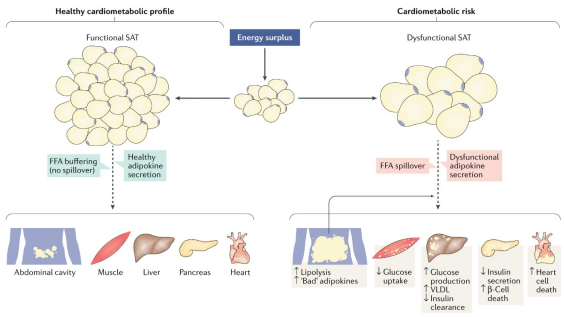
Slide 50

MB3 Mark Baldwin, 11/19/2023

Type 2 Diabetes

- **Type 2**: insulin resistance
  - normal or elevated insulin levels with elevated glucose
- Directly related to obesity
- Alteration of **multiple neuroendocrine systems**
  - SNS, RAAS, glucagon, cortisol, growth hormone, etc.
- **~77% incidence** of DN when retinopathy present
- **Quiescent** period of 10-15 years may be masked as end organ(s) damage is frequently present at time of presentation of DM

Parving *Kidney Int*. 1992;41:758.



Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol* **16**, 177–189 (2020). https://doi.org/10.1038/s41574-019-0310-7

Screening for NAFLD/MAFLD

- **Infiltration** of **fatty acids** into **liver** leading to **inflammation** & **fibrosis**
- **Truncal**/**visceral**/**abdominal obesity**
- **Most common cause** of **51%** of **chronic liver disease**/**cirrhosis and liver transplantation**
- **2016 meta-analysis** showed a **prevalence of 25.24%**
- **NAFLD** predicted **risk** of overt **Type-2 DM** in **prediabetes**:
  - **6.9 fold** increase risk in **men**
  - **5.8 fold** increase risk in **women**

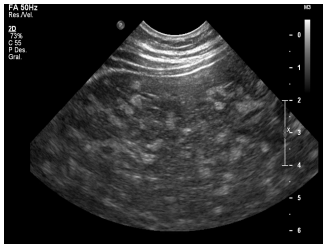
Gastroenterol Hepatol (N.Y.) 2019;15:357-365

Screening for NAFLD/MAFLD

- Right upper quadrant/hepatic ultrasound
- **AST**:**ALT** elevated with ratio of **2:1** (**≥2X** normal)
- Elevated gamma glutamyl transferase **(GGT)**
- Occasionally elevated alkaline phosphatase **(AP)**
- **NAFLD**/**MAFLD** **&** risk of **hepatocellular carcinoma**:
  - **2.3%** in **7 years**
  - Up to **12.3 %** in **3 years** **(Clin Gastroenterol Hepatol 2012;10:1342.)**
- Rule out **Hepatitis B**, **C**

***AFP*. 2013;42, 444-447** Int J Biol Sci. 2019; 15(3): 610–616.

Multinodular Hepatic Steatosis



EPOS™ (myesr.org)

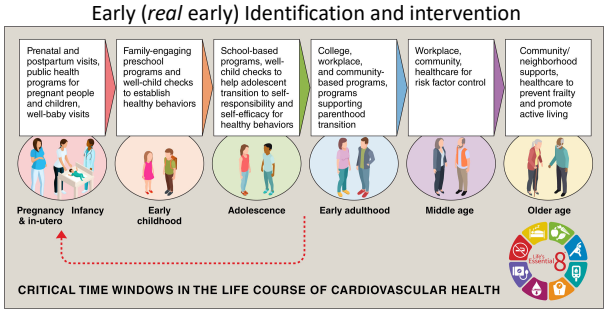
Approach to CKM

- Early recognition and intervention is key
- Access to health care, education, healthy food, activities

Life's Essential 8

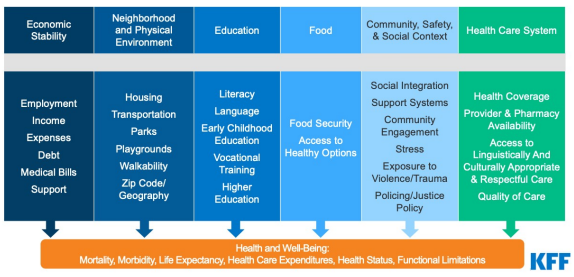
- **Life's Essential 8** includes the 8 components of **cardiovascular health**:
  - Healthy diet
  - Physical activity
  - Avoidance of nicotine (ETOH)
  - Healthy sleep
  - Healthy weight
  - Healthy levels of blood lipids
  - Normal blood glucose
  - Normal blood pressure.

Early (*real* early) Identification and intervention



Donald M. Lloyd-Jones. Circulation. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association, Volume: 146, Issue: 5, Pages: e18-e43, DOI: (10.1161/CIR.0000000000001078)

Social Determinants of Health



Chronic Care Model

- Primary focus on **cardiorenal risk**
- Education
- Addressing "environmental" issues facing the patient
  - Social services/advocacy to address the SDOH
  - Adequate housing, safe neighborhoods
  - Nutritional needs/access
  - Access to healthcare, medication, follow up, healthcare coverage, mental health care

Chronic Care Model

- Comprehensive team based approach
- Physician, CNP, PA-C,
- Nurse manager
- Dietician/Certified diabetic educator
- Social worker
- Mental health facilitator
- Optometrist/ophthalmology
- Podiatry
- Nephrology
- Cardiology
- Endocrinology

Stage 0/1 CKM: Interventions

- Identification of **high risk groups**
- **Promotion of CV health**:
  - BMI/ waist circumference
  - Glucose
  - BP
- **Systematic screening for the SODH/mental health**
- **Intensive lifestyle interventions**:
  - **Diet, activity, smoking, ETOH cessation**
- **Pharmacotherapies, BMI: ≥ 30** kg/m
  - **Metformin, GLP-1, SGLT-2**
- **Bariatric surgery, BMI: ≥ 40** kg/m (w/o comorbidities)

Chiadi E. Ndumele. Circulation. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association, Volume: 148, Issue: 20, Pages: 1606-1635, DOI: (10.1161/CIR.0000000000001184)

Stage 2 CKM: Interventions

- **Hyperlipidemia:**
  - **Maximize statin therapy**
  - **Triglycerides ≥500 mg/dL: fibrates**
  - **Glucose control**
- **Hypertension:**
  - Follow guidelines JNC-8, ACC, KIDIGO, ADA, etc.
  - **BP: <130/85 mm Hg (SPRINT <120/80 mm Hg)**
  - Any evidence of **CKD/ albuminuria: ACEi/ARB**

Chiadi E. Ndumele. Circulation. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association, Volume: 148, Issue: 20, Pages: 1606-1635, DOI: (10.1161/CIR.0000000000001184)

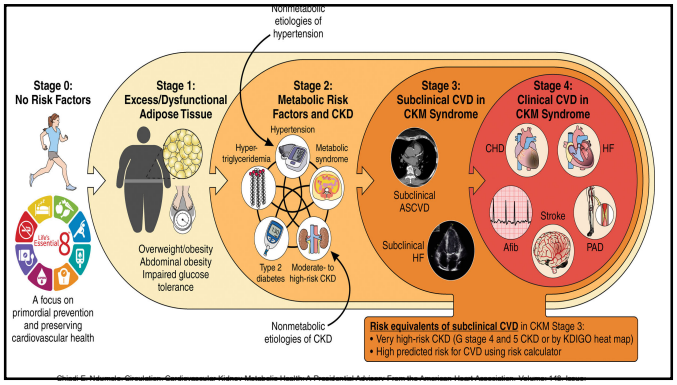
Stage 2 CKM: Interventions

- **CKD:**
  - Any type
  - **Elevated serum creatinine** (n 0.6-1.2 mg/dL)
    or
  - Urinary albumin/creatinine ratio ≥ 30 mg/dL
  - ACR > 30 mg/m on ACEi/ARB tx
    - Add spironolactone, eplerenone, finerenone, SGLT-2
- **Diabetes:**
  - Intense **statin** therapy
  - **Metformin**
  - **RAAS inhibition: ACE-i/ARB**
  - **SGLT-2**
  - **Co-morbidities (CVD/CKD)**
    - **BMI: > 35 kg/m² -GLP-1 RA**
    - **HbA1c: >9%** or high dose insulin-**GLP-1 RA**
    - **CKD/DKD: SGLT-2, GLP-1**
  - **ACR: > 30 mg/m²** on **ACEi/ARB tx**
    - Spironolactone, eplerenone, finerenone

Chiadi E. Ndumele. Circulation. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association, Volume: 148, Issue: 20, Pages: 1606-1635, DOI: (10.1161/CIR.0000000000001184)

Stage 3: Interventions

- **Subclinical Atherosclerosis:**
  - **Coronary calcium score (CAC)**
    - **CAC: >0**
    - **CAC: >100**
      - **High dose statin, low dose ASA, PCSH9i, GLP-1RA**
- **Subclinical HF:**
  - **EF: <40%**
    - **ACEi/ARB**
    - **SGLT-2**, esp. in DM
- **CVD risk equivalent for Stage 3 CKM:**
  - **Very high risk: CKD** Stage **G4, 5 or ESKD**
- **Low dose aspirin:**



Questions?
Thank you
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