

Metabolic Syndrome: *Insulin Resistance Syndrome (IRS)*

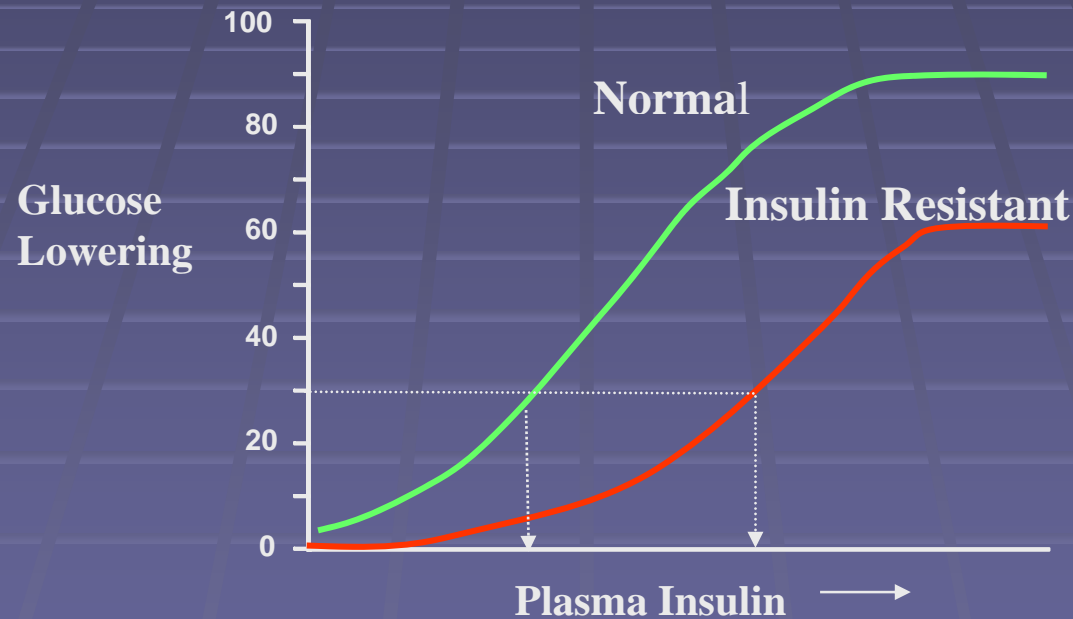
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Carson Tahoe Endocrinology
Carson City, NV

KCOM 1989

Resistance to insulin-mediated glucose disposal

INSULIN SENSITIVITY and INSULIN RESISTANCE



Insulin Resistance Contributors

- Obesity
- Pregnancy
- Stress
- Infection
- Uremia
- Glucocorticoid excess
- Acromegaly

Definition of Endogenous Insulin Resistance

Elevated insulin level with normal or elevated blood glucose

Clinically: Rarely check insulin level

ASSESSING INSULIN RESISTANCE

- ◆ Insulin Clamp
- ◆ HOMA (fasting values)

$$I \approx \frac{\text{Insulin} \times \text{Glucose} \times 0.055}{22.5}$$

- ◆ “Scale and Eyeball”



Lab Evaluation of Insulin Level

- Not fully standardized
- Used mostly for evaluation of hypoglycemia and insulinoma
- Fasting value recommended to exclude a rise the insulin level due to feeding

Insulin Resistance Variables

- Genetic
- Life-style
- Ethnicity
- Glucose uptake of muscle and lipolysis is an individual response
- One site of insulin resistance does not necessarily involve all sites in same patient

IRS Lab and Exam: ATP III

- Abdominal Obesity
- Hypertriglyceridemia
- Low HDL
- Elevated blood pressure
- Hyperglycemia

***Adult Treatment Panel III indicates IRS is three of these five factors

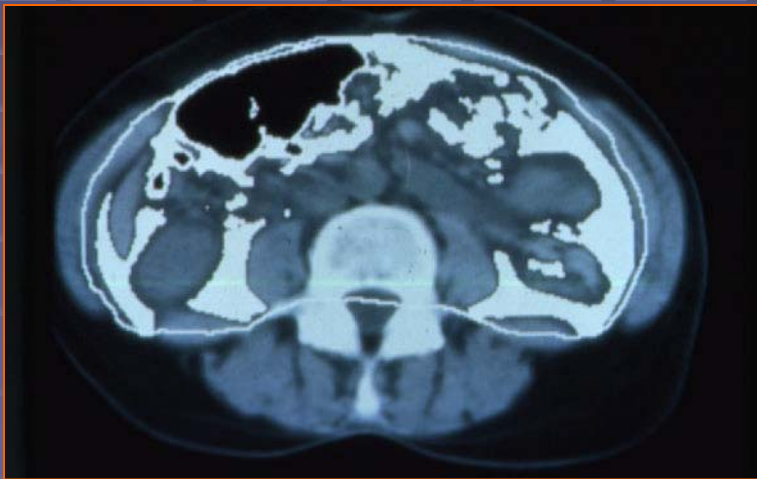
Abdominal Obesity

Adult Treatment Panel III

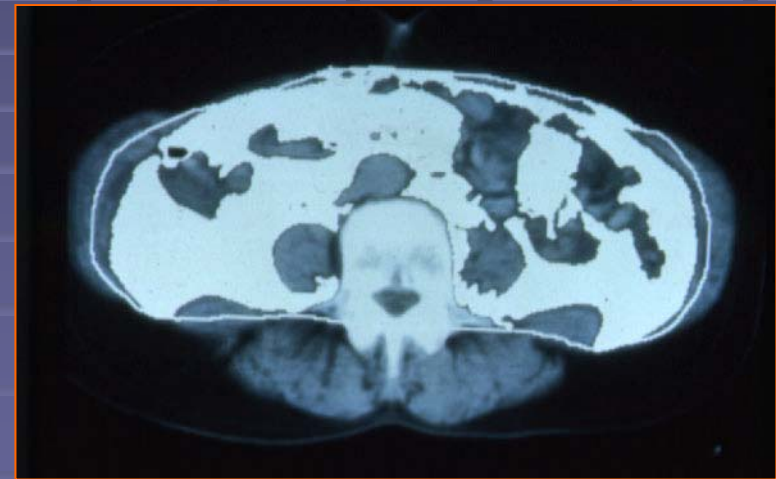
Waist in Men > 40 inches

Waist in Women > 35 inches

VISCERAL FAT DISTRIBUTION

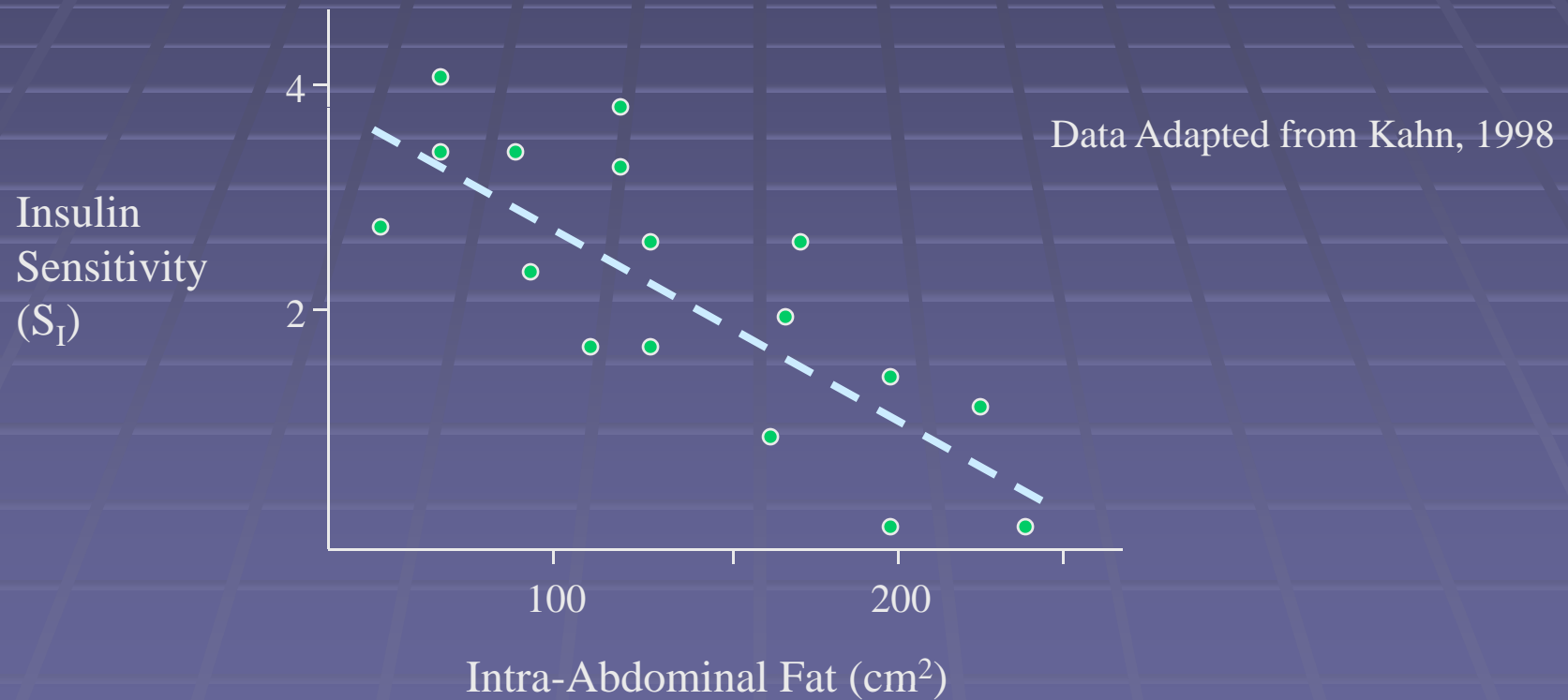


Normal



Type 2 Diabetes

INTRA-ABDOMINAL FAT vs INSULIN SENSITIVITY



Lipids (ATP III)

- Triglycerides 150 mg/dL or >
 - HDL < 40 mg/dL in men
 - HDL < 50 mg/dL in women

Blood Pressure (ATP III)

130/85 or greater

Plasma Glucose

- 2001 National Cholesterol Education Program/Adult Treatment Panel III: Fasting glucose 110 mg/dL or greater
- 2003 ADA Impaired fasting glucose 100 mg/dL or greater
- ADA previous normal glucose < 110 mg/dL (1997)

Plasma
Glucose

126 mg/dL

Prediabetes

Postmeal
glucose

Fasting glucose

Relative β -Cell
Function

Insulin resistance

Insulin secretion

-20

-10

0

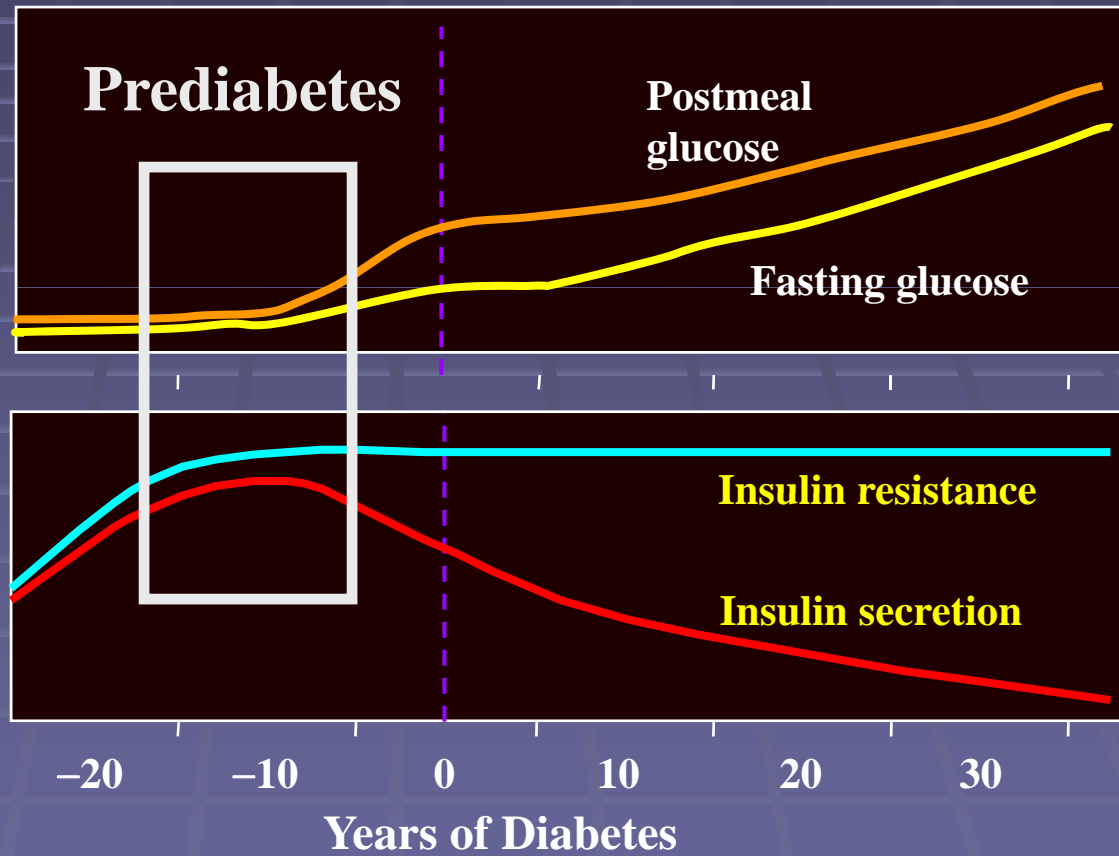
10

20

30

Years of Diabetes

Adapted from International Diabetes Center (IDC). Minneapolis, Minnesota.



DIAGNOSTIC CRITERIA FOR DIABETES

DIAGNOSIS	FPG (mg/dl)	2H Postglucose (mg/dl)
Impaired Fasting Glucose*	100-125	
Impaired Glucose Tolerance*		>140-199
Diabetes Mellitus	≥ 126	≥ 200

Or a random glucose ≥ 200 mg/dl with symptoms

*Now collectively termed 'pre-diabetes'

IMPLICATIONS of PRE-DIABETES

- Yearly risk for progression to type 2 diabetes is 6.5 to 17%
 - Compared to a 10% lifetime risk for normal adults
 - Growing incidence has been labeled an 'epidemic' by the CDC
- Significant risk for both CAD and all cause mortality

MORTALITY AND ABNORMAL GLUCOSE TOLERANCE

RISK RATIO

STUDY	N	ENDPOINT	RISK RATIO		
			DM	IFG*	IGT**
DECODE	25364	Mortality	2.0	1.2	1.6
Hoorn	2468	Mortality	1.6	---	1.3
Mauritius	9179	Mortality	1.6	---	---
Funagata	2534	Mortality	1.7	---	1.2
Cardio HS	4515	CVD	1.7	---	1.2
Strong HS	6483	CVD	2.7	0.7	0.7

*Impaired Fasting Glucose: >110-125 mg/dL (used in these reports)

**Impaired Glucose Tolerance (2h value): >140-199 mg/dL

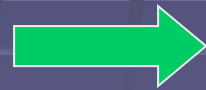
'TICKING CLOCK' HYPOTHESIS

FOR:

THE CLOCK STARTS TICKING:

Microvascular

Complications



Onset of Hyperglycemia

Macrovascular

Complications



During the Prediabetic Phase

Haffner et al: JAMA 1990;263:2893-2898

World Health Organization (WHO) 1998

- HDL < 35 with similar TG standard
- BP 140/90 or greater
- Waist to hip ratio 0.9, Body Mass Index 30 kg/m² or greater , waist 37 inches or greater

Inflammation and Thrombosis

- C-reactive protein (CRP)
- Interleukin (IL)-6
- Plasminogen Activator (PAI)-1

- Fat cells may be a cytokine source

***Increased risk of DM2 and cardiovascular disease

ATP III

Not enough evidence to suggest
biochemical evaluation of insulin
level, CRP, Fibrinogen, PAI-1

NHANES III & IRS Prevalence

- 8000+ subjects
- Metabolic Syndrome Prevalence 22 %
- Prevalence higher with aging
- Mexican-Americans highest age adjusted prevalence
- 5 % normal weight & 60 % Obese with IRS

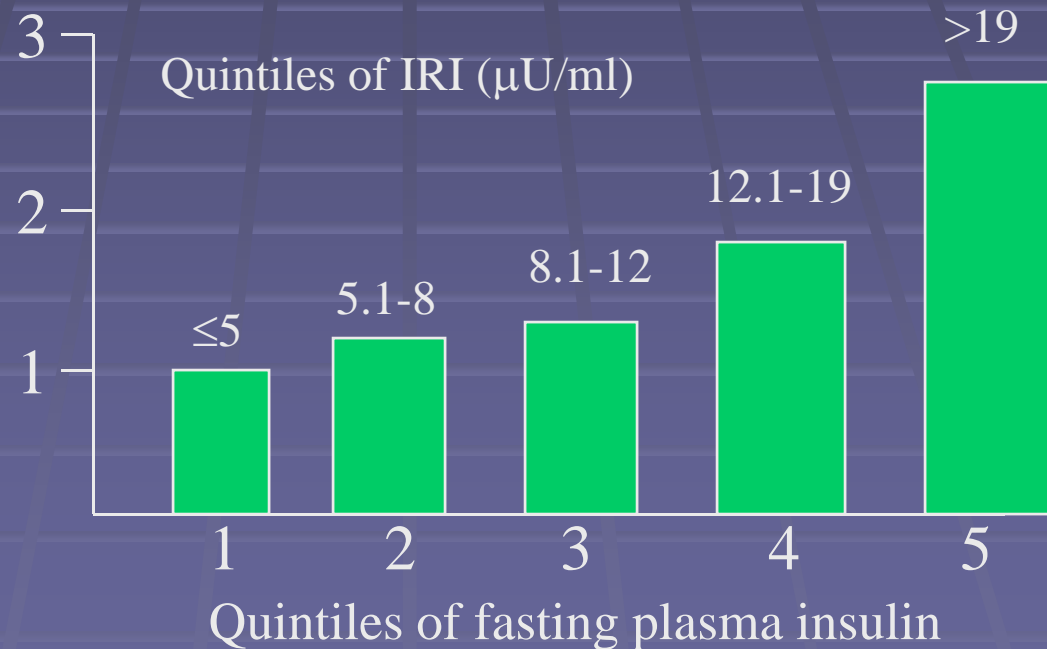
METABOLIC RISK AND FASTING INSULIN LEVELS

# of Metabolic Risk Factors*	Fasting Insulin (pM)
0	57
1	101.8
2	117.1
4	148.9

*Low HDL, Hypertriglyceridemia, HTN, Type 2 DM

PARIS PROSPECTIVE STUDY

CAD
Mortality
(per 1000)



N = 7028 men; 943
with IGT or DM

PROGRESSION of IGT PARALLELS CAD

Insulin Resistance



Hyperinsulinemia
Normal Glucose
Tolerance



Endothelial
Dysfunction



Impaired Glucose
Tolerance



2 Fold Increase in
CV Mortality

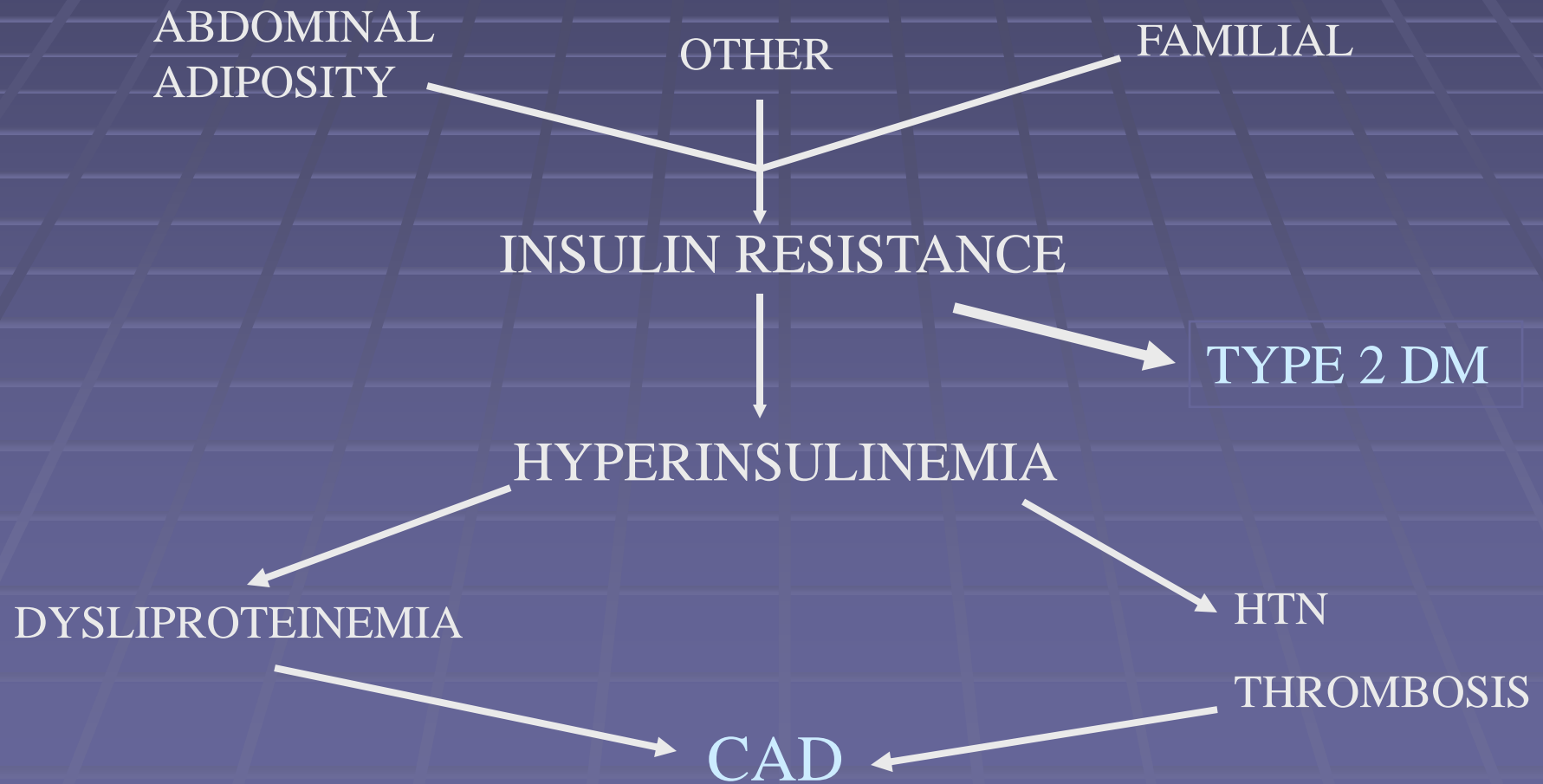


Type 2 Diabetes



3 to 6 Fold Increase in
CV Mortality

INSULIN RESISTANCE



Treatment Plan for IRS

- ATP III (2001) weight management and physical activity; Tx persistent CVD risk factors
- AHA and NIH reinforced these (2003)
- TZD's and Biguanides over lifestyle?
[Pioglitazone, Rosiglitazone, Metformin]

Lifestyle Modification

- Diet
- Exercise
- Medication can be considered: Orlistat or weight loss medication like Sibutramine







Diabetes Prevention Program

- 3234 with abnormal glucose levels
- Placebo, Metformin, Lifestyle modification with 7 % weight loss as the goal and 150 minutes of exercise weekly
- Follow-up 2.8 years with 11 % DM in placebo and 4.8 % lifestyle
- Lifestyle change more effective than drug

Physical Exercise

- May prevent the development of DM
- Aerobic exercise has positive effects on lipid profile and BP
- Prolonged exercise lowers abdominal fat > than lower body fat
- CVD benefit
- Risk injury, arrhythmia, MI, bronchospasm

Calories vs Exercise

- Patient eats 500 less calories per day than previous. Weight loss at 3500 calories less per pound would be 1 pound per week.
- Patient exercises by walking 3 miles per hour. 200 pound patient uses 3 calories per minute. 167 minutes to use 500 calories

Polycystic Ovarian Syndrome (PCOS)

The gonadal manifestation of the
Insulin Resistance Syndrome

Polycystic Ovarian Syndrome

- Chronic anovulation and hyperandrogenism
- Infertility (Consider Metformin for induction of fertility)
- 5 million reproductive age women in the US affected
- Insulin resistance in the obese and lean PCOS patient

TZD's vs Biguanides

- TZD's can promote weight gain
- TZD's not likely safe in hepatic dysfunction
- Metformin may promote weight loss
- Metformin not safe with renal insufficiency, active liver disease and pulmonary disease
- Neither should be used in CHF

Pharmacological Treatment IRS

Current research data do not
support medication treatment

***Search for DM diagnosis

Nonalcoholic Fatty Liver Disease (NAFLD)

- Most important risk factor for development: Insulin Resistance
- Advanced Fibrosis associated aging, rising BMI, and diabetes
- Increased peripheral lipolysis and fatty acid beta oxidation pose oxidative stress on the liver as well as intrahepatic abnormalities

NAFLD

“The Hepatic Manifestation of the Insulin Resistance Syndrome”—A. Sanyal, MD

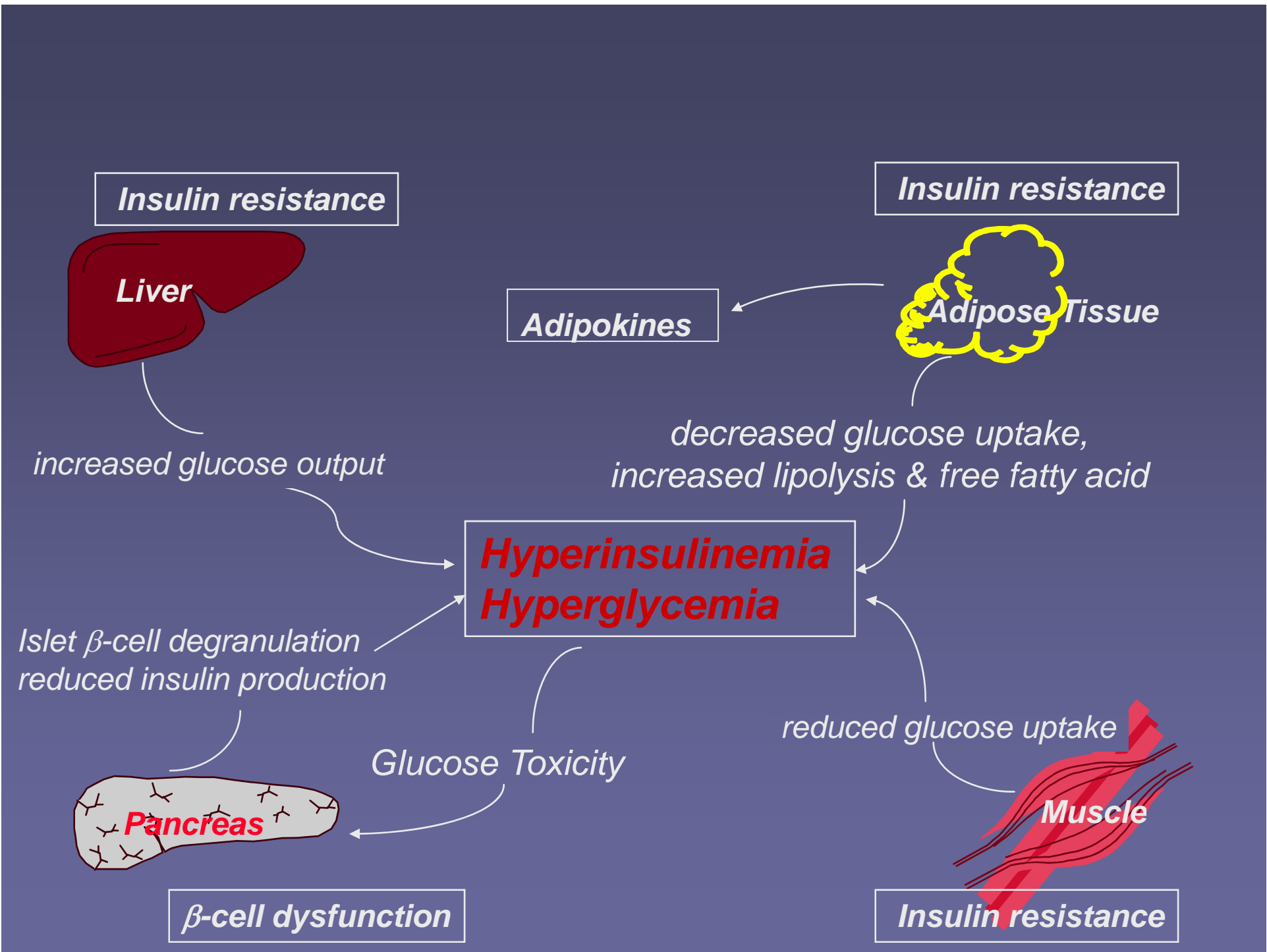
***World Congress IRS November 2003

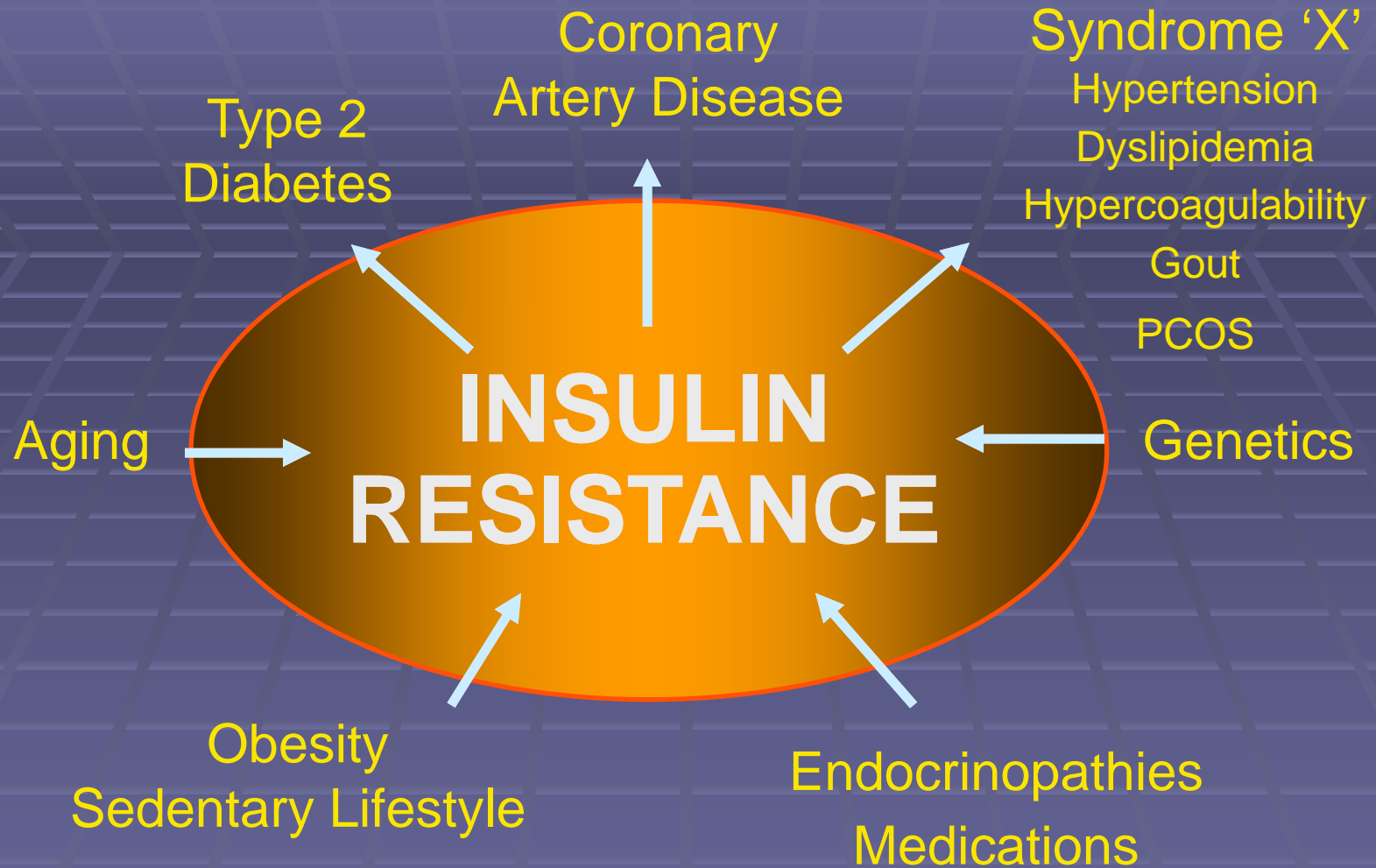
INSULIN RESISTANCE SYNDROME

- Glucose Metabolism
 - IFG
 - IGT
- Uric Acid
 - ↑ Serum UA
 - ↓ Renal Clearance
- Dyslipidemia
 - ↑ Triglycerides
 - ↓ HDL
 - ↓ LDL Diameter
- Hemodynamic
 - ↑ SNS Activity
 - ↑ Na⁺ Resorption
 - ↑ Blood Pressure
- Procoagulant State
 - ↑ PAI-1
 - ↑ Fibrinogen
- Reproductive
 - PCOS
- Fatty Liver

IRS & Cancer

- Increased risk of breast cancer by insulin mediated actions on mammary cells and indirect actions
- Hypothesis IRS as a mechanism connecting colorectal cancer with dietary/lifestyle risk factors
- Connection to prostate cancer and IRS unclear





Olefsky JM. In: *Endocrinology*. 2nd ed. 1989:1369-1388.
Reaven GM. *Clinical Diabetes*. March/April 1994:32-36.

Insulin Resistance Syndrome

ICD-9

277.7

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