METABOLIC SYNDROME – REALITY AND CONTROVERSIES

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METABOLIC SYNDROME

- Background
- History
- Definition
- MS vs IRS
- Significance
- Management
- Controversies

BACKGROUND

- Cardio vascular disease [CVD] is the major cause of mortality

- Clustering of Risk Factors For CVD:
  Obesity, abdominal obesity, type 2 diabetes, abnormal lipids and hypertension

- Unifying Hypothesis:
  Insulin Resistance and compensatory hyperinsulinemia predisposed patients to these conditions.

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HISTORY OF SYNDROME X

1923 Kylin describes clustering of hypertension, gout and hyperglycemia

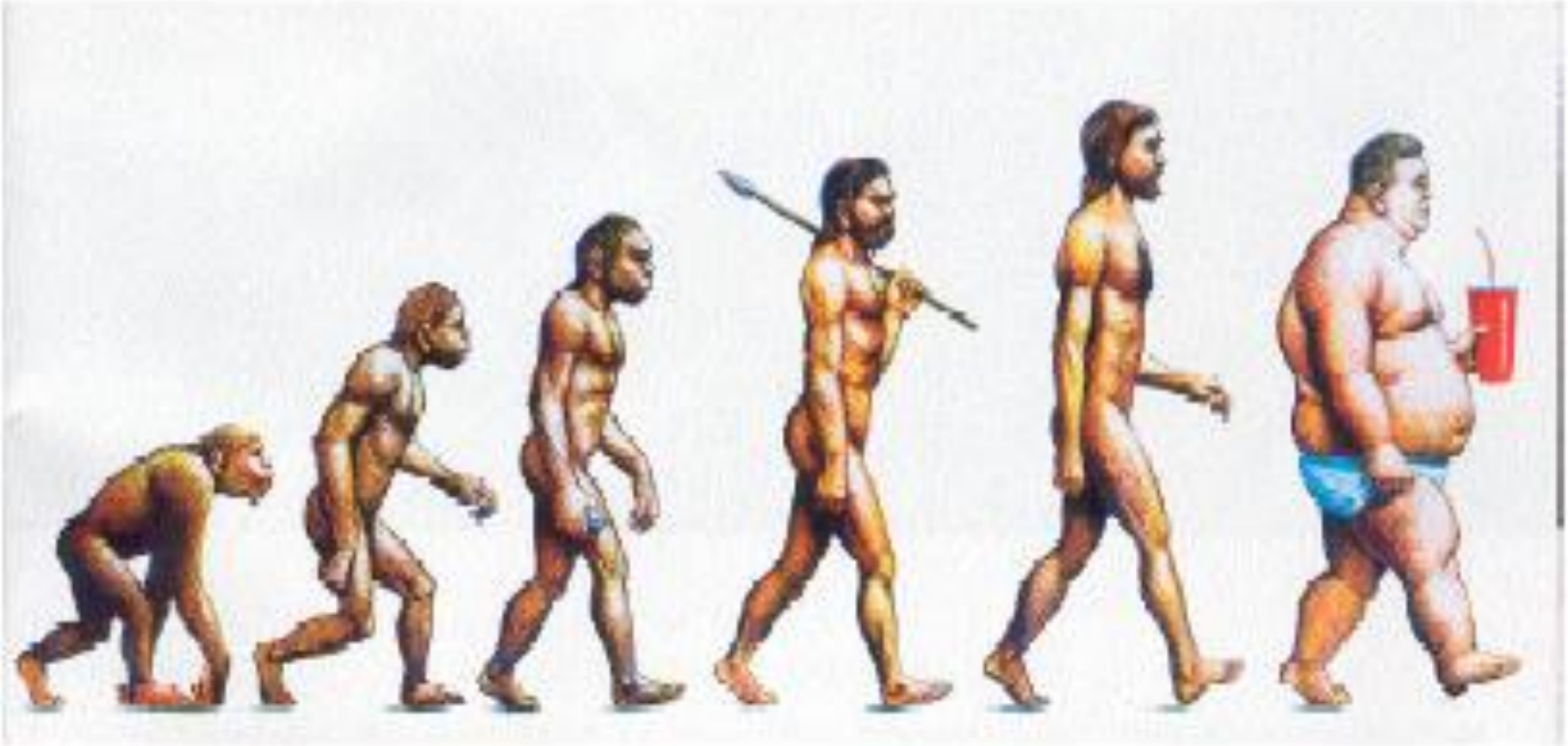
1988 Reaven describes “Syndrome X” – hypertension, hyperglycemia, glucose intolerance, elevated triglycerides and low HDL cholesterol

1998 WHO focuses on insulin resistance

2001 NCEP describes “metabolic syndrome” and gives ICD code

2005 IDF describes ethnic specific criteria for metabolic syndrome

Evolution of the Modern 'CardioMetabolic' Man



Source: The Economist, Dec 11, 2003

DIFFERENT NAMES BUT SAME DISORDER

- Syndrome X
- Insulin resistance syndrome
- Metabolic syndrome
- Beer-belly syndrome
- Dysmetabolic syndrome
- Reaven’s syndrome

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Different Definitions for

“Metabolic Syndrome”

WHO vs ATP III vs IDF definitions

DEFINITION

"Metabolic Syndrome" describes a cluster of CVD risk factors and metabolic alterations associated with excess fat / weight

DIFFERENT DEFINITIONS OF METABOLIC SYNDROME

	Risk factors	IDF Consensus (2005)	NCEP ATP III Criteria (2001)	WHO Criteria (1999)
1	Obesity / Abdominal obesity	Waist circumference ≥ 90 cm (m), ≥ 80 cm (f) – South Asians	Waist circumference ≥ 102 cm (m), ≥ 88 cm (f)	Body mass index (BMI) ≥ 30 kg/m^2 and/or waist-to-hip ratio > 0.90 (m), > 0.85 (f)
2	Blood pressure	≥ 130 / ≥ 85 mm Hg	≥ 130 / ≥ 85 mm Hg	≥ 140 / ≥ 90 mm Hg or on medication
3	Fasting glucose	≥ 100 mg/dl or pre-existing DM	≥ 110 mg/dl or on medication	Diabetes, impaired glucose tolerance or insulin resistance
4	Microalbuminuria	Not used for diagnosis	Not used for diagnosis	Urinary albumin excretion rate ≥ 20 µg/min
5	Triglycerides	≥ 150 mg/dl	≥ 150 mg/dl	Triglycerides ≥ 150 mg/dl and/or HDL-C < 35 mg/dl (m), < 39 mg/dl (f)
6	HDL Cholesterol	< 40 mg/dl (m), < 50 mg/dl (f)	< 40 mg/dl (m), < 50 mg/dl (f)	
Metabolic syndrome – definition		Abdominal obesity plus any two or more risk factors	Atleast three risk factors	Diabetes, impaired glucose tolerance or insulin resistance plus any two or more risk factors

- **In 2009, IDF, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for theStudy of Obesity jointly adopted the revised NCEP criteria, where abdominal obesity is not a necessary component, as worldwide criteria of MetS.**

- **In 2010, WHO Expert Consultation warned that MetS is a concept that focuses attention on complex multifactorial health problems but has limited practical utility as a tool for management or epidemiological study**

MEDICAL EVALUATION OF METABOLIC SYNDROME

Physical Exam

- Blood Pressure
- Body mass index
- Waist circumference

Lab Evaluation

- Fasting Glucose
- Serum triglycerides
- HDL Cholesterol
- Fasting insulin
- Microalbuminuria

Waist line is your life line (80 cms)

Prevalence of Metabolic Syndrome by various studies and criteria

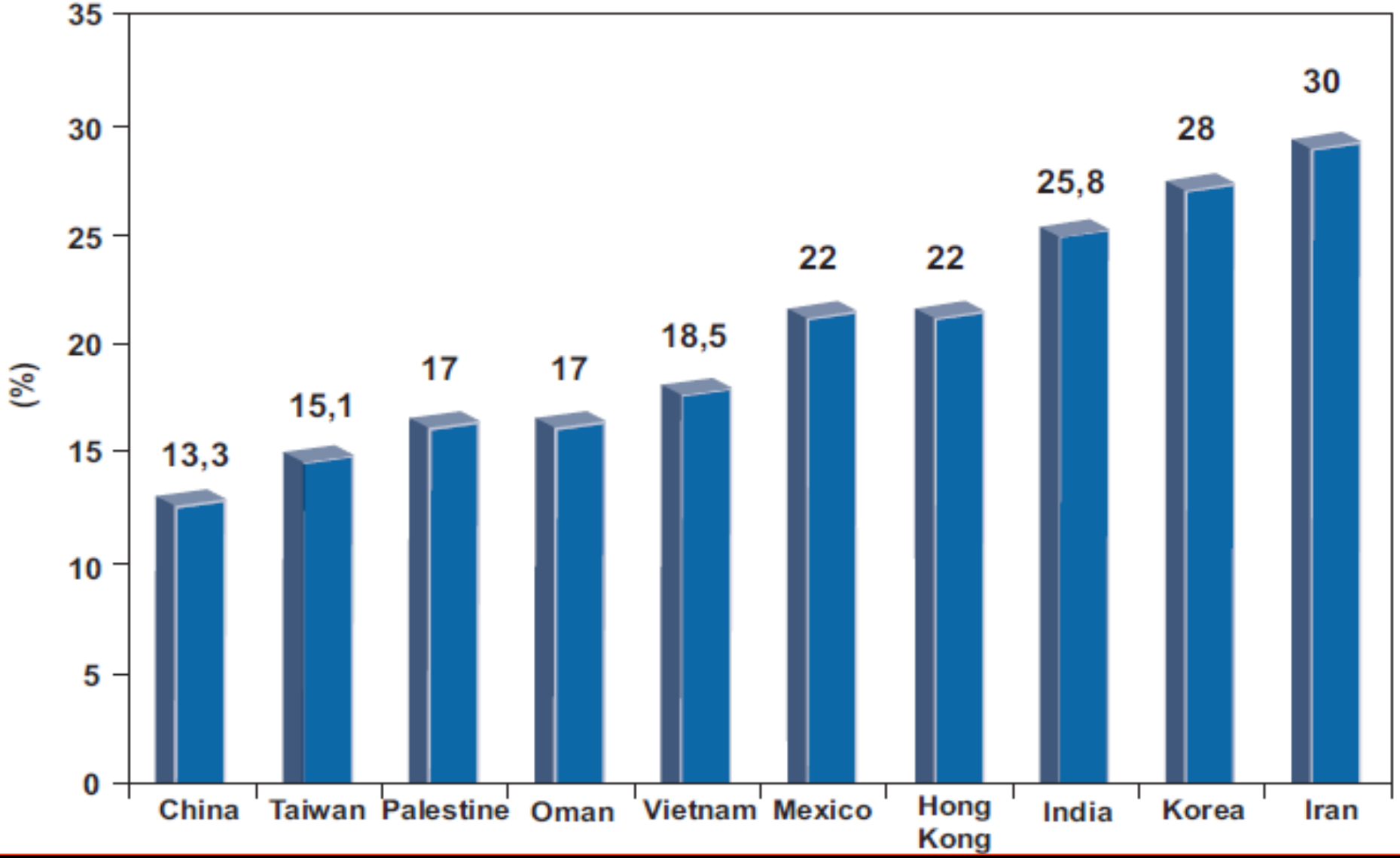
Reference	Country	Year	Prevalence	Diagnostic criteria
Kotokey et al 2013	Dibrugarh, India	2010-2011	32.87%	Revised ATPIII
Suttajit et al 2013	Thailand	2.010	modified NCEP-ATP III 37% ; IDF 35%,	Modified ATP III IDF
Liu et al 2013	China	2009–2010	35.1% for men and 32.5%	Consensus criteria for chinese
Setayeshgar, 2012	Canada	2007-2011	18.31	IDF and AHA/NHLBI
Al Zenki et al 2012	Kuwait	2008-2009	37.7% in females and 34.2% in males	NCEP criteria
Osuji et al 2012	Nigeria	2009	31.2%	NCEP-ATPIII
Lim et al 2011	Korea	2007	31.3	Revised ATPIII
Gundogan et al 2009	Turkey	2007	34.6%	Revised ATPIII
Soewondo P et al 2010	Indonesia	2006	28.4%	Revised ATPIII

Prevalence of Metabolic Syndrome by various studies and criteria

Contd….

Reference	Country	Year	Prevalence	Diagnostic criteria
Cameron et al 2007	Australia	2007	30.7%	IDF
Deepa et al 2007	Chennai, India	2002-2004	23.2%	WHO criteria
Bo et al 2005	Northwestern italy	2001-2003	23.1 %	ATPIII
Scuteri et al 2005	Cardiovascular health study	1989-1990	ATP III- 28.1% WHO- 21 %	ATPIII and WHO
Gu D, et al 2005	China	2000–2001	Men: 9.8% Women: 17.8%	ATP III
Ford et al 2005	United States.	1999–2002	ATPIII: 34.5%a; IDF: 39.0%a	IDF
Thomas GN et al., 2005	Hong Kong	1994–1996	21.9%	ATPIII [modified]
Resnick HE et al., 2003	Arizona, Oklahoma & Dakota	1988	35%a	ATPIII
Mohan V et al 2001	Chennai, India	1996-2001	11.2%	EGIR

Prevalence of the metabolic syndrome in developing



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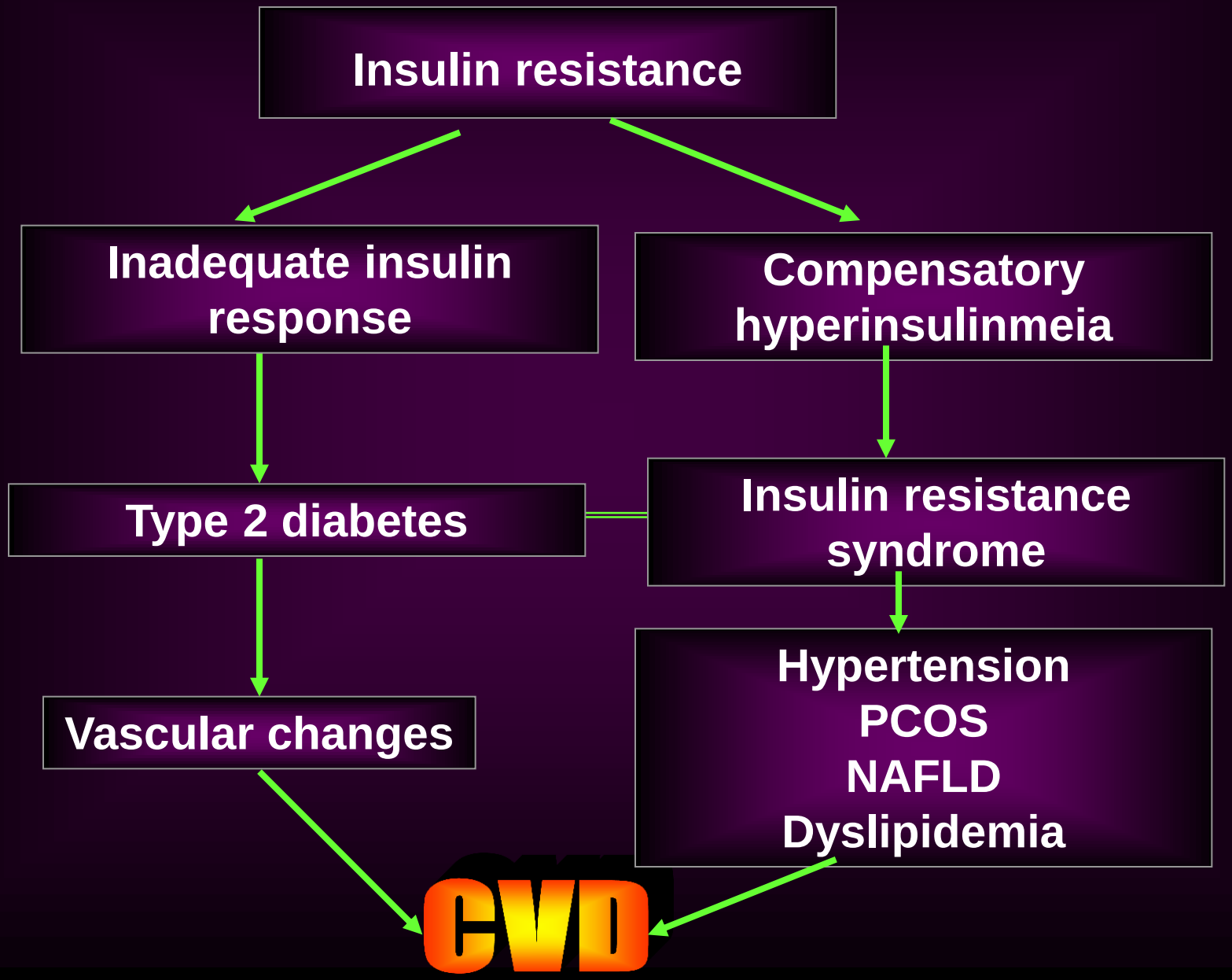
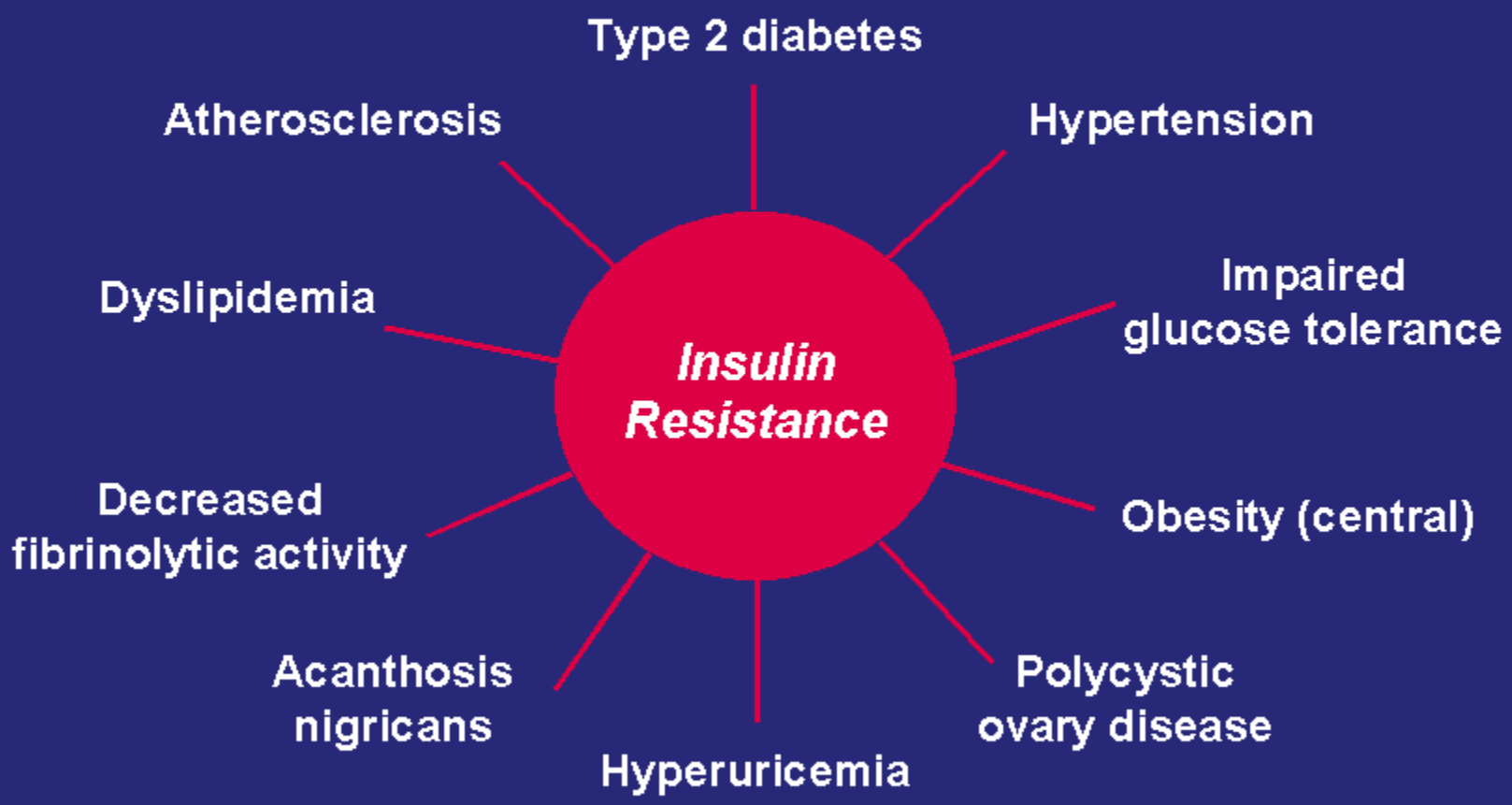
DEFINITION OF INSULIN RESISTANCE

A state in which a normal amount of insulin produces a sub-normal response

INSULIN RESISTANCE SYNDROME



Insulin Resistance: Associated Conditions

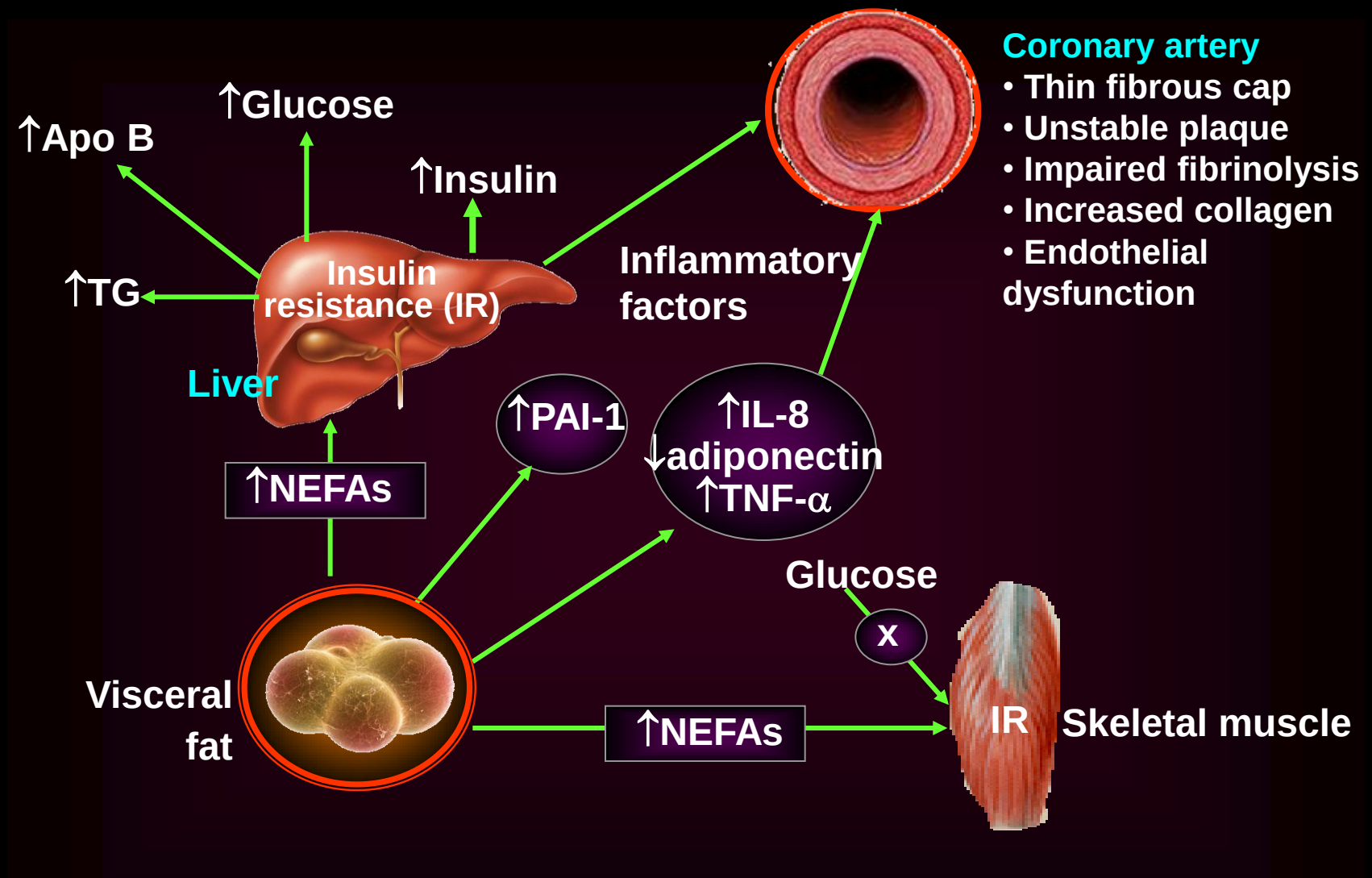


Adapted from Consensus Development Conference of the American Diabetes Association. *Diabetes Care*. 1998;21:310-314.

PRODUCTS OF ADIPOSE TISSUE

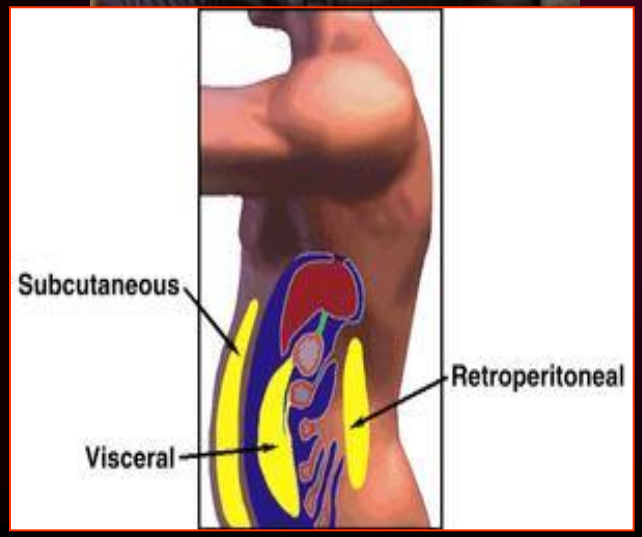
- Inflammatory cytokines (TNF alpha and IL-6)
- Increased CRP
- Prothrombotic substance: Plasminogen activator inhibitor 1 (PAI-1)
- Adipocytokines : Adiponectin, Leptin, Resistin, Visfatin etc

ABDOMINAL OBESITY

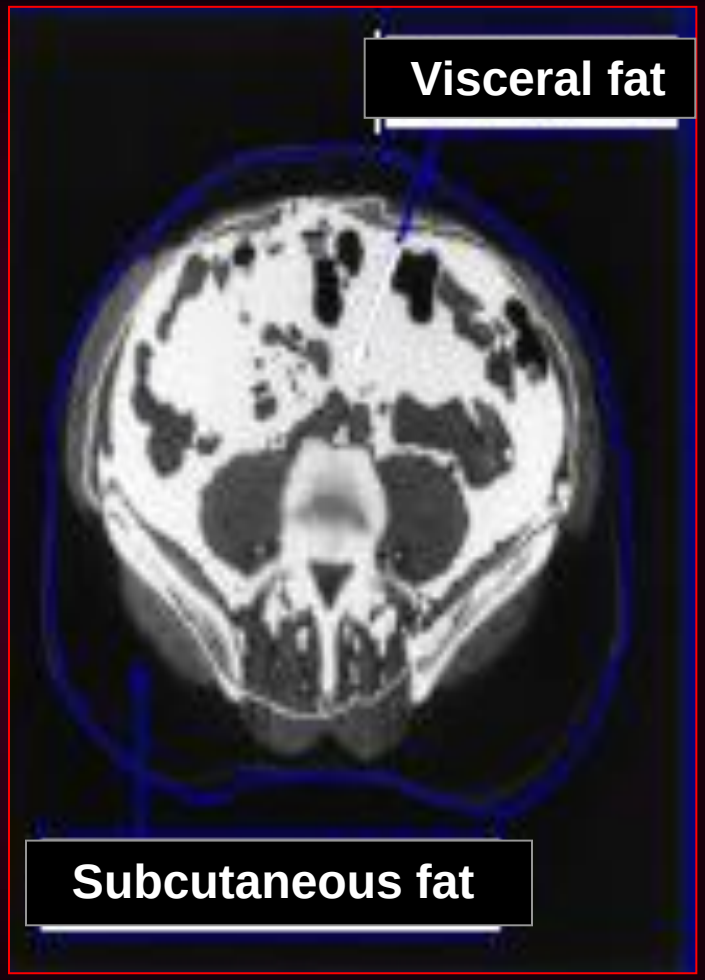


Adapted from Despres et al
Ann. Endocrinol (2001) 61 (Suppl 1):31 - 38

FOCUS ON CENTRAL OBESITY

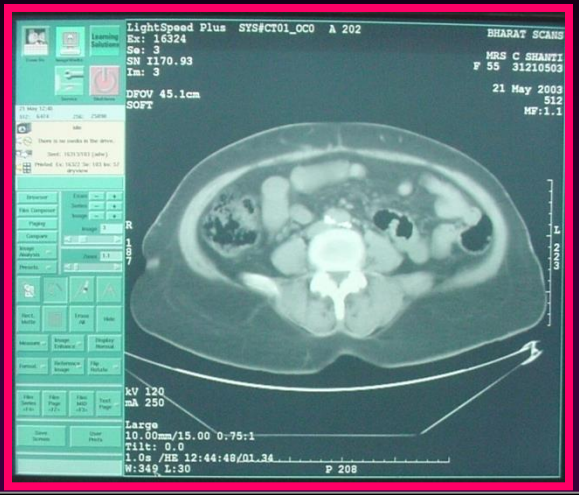


Front



Back

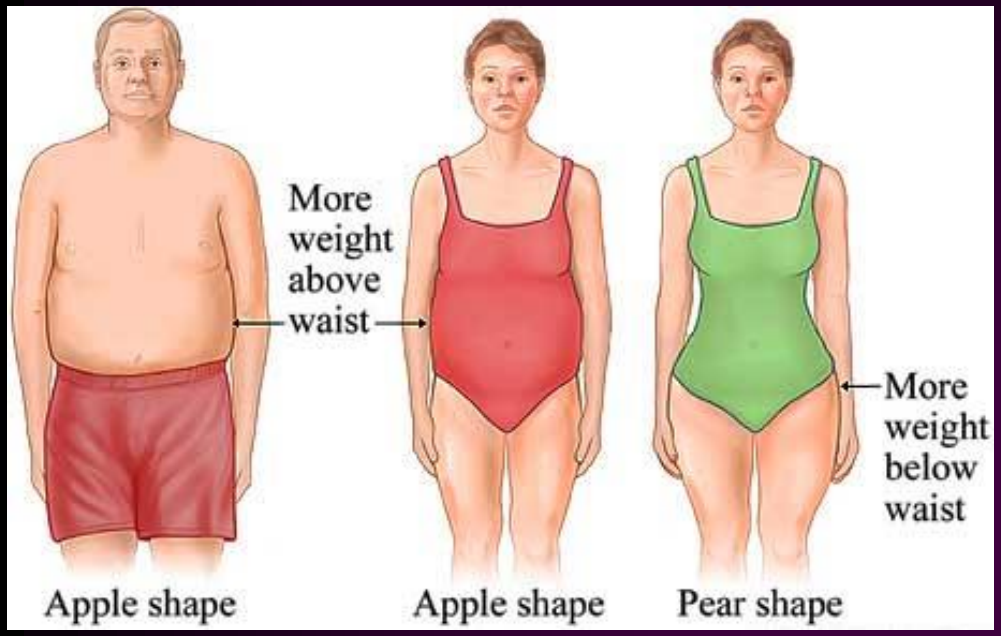
VISCERAL vs SUBCUTANEOUS FAT



Visceral Fat : Highest fractional lipolytic rate (Releases 26% of FFAs)

Factors released	Visceral Fat	Subcutaneous Fat
Plasminogen activator Inhibitor – 1 (PAI – 1)	↑↑	↑
Leptin	↑	↑↑
Angiotensinogen	↑↑	↑
Adiponectin	↓↓	↓
Tumor necrosis factor - α (TNF α)	↑	↑
Interleukin – 6	↑↑	↑

Wajchenberg, Endo. Rev. 2000



INCREASED WC

Early Detection Of Metsyn

TGL>200

and Intervention Will

TGL/HDL RATIO >3

Prevent Dm, HTN And CVD

HYPERTENSION

- Despite insulin resistance in adipose tissue and muscles, the kidneys remains insulin sensitive.
- High insulin levels increases renal sodium retention.
- 50% of patients with essential hypertension have insulin resistance.
- Insulin resistance patients with HTN are at greater risk of CVD than non-insulin resistant patients.

Intra-abdominal adiposity and dyslipidaemia

Triglycerides	↑↑
Fasting VLDL	↑
Non-HDL cholesterol	↑
Apolipoprotein B	↑
HDL cholesterol	↓↓
LDL cholesterol	(↑)
LDL small and dense particles	↑

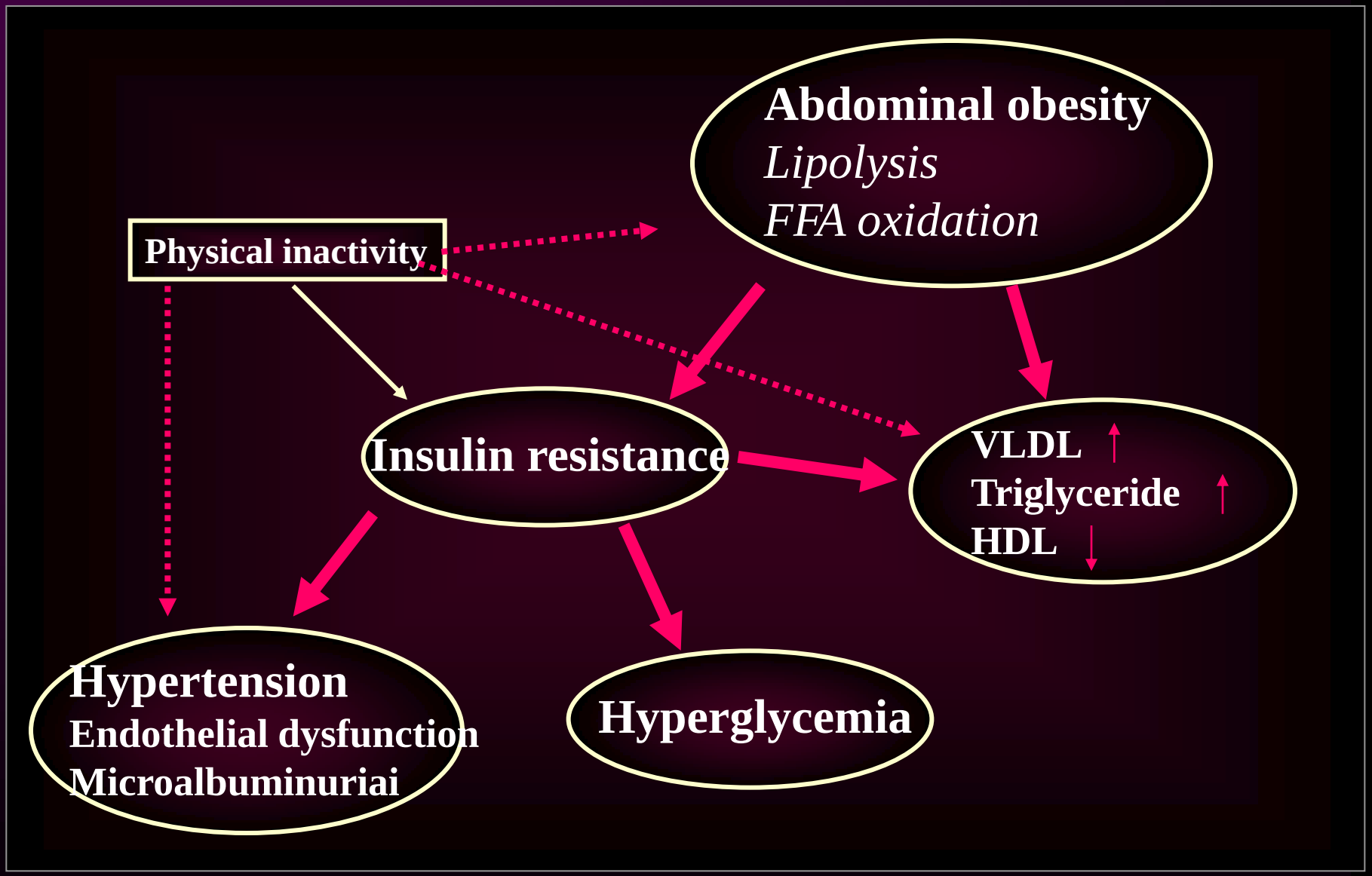
Causes of Metabolic Syndrome:

- Abdominal obesity
- Low physical activity
- Genetic factors

Mechanisms of metabolic syndrome

1) High energy fast-food environment, sedentary life style, and other obesogenic socioeconomic stress
2) Genetic predisposition to obesity and proinflammatory reactions
3) Obesity and fatty liver
4) Cell stress due to energy overload
5) Adipose tissue inflammation
6) Disregulation of adipokines such as leptin and adiponectin
7) Insulin resistance or selective insulin resistance
8) Cross-talks between insulin and angiotensin signaling systems
9) Leptin resistance or selective leptin resistance
10) Neurohormonal disregulation in hypophyseal-pituitary-adrenal axis
11) Dysfunction in autonomic nervous system
12) Endothelial dysfunction and oxidative stress
13) Low-grade systemic inflammation with hypercoagulability

THE METABOLIC SYNDROME



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SIGNIFICANCE OF METABOLIC SYNDROME

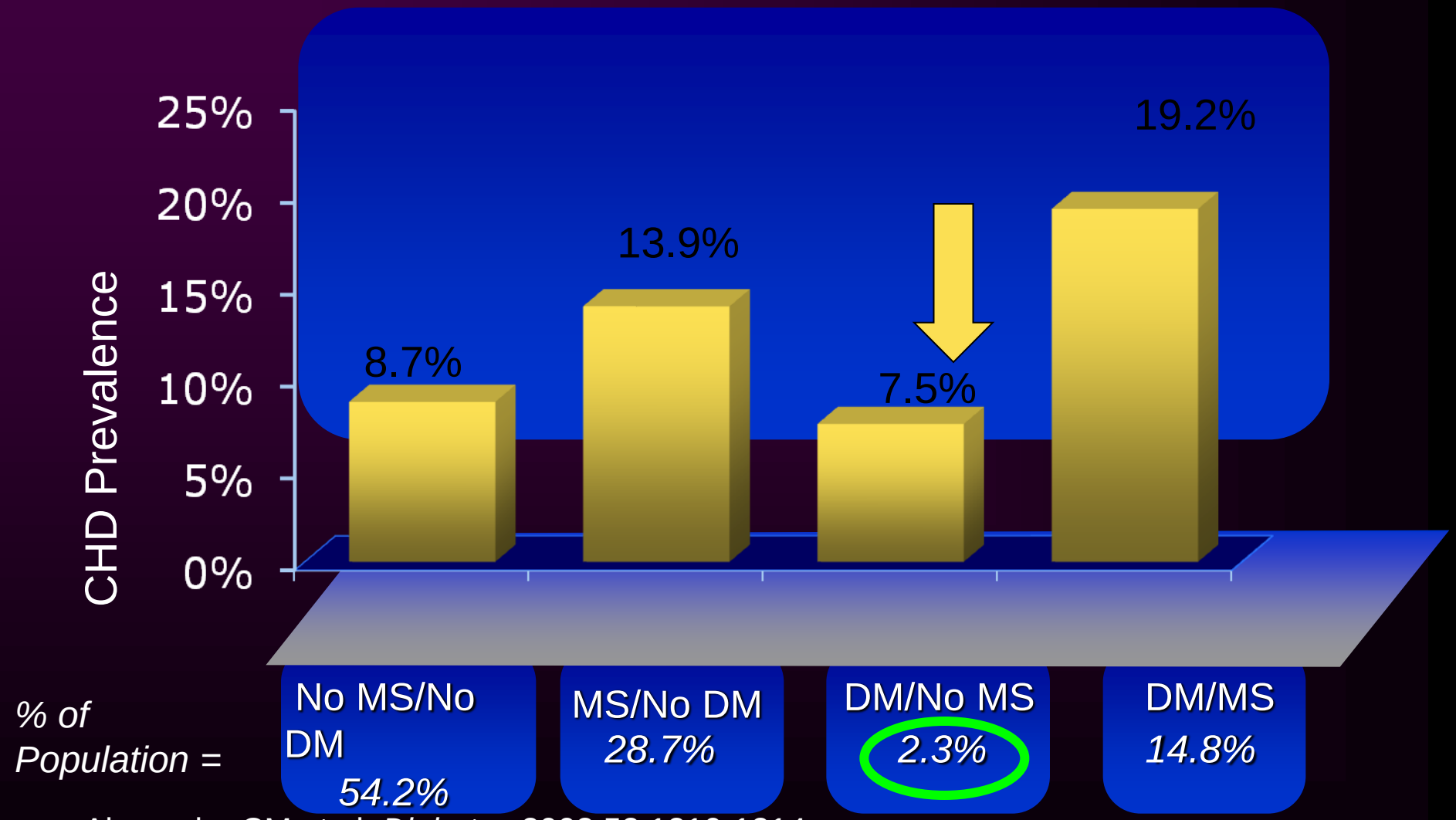
MS :

- **Is characterized by metabolic and hemodynamic abnormalities which increase the risk of cardiovascular disease.**
- **Is considered an independent risk factor for cardiovascular disease.**
- **Has been identified by NCEP ATP III as a trigger for intensive lifestyle modification, even in individuals with LDL cholesterol <100 mg/dL**

SIGNIFICANCE OF METABOLIC SYNDROME

- In diabetics, there is a strong correlation between metabolic syndrome and cardiovascular disease.
- Metabolic syndrome patients with Type II diabetes showed a higher prevalence of microalbuminuria or macroalbuminuria.
- Metabolic syndrome correlates with small LDL particle size pattern and the occurrence of preclinical atherosclerosis.

Prevalence of CHD by the Metabolic Syndrome and Diabetes in the NHANES Population Age 50+



Alexander CM et al. *Diabetes* 2003;52:1210-1214..

Prevalence of CHD by the metabolic syndrome and diabetes in the NHANES population age 50+

- NHANES subjects age 50 or higher, about 85% of diabetic subjects had the metabolic syndrome.
- The 15% of diabetic subjects without the metabolic syndrome did not have a high prevalence of CHD.
- Diabetic subjects without the metabolic syndrome have low triglyceride levels, high HDL-C levels, and blood pressure <130/85 mm Hg

Clinical outcomes of Metabolic syndrome

- Type 2 diabetes
- Essential hypertension
- Polycystic ovary syndrome (PCOS)
- Nonalcoholic fatty liver disease
- Sleep apnea
- Cardiovascular Disease (MI, PVD, Stroke)
- Cancer (Breast, Prostate, Colorectal, Liver)

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TREATMENT RATIONALE

Reducing underlying causes

Treat associated risk factors

Weight reduction

Increased physical activity

Antihypertensives

Aspirin

Lipid lowering agents

Insulin sensitizers

Healthy diet

Fast food ends life fast

TREATMENT OF RISK FACTORS SHOULD BE PRIORITIZED

- The most common clinical feature of metabolic abnormalities is excess body fat, which is associated with many of the additional defining characteristics
  - Reducing excess body fat should therefore be the focus of treatment and prevention
- Physical activity and diet modifications are indicated for the long-term treatment of metabolic syndrome
- Pharmacotherapy of dyslipidemia is indicated in high-risk groups

DIETARY INTERVENTIONS

- Reduce calories
- Reduce salt intake
- Reduce saturated fat
- Increase whole grains
- Increase fruits and vegetables
- Eat fish 1-2 times per week
- Use monounsaturated or polyunsaturated oils

  Olive, Canola, and Peanut Safflower, Sunflower or Sesame seed, Corn, or Soy

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CONTROVERSIES

1) Criteria are ambiguous or incomplete.
2) Rationale for thresholds are ill defined.
3) Value of including diabetes in the definition is questionable.
4) Insulin resistance as the unifying etiology is uncertain.
5) No clear basis for including / excluding other CVD risk factors. such as high-sensitivity CRP, fatty liver, and adiponectin
6) CVD risk value is variable and dependent on the specific risk factors present.
7) The CVD risk associated with the "syndrome" appears to be no greater than the sum of its parts.

CONTROVERSIES

8) Treatment of the syndrome is no different than the treatment for each of its components.

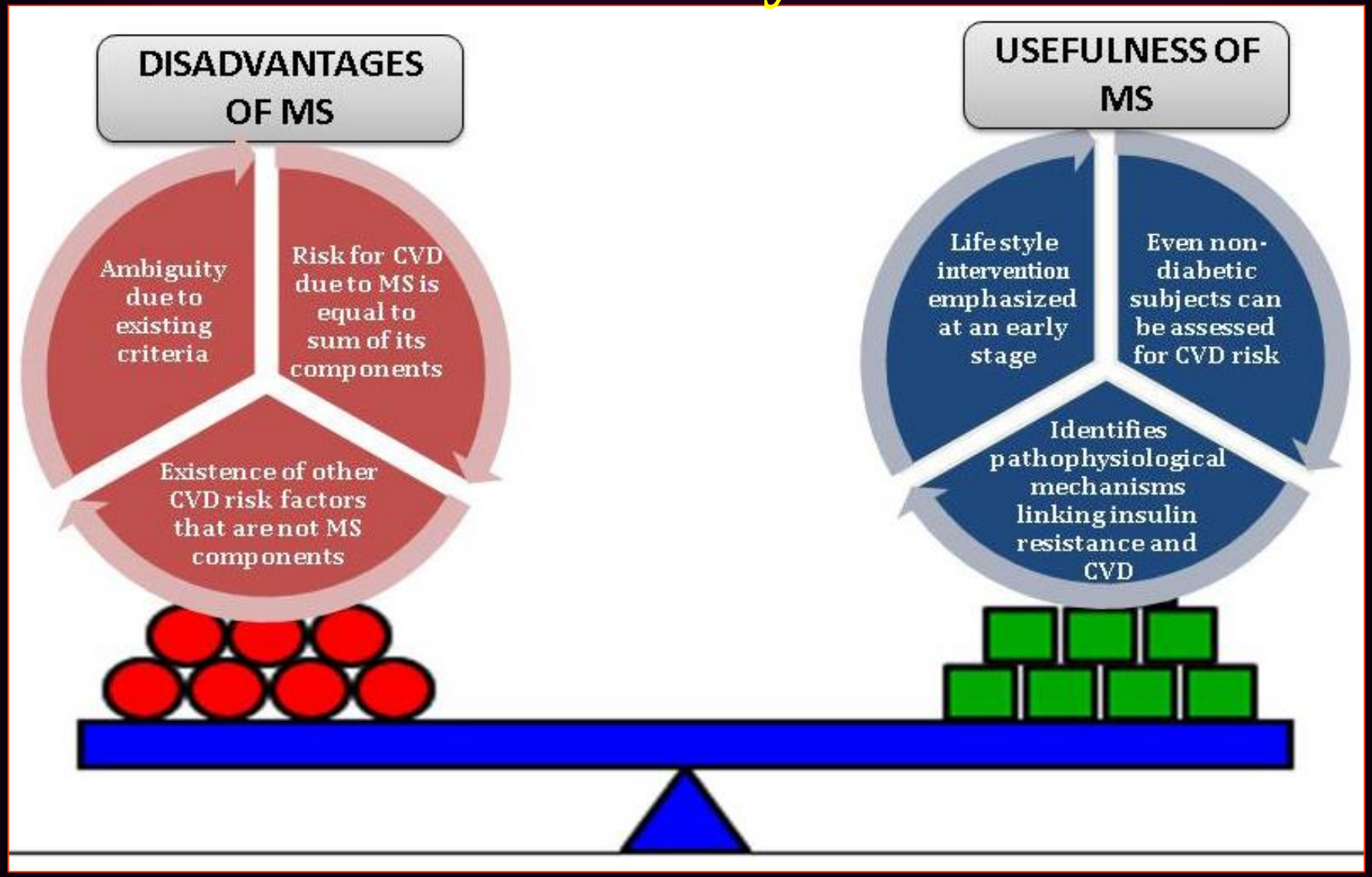
9) The medical value of diagnosing the syndrome is unclear.

10) Predicting diabetes and predicting cardiovascular disease are different issues which MetS seeks simultaneously

11) Superiority of waist circumference to body mass index is not scientifically established for defining obesity within MetS criteria

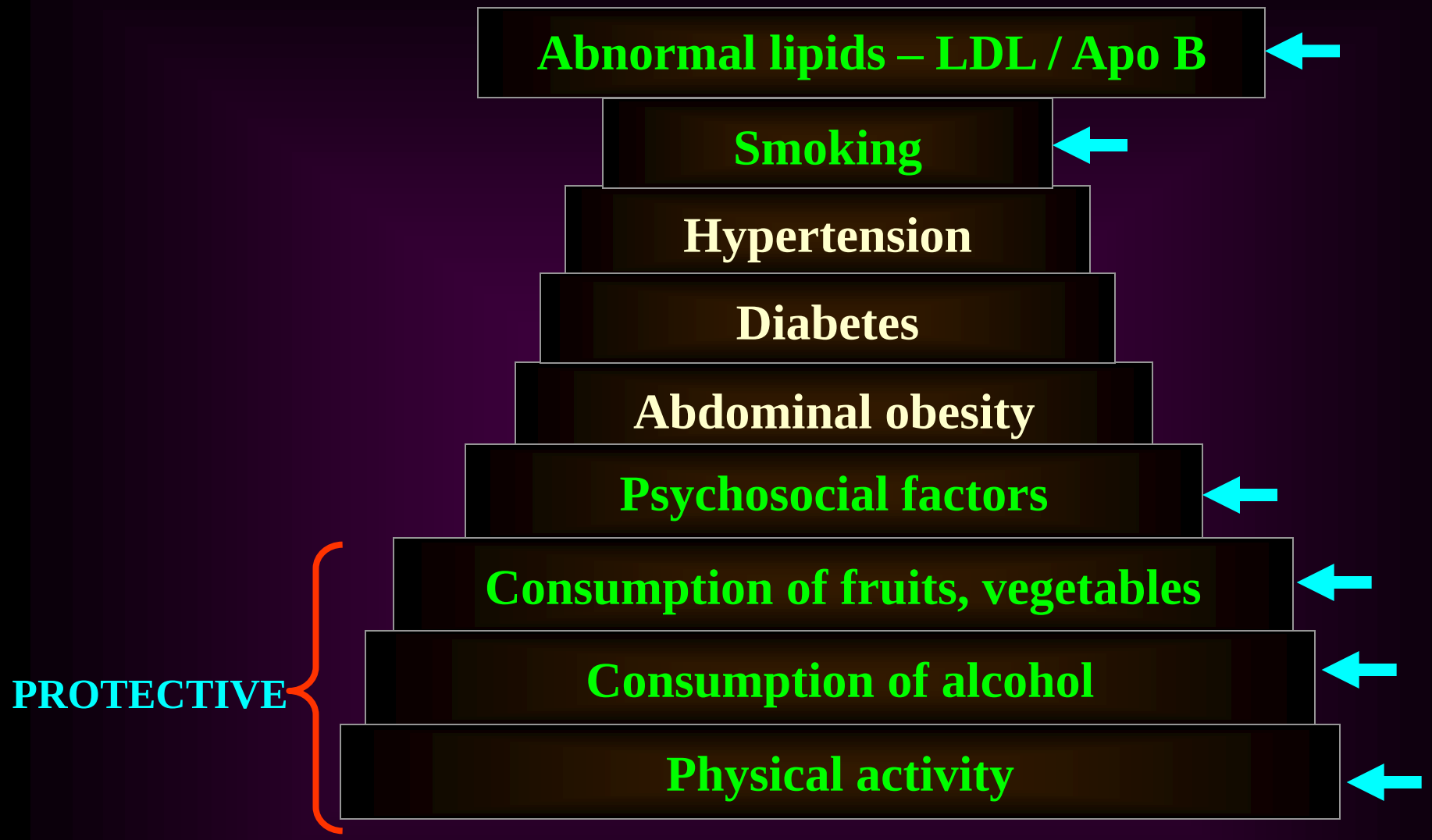
12) MetS has limited utility in epidemiological studies in which different ethnic-specific cutoff points of waist circumference are used

Usefulness and disadvantages and usefulness of metabolic syndrome



Indulekha K, Pitchumoni CS & Mohan V. Bentham eText. 2013 (in press)

RISK FACTORS FOR CAD



These 9 factors explain more than 90% of the risk of an acute myocardial infarction.
However 6/9 of these are not included in MS !

Yusuf S et al. INTERHEART STUDY. Lancet. 2004

OTHER PROBLEMS WITH MS

- Conveys to patients that they have a distinct disease – when they don't.
- Confounds research since the definition covers a wide range of parameters/values/risks.
- Detracts from the need to prioritize treatment based on benefits, risks and cost.
- Multiple definition make the diagnosis of MS a nightmare.
- There is no specific treatment for MS per se
- Not useful to initiate treatment as each risk factor has to be treated anyway

COMPARISON OF MS AND FRAMINGHAM RISK ASSESSMENT TOOL FOR PREDICTING CVD RISK WITH AN EXAMPLE

	Patient A	Patient B
Age / Sex	35 years / female	60 years / male
Family history of CVD	No	Strongly positive
Smoking	No	Smokes 50 cigarettes / day
Obesity (WC) in cm	81	89
Fasting plasma glucose (mgs%)	120	120
Blood pressure (mm Hg)	138 /86	120 / 75
Total cholesterol (mgs%) HDL cholesterol (mgs%) LDL cholesterol (mgs%)	150 35 70	300 46 200
Serum triglycerides (mg%)	180	148

"Patient A" has MS but "Patient B" has no MS However, the FRAMINGHAM RISK SCORE for "Patient A" is < 1 % and for "Patient B" is 24%

The Value of the Syndrome as a Concept

- Sufficient evidence exists to conclude that diabetes mellitus, hypertension, high triglycerides, low high-density lipoprotein cholesterol, and obesity, taken 2, 3, 4, or 5 at a time, occur more often than chance would dictate.
- The obvious utility of this knowledge is that the identification of 1 of these CVD risk factors in a patient should prompt a search for the others.

- **A syndrome exists associated with insulin resistance, or a syndrome associated with a handful of factors that portend CVD and whose origin includes and extends beyond insulin resistance.**

- **The risk of malignancies is increased in the presence of MetS or diabetes, with a linear relationship between cancer risk and plasma insulin levels.**
- **Thus, MetS suggests a more extended systemic pre-disease state beyond type 2 diabetes and cardiovascular disease.**

Role for MS, if at all

- A joint scientific statement from the American Heart Association and National Heart, Lung and Blood Institute assessment of short – term cardiovascular risk but in identifying people at increased long-term cardiometabolic risk who could benefit from early intensive lifestyle management.
- also useful in raising public awareness regarding the importance of central obesity ---also have MS.
- important avenues for medical research.

Finally, Is The Metabolic Syndrome A Useful Entity at All

Yes, it probably is!

- To gain knowledge about the pathophysiology linking lifestyle factors, insulin resistance, and CVD risk factors
- To enable comparisons of metabolic risk between groups
- To predict incident Diabetes and CVD in non-diabetic subjects
- To predict incident CVD in patients with diabetes
- Useful as a reseach tool
- Useful to identify individuals at high risk of diabetes and cardiovascular disease

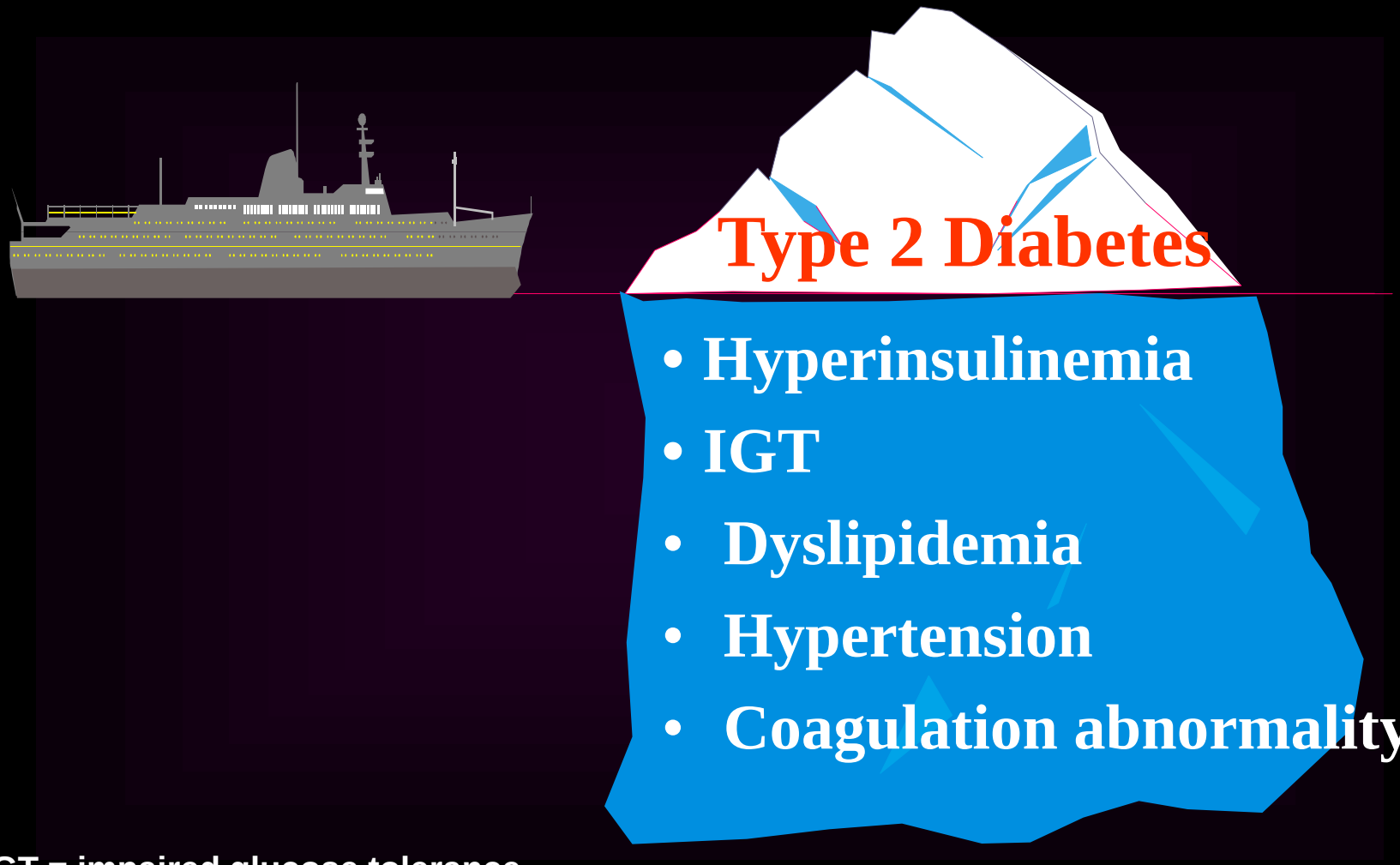
Disaster Not Under our Control

THANK YOU

FOR FOLLOWING LIFESTYLE MODIFICATION.

Thank you for your attention

INSULIN RESISTANCE - HIDDEN DANGERS



IGT = impaired glucose tolerance

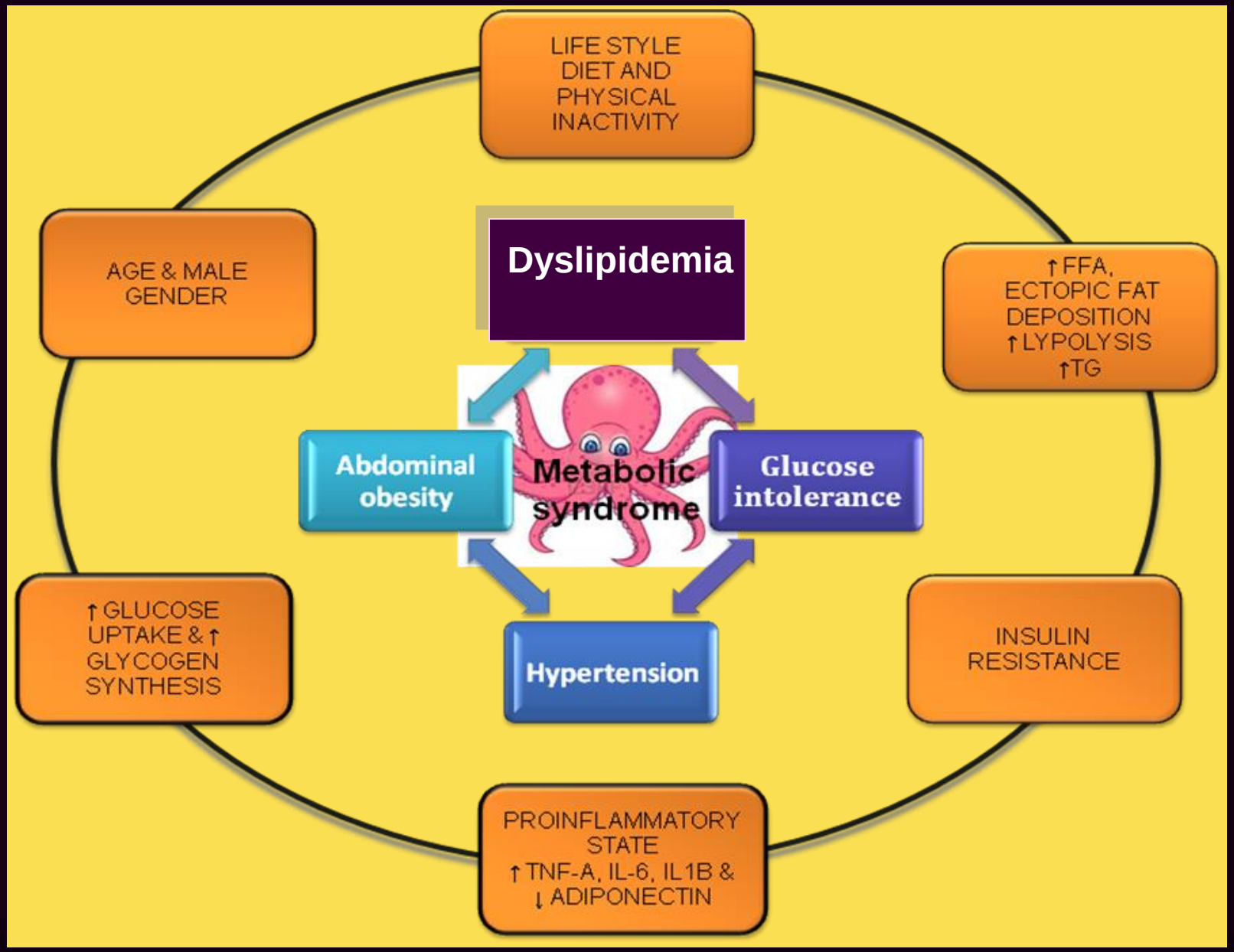
QUESTION:

Is MS really needed to predict CAD ?

EFFECTS OF EXERCISE

- Physical activity level is negatively associated with fasting insulin level.
- Regular moderate exercise promotes alterations of lipolytic enzymes and a significant increase in plasma HDL.
- Should include components that improve cardio-respiratory fitness, muscular strength and endurance.

Components and causes of metabolic syndrome



Indulekha K, Pitchumoni CS & Mohan V. Bentham eText. 2013 (in press)

MS *vs* IRS

Metabolic syndrome

- Cardiology concept
- A constellation of risk factors for cardiovascular disease
- The purpose of the concept is to heighten awareness of risks associated with obesity and sedentary life habits

Insulin resistance syndrome

- Endocrinology concept
- Describes a physiologic state that increases chances of
  - Type 2 diabetes
  - CVD
  - Hypertension
  - PCOS
  - NASH

The health consequences of obesity

Type 2 diabetes, the metabolic syndrome and cardiovascular disease in Europe

DYSLIPIDEMIA IN THE METABOLIC SYNDROME

Dyslipidemia in the metabolic syndrome

is characterized by:

- **Elevated triglyceride levels (VLDL)**
- **Reduced levels of HDL-C**
- **Increased incidence of small, dense LDL particles**

ATP III GUIDELINES FOR TREATMENT OF METABOLIC SYNDROME

Treat LDL cholesterol first

Targeted Area	Goal
CHD and CHD risk equivalent *(10-y risk for CHD >20%)*	<100 mg/dL
Multiple (2+) risk factors and 10-y risk < 20%	<130 mg/dL
Institute weight control	-10% from baseline
Institute physical activity	30 to 40 min/d for 3 to 5 d/wk
Monitor treatment of hypertension	<130/85 mm Hg

ATP III GUIDELINES FOR TREATMENT OF METABOLIC SYNDROME

Treat elevated triglycerides and low HDL cholesterol

Targeted Area	Goal
Goal of non-HDL cholesterol for patients with triglyceride >200 mg/dL and <499 mg/dL	**High CHD risk: <130 mg/dL** **Intermediate CHD risk: <160 mg/dL** **Low CHD risk: <190 mg/dL**

IS METABOLIC SYNDROME A USEFUL ENTITY?

Is insulin resistance a significant predictor of

- **CVD ?**
- **Diabetes ?**

DOES THE METABOLIC SYNDROME PREDICT CVD? (Data from MRFIT)

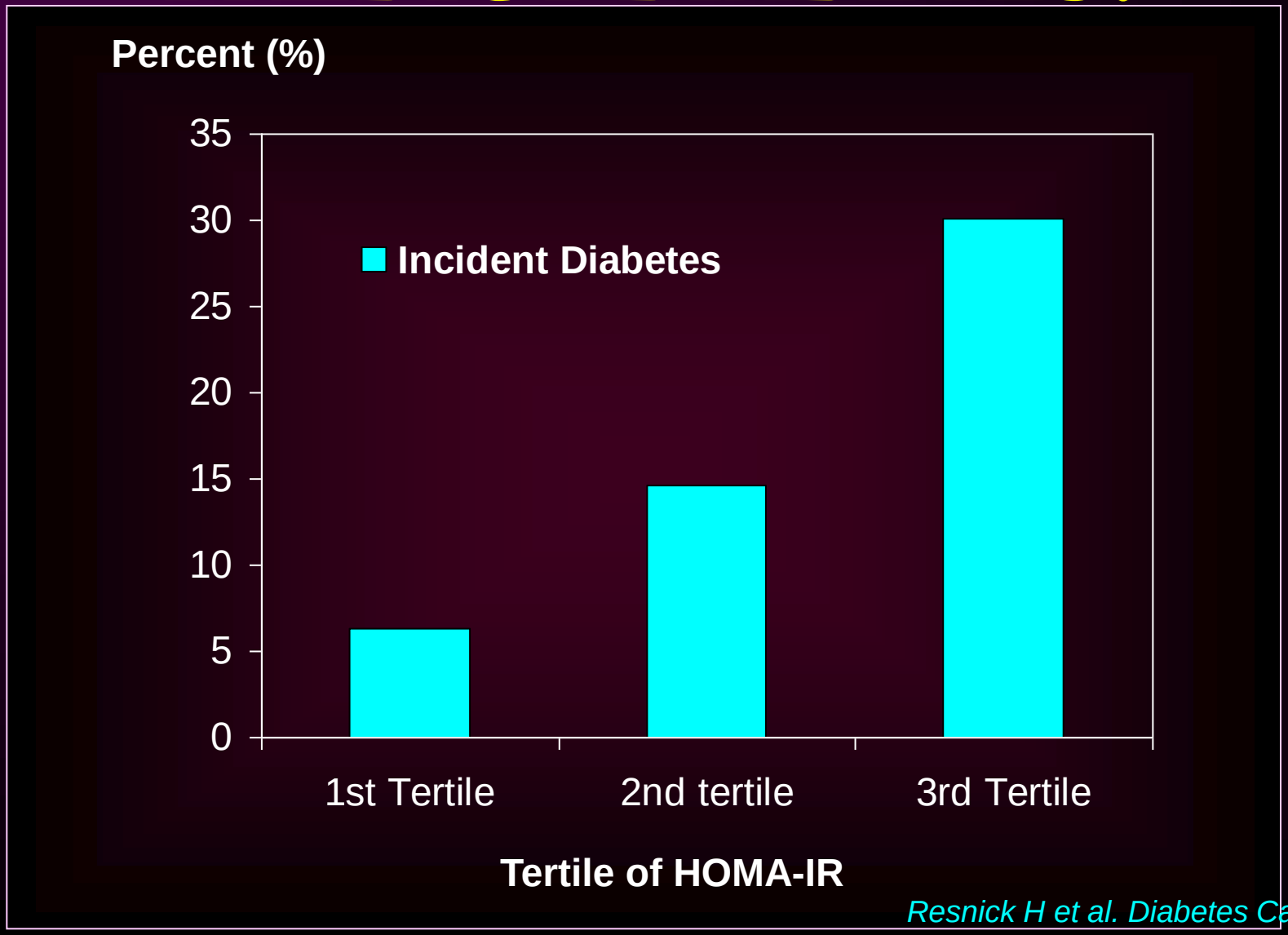
Variable (CVD Mortality)	Odds Ratio **
ATP III definition	1.49 (1.35 – 1.64)
One condition	1.09 (0.86 – 1.39)
two conditions	1.29 (1.02 – 1.63
three conditions	1.51 (1.19 – 1.92)
four conditions	1.98 (1.55 – 2.53)
five conditions	2.98 (2.24 – 3.95)

* Incident CVD in 4,588 men, 35 – 57 y.o. followed for 18 years

** Adjusted for age, race, education, family hisotry, smoking.

Eberly LE et al, Diabetes Care, 29: 123 – 130, 2006

DOES HYPERINSULINEMIA PREDICT DIABETES?



Resnick H et al. Diabetes Care 2003

Demonstrated in:

- San Antonio Heart study
- Mexico city Study
- IRAS **(Insulin resistance Atherosclerosis study)**

DOES HYPERINSULINEMIA PREDICT CVD?

	N	Follow up	Men	Women
Busselton	3390	12 years	√	ns
Helsinki Policemen	970	9.5 years	√	--
Helsinki Policemen	970	22 years	√	--
SAHS	2569	8 years	√	√
DECODE6156 men	12507	8.8 years	√	√

DOES THE METABOLIC SYNDROME PREDICT CVD IN PATIENTS WITH DIABETES?

	N	Follow up	HR
Botnia Study	1697	6.9 years	2.23 (1.52-3.26)
Verona D&C Study	946	4.5 years	4.89 (1.16-20.7)
Kuopio	902	7 years	1.43 (1.18-1.73)

A concise chronological table of metabolic syndrome (MetS)

2001:	National Cholesterol Education Program (NCEP) Criteria of MetS: The clustering of 3 or more of the following 5 components: abdominal obesity, high blood pressure, impaired fasting glucose, hypertriglyceridemia, and hypoHDL cholesterolemia
2005:	International Diabetes Federation (IDF) Criteria of MetS: Abdominal obesity is necessary among the 5 components Japanese Criteria of MetS: Visceral fat syndrome as Japanese MetS coordinating with the IDF Criteria American Heart Association (AHA)/National Heart, Lung, and Blood Institution (NHLBI): Revised NCEP Criteria American Diabetes Association (ADA)/European Association for the Study of Diabetes: Do not label individuals with MetS
2007:	ADA/Obesity Society/American Society for Nutrition: The clinical usefulness of waist circumference is limited
2009:	IDF/AHA/NHLBI/World Heart Federation/International Atherosclerosis Society/International Association for the Study of Obesity: Revised NCEP Criteria were adopted as harmonizing worldwide criteria of MetS although cutoff points of waist circumference could not be determined for any particular ethnic group
2010:	WHO Expert Consultation report: MetS has limited utility as a tool for clinical management or epidemiological study

- **That is; IDF withdrawn its 2005 definition of MetS. However, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) jointly stated that no existing definition of MetS meets criteria as a syndrome , and**
- **WHO Expert Consultation reported that MetS is an educational concept that focuses attention on complex multi factorial health problems, is a pre-morbid condition rather than a clinical diagnosis, and has limited practical utility as a diagnostic or management tool and that there is limited utility in epidemiological studies in which different criteria of MetS are compared.**

- **Established components of MetS are**
- **increased waist circumference (WC), high blood pressure, increased serum triglyceride levels, decreased serum highdensity lipoprotein (HDL) cholesterol levels, and impaired fasting glucose.**

Brief history of MetS

- In 1956, Vague suggested that abdominal obesity may predispose to diabetes and cardiovascular disease.
- In 1981, Ruderman et al. pointed out that there were metabolically obese, normal-weight (MONW) individuals who might be characterized by hyperinsulinemia and possibly increased fat cell size .
- In 2003, the American Association of Clinical Endocrinologists modified this definition to refocus on insulin resistance as the primary cause of MetS and again excluded diabetic subjects from MetS and returned to the name IRS.

- **2009: IDF/AHA/NHLBI/World Heart Federation/International**
- **Atherosclerosis Society/International Association for the Study of Obesity: Revised NCEP Criteria were adopted as harmonizing worldwide criteria of MetS although cut off points of waist circumference could not be determined for any particular ethnic group**

Definition of Metabolic Syndrome in Women

Any 3 of the following:

- Abdominal obesity (waist circumference ≥ 80cm)
- High triglycerides ≥ 150 mg/dL
- Low HDL-C cholesterol < 50 mg/dL
- Elevated BP ≥ 130/85 mm Hg
- Fasting glucose ≥ 100 mg/dL

Source: AHA/NHLBI 2011

- **In Japan, visceral fat syndrome was adopted as the**
- **Japanese MetS by the Examination Committee for Criteria of Metabolic Syndrome in 2005.**

- **The conclusions of these studies showed that the risk contribution of the two fat compartments is not substantially different and subcutaneous adipose tissue cannot be ignored as a risk contributor.**

- **In 2009, it was clarified that the MetS definition requiring obesity is dangerous because normal-weight individuals have a high mortality risk and are more prevalent than overweight or obese subjects, and that IDF MetS is inferior to revised NCEP**
- **MetS as a predictor of cardiovascular disease by studies using Japan Public Health Center-based (JPHC) data.**

Mechanisms of MetS

- Katagiri et al. emphasized dysfunction of autonomic nervous system and leptin resistance as underlying mechanisms of MetS and Dandona et al. emphasized the reciprocal relationship between insulin resistance and inflammation as a core mechanism of MetS.

Limitations and prospects of MetS concept

- ADA and EASD summarized concerns regarding MetS as followings.
- (1) Criteria of MetS are ambiguous or incomplete and rationale for thresholds of MetS components are ill-defined.
- (2) Value of including diabetes in MetS definition is questionable.
- As WHO Expert Consultation reported, MetS is an educational concept that focuses attention on complex multifactorial health problems and is a pre-morbid condition rather than a clinical diagnosis.

Table 1. Existing definitions of metabolic syndrome

NCEP ATP III ≥ 3 criteria	AHA / NHLSI ≥ 3 criteria	IDF (obesity + ≥ 2 other criteria)	WHO (Insulin resistance + ≥ 2 other criteria)
Waist circumference: > 102 cm (men) > 88 cm (women)	Waist circumference: ≥ 102 cm (men) ≥ 88 cm (women)	Waist circumference: Ethnicity specific*	Body mass index: > 30 kg / sq.m and / or WHR: > 0.9 (men) > 0.85 (women)
Triglycerides (mg/dl): >150 mg/ dl	Triglycerides: (mg/dl) ≥ 150 mg/dl or treatment for hypertriglycreidemia	Triglycerides: (mg/dl) ≥ 150 mg / dl or treatment for hypertriglycreidemia	Triglycerides: (mg/dl) >150 mg/ dl
HDL (mg/dl): < 40 (men) < 50 (women)	HDL (mg/dl): < 40 (men) < 50 (women) or treatment for low HDL-c	HDL (mg/dl): < 40 (men) < 50 (women) or treatment for low HDL-c	HDL (mg/dl): < 40 (men) < 50 (women)
Blood pressure: ≥130/85 mm Hg or treatment for hypertension	Blood pressure: ≥130/85 mmHg or treatment for hypertension	Blood pressure: ≥130/85 mmHg or treatment for hypertension	Blood pressure: ≥140/90 mmHg or treatment for hypertension
Fasting glucose: 100 – 125 mg/dl	Fasting glucose: ≥ 100 mg/dl or treatment for hyperglycaemia	Fasting glucose: ≥ 100 mg/dl or diagnosis of diabetes mellitus	Insulin resistance: Type 2 diabetes mellitus, impaired fasting glucose and impaired glucose tolerance
			Urinary albumin: > 20 mg/dl Albumin- creatinine ratio : 30 mg /g

NCEP ATP III : National Cholesterol Education Program Adult Treatment Panel III; AHA/NHLBI : American Heart Association/ National Heart, Lung, and Blood Institute; IDF : International Diabetes Foundation; WHO : World Health Organization HDL : high-density lipoprotein
*Europeans: men >94 cm, women >80 cm; South Asians: men >90 cm, women > 80 cm; Chinese: men > 90 cm, women > 80 cm; Japanese: men > 85 cm, women >90 cm ; South and Central Americans: men > 90 cm, women > 80 cm; Sub-Saharan Africans: Men > 94 cm, Women > 80 cm; Eastern Mediterranean and Middle East (Arab) populations: men > 94 cm, women > 80 cm

- **The question of how to define a syndrome rests in a large part on the purpose of the construct. A syndrome can be defined on the basis of its ability to predict future adverse events. Such definitions imply that the syndrome is greater than the sum of its parts and that the factors included have greater predictive power than do other combinations.**

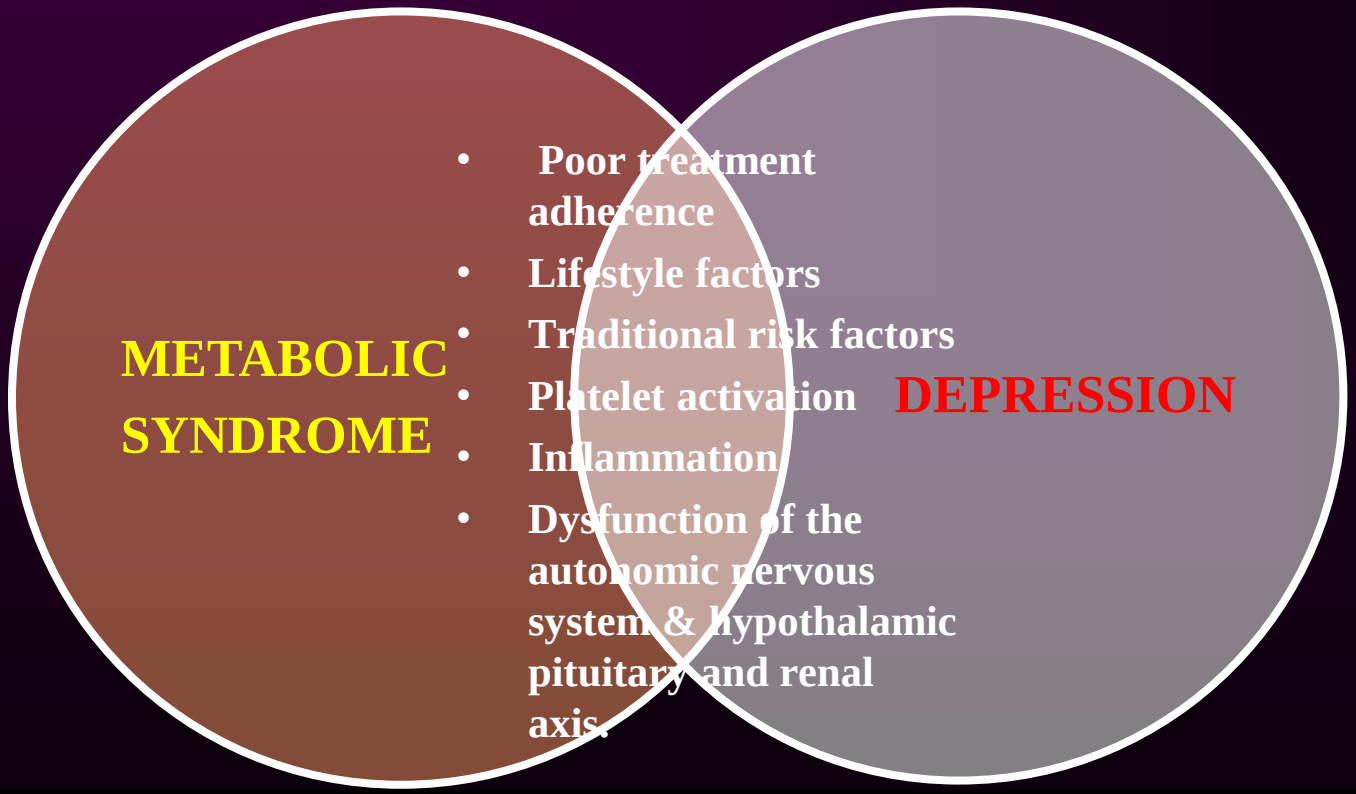
- **Only about half to two thirds of those people with the diagnosis of the metabolic syndrome are indeed insulin resistant, and a smaller proportion of those with insulin resistance meet the criteria for metabolic syndrome.**
- **As to the relationship between each component of**
- **On the other hand, when hypertension and dyslipidemia occur by themselves or in the absence of diabetes mellitus and obesity, they are far less frequently associated with insulin resistance.**

- **First, as mentioned above, obesity is not a result of insulin resistance but a cause of it, and only about half of those who are obese are insulin resistant.**

- **Fasting plasma glucose is a far better predictor of diabetes mellitus than any of the combinations of factors that denote the presence of the metabolic syndrome.**

Metabolic Syndrome & Depression

- A strong relationship between the metabolic syndrome and depression 70% higher prevalence of depression in women.
- In the WISE study, approximately one in four women reported prior treatment for depressive symptoms.
- POSSIBLE MECHANISMS LINKING DEPRESSION AND THE METABOLIC SYNDROME

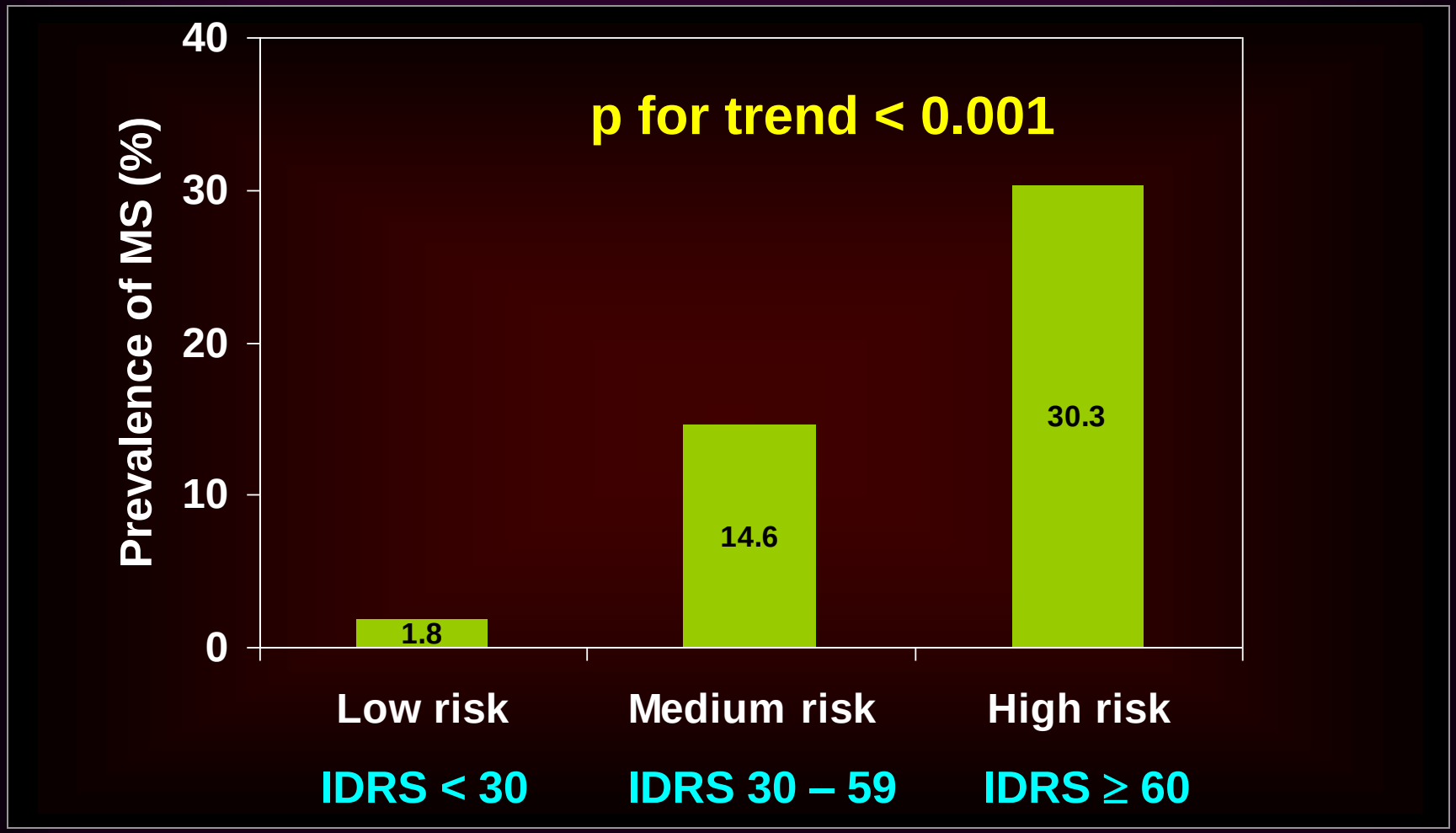


METABOLIC SYNDROME & INCIDENT DIABETES

Lorenzo et al, Diabetes Care, 26: 3153 – 3159, 2003

PREVALENCE OF METABOLIC SYNDROME IN RELATION TO INDIAN DIABETES RISK SCORE (IDRS)

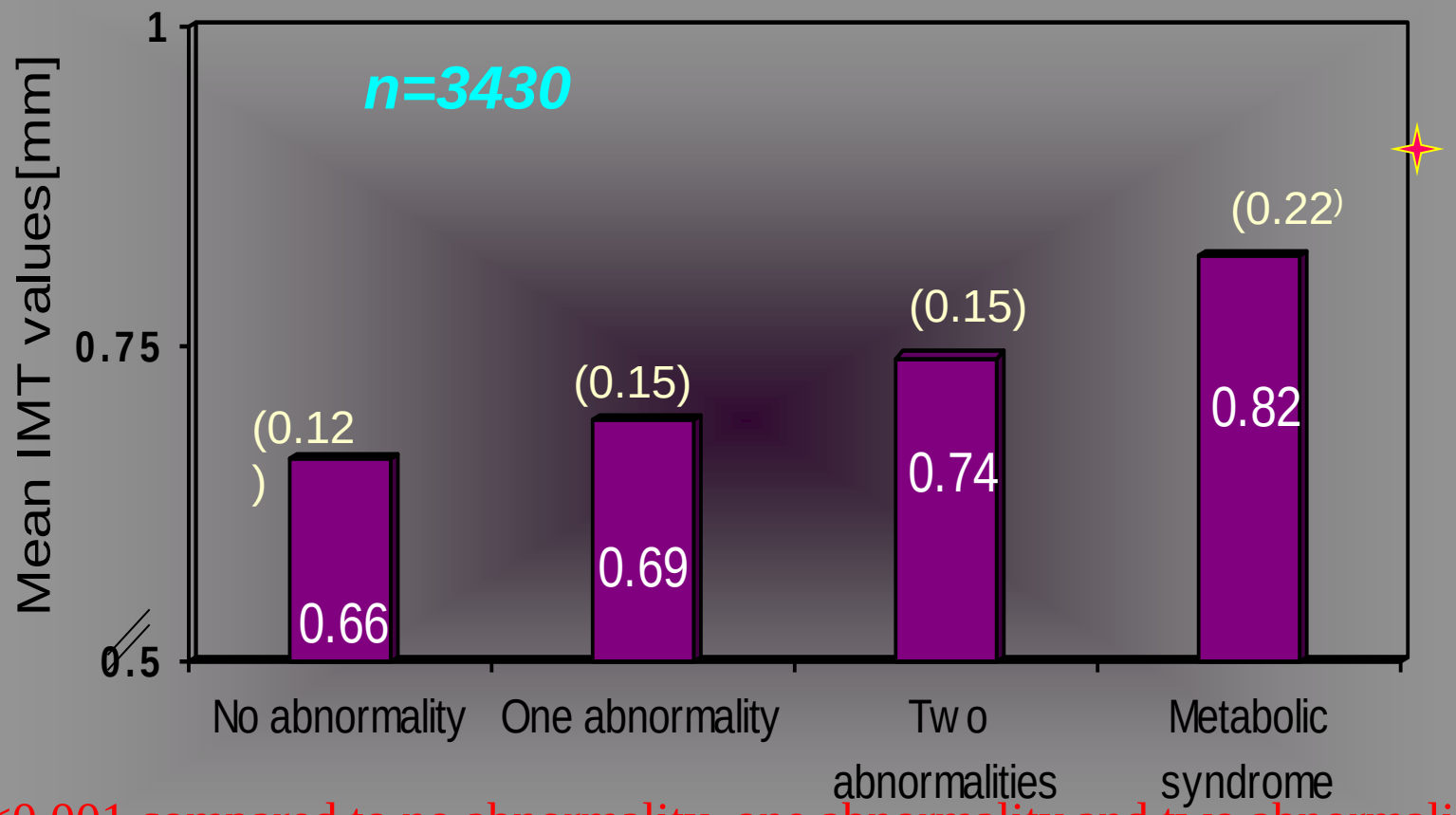
(n = 1734)



Mohan V, Sandeep S, Deepa M, Gokulakrishnan K, Datta M, Deepa R, Diabetes Obesity Metabolism, UK. 2007;9:337-43.

METABOLIC SYNDROME AND CAROTID INTIMAL MEDIAL THICKNESS

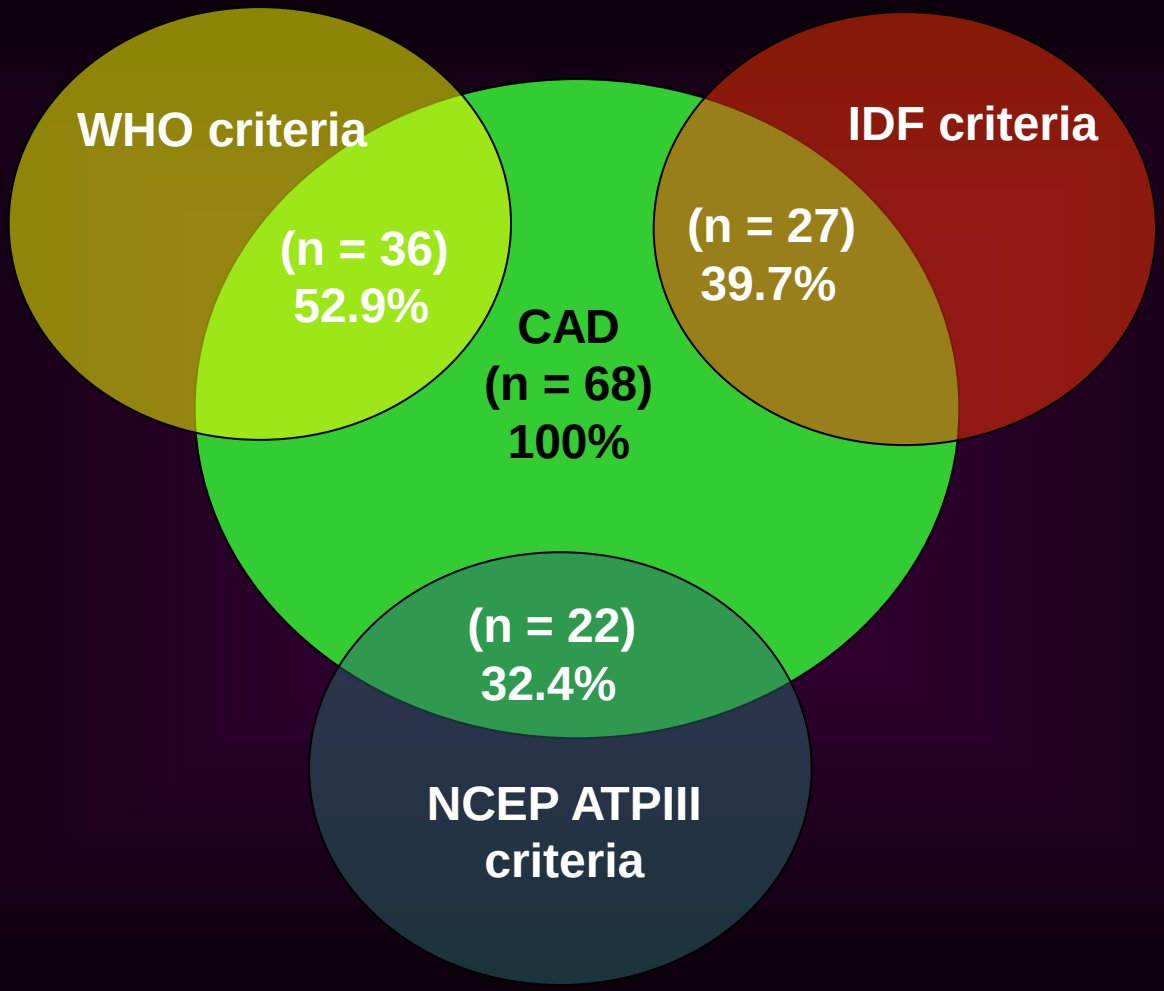
The Chennai Urban Rural Epidemiology Study [CURES]



p<0.001 compared to no abnormality, one abnormality and two abnormalities

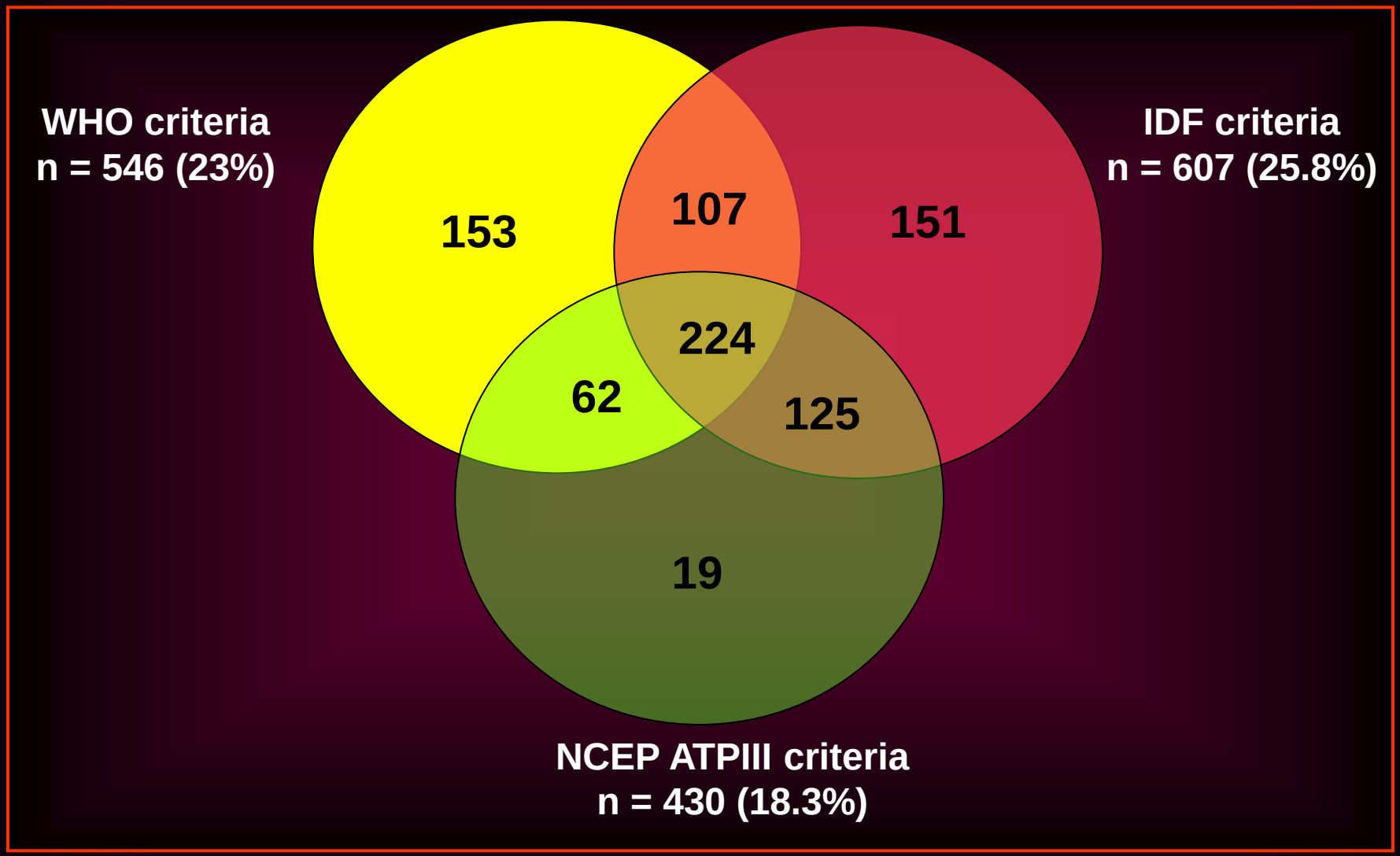
Mohan V et al, Diabetic Medicine, UK, 2006; 23: 845 - 850

PREDICTION OF CORONARY ARTERY DISEASE BY DIFFERENT CRITERIA OF METABOLIC SYNDROME



Deepa M, Farooq S, Datta M, Deepa R, Mohan V. Diabetes Metabolism Research & Reviews, UK. 2007;23:127-34.

METABOLIC SYNDROME DEFINED BY DIFFERENT CRITERIA CURES Phase 3 – 2350 / 2600 (Response Rate – 90.7%)



Deepa M, Farooq S, Datta M, Deepa R, Mohan V. Diabetes Metabolism Research & Reviews, UK. 2007;23:127-34.

1 ST STEP OF PREVENTION OF DIABETES – IDENTIFYING SUBJECTS WITH HIGH RISK

INDIAN DIABETES RISK SCORE [IDRS]

? Website: www.drmohansdiabetes.com	SCORE
Age	
< 35 years	0
35 – 49 years	20
≥ 50 years	30
Waist circumference [Pant size]	
Waist <80 cm (32″) [female] , <90 (36”) [male]	0
Waist ≥ 80 – 89 cm (32″ – 35″) [female] ≥ 90 – 99 (36″ – 39″) cm [male]	10
Waist ≥90 cm (36″) [female] ≥ 100 cm(40″) [male]	20
Physical activity	
Vigorous exercise [regular] or strenuous [manual] labour at home / work	0
Moderate exercise [regular] or moderate physical activity at home / work	10
Mild exercise [regular] or mild physical activity at home / work	20
No exercise and sedentary activities at home / work	30
Family history	
No family history	0
Either parent	10
Both parents	20

Score

≥60:	Very high risk
30-50:	Moderate risk
<30:	Low risk

Mohan V et al, Journal of Association of Physicians of India,2006; 53,759-63

Risk Factors for Abdominal obesity

- Dyslipidemia
  - Elevated TG
  - Elevated apo B
  - Small LDL
  - Low HDL
- Elevated BP
- Elevated Glucose
- Prothrombotic state
- Proinflammatory state

- Abdominal Obesity

Measuring obesity Body Mass Index

- Obesity is most commonly assessed by a single measure, the Body Mass Index (BMI), which uses a mathematical formula based on a person's height and weight.

$$BMI = weight\ (kg)/height\ (m^2)$$

- Individuals with a BMI
  - between 25 to 29.9 are considered overweight
  - of 30 and above are considered obese.
- The risk of serious health consequences such as type 2 diabetes, coronary heart disease, hypertension, dyslipidaemia, albuminuria and a wide range of other conditions increases with BMI.

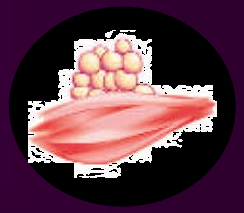
Measuring obesity up to here
The limitations of the Body Mass Index

- **BMI DOES NOT**
  - **show the difference between excess fat and muscle.**
  - **identify whether the fat is laid down in particular sites. For example, abdominal fat has more serious health consequences than fat located elsewhere.**
- **The relation between fatness and BMI differs with age, race and gender.**

Adverse consequences of chronic adiposity and ectopic fat

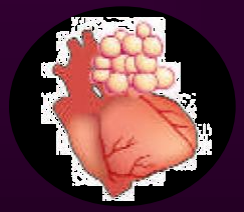
Lipid overflow ectopic fat

Altered FFA metabolism
Altered release of adipokines



↑Muscle fat

(↑Intracellular lipid)



↑Epicardial fat

↑Liver fat and altered function

↓Cardiac function

↓Insulin sensitivity
Dyslipidemia

↓β-cell function
Atherosclerosis
NASH

FFA = free fatty acids

NASH = nonalcoholic steatohepatitis

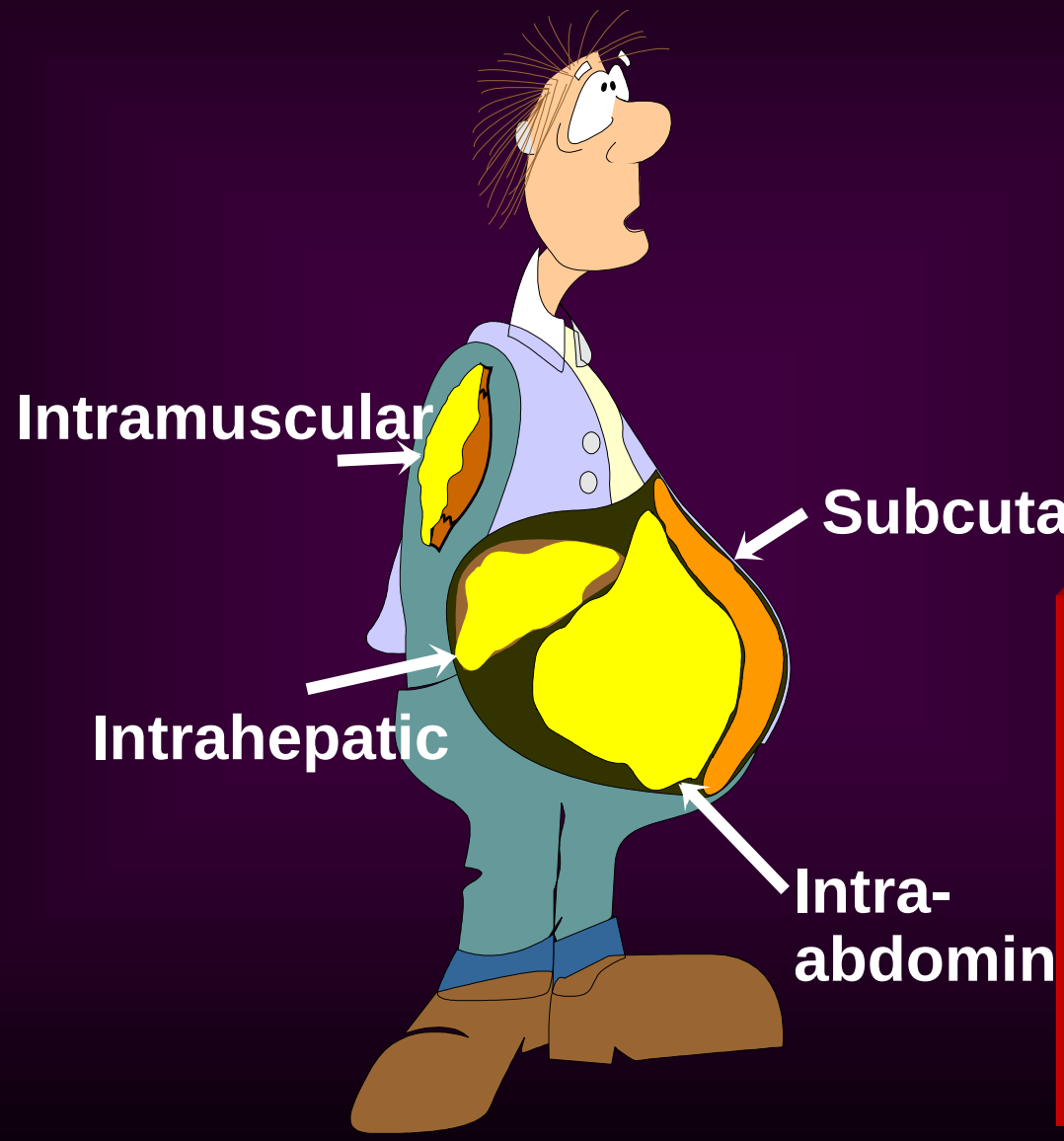
Adapted from Després J-P, Lemieux I. *Nature*. 2006;444:881-7.

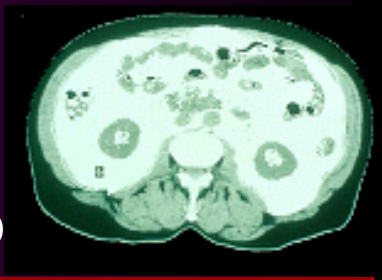
Molavi B et al. *Curr Opin Cardiol.* 2006;21:479-85.

Insulin resistance: the link between obesity and type 2 diabetes?

- **Obesity and type 2 diabetes are causally linked.**
- **The means by which excess body fat causes type 2 diabetes is not clearly defined, but it appears that excess fat increases insulin resistance, raising blood glucose levels and the likelihood of developing diabetes.**

The Evolving View of Adipose Tissue: an Endocrine Organ





FFA*

TNF-alpha*

Leptin*

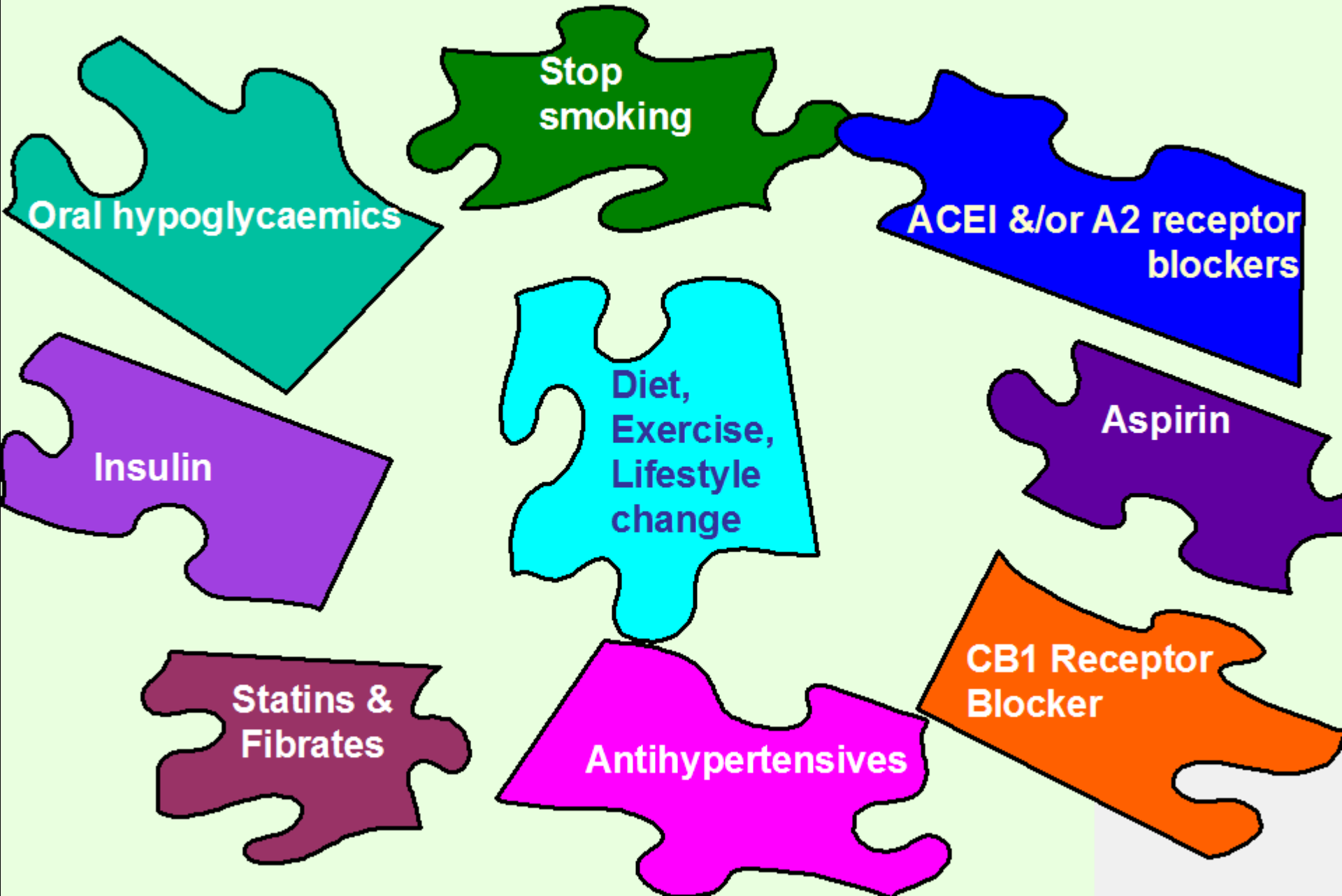
Metabolic Syndrome/Insulin Resistance: Cardiovascular Risk

- Increased vascular inflammation
- Accelerated platelet activity
- Impaired fibrinolysis

Metabolic Syndrome and the Risk for Cardiovascular Disease

- Risk for CVD disease X2-4 fold
- Calculate10-yr risk using Framingham risk scores: double the score if patient has the metabolic syndrome

Treatment of Metabolic Syndrome



Medications:

- **Hypertension:**
  - ACE inhibitors, ARBs
  - Others - thiazides, calcium channel blockers, beta blockers, alpha blockers
- **Dyslipidemia:**
  - Statins, Fibrates, Niacin
- **Anti obesity:**
  - Sibutramine, Cannibinoid receptor blockers, Orlistat
- **Platelet inhibitors:**
  - ASA, clopidogrel

Managing obesity

- **Obesity is the main modifiable risk factor for type 2 diabetes.**
- **Small amounts of weight loss (5%–10%) can prevent or delay the development of type 2 diabetes in individuals with a high risk of the disease.**
- **Even a 5% weight reduction in those who are overweight or obese improves the risk of complications such as heart disease.**

Diet for the Metabolic Syndrome

- Primary emphasis is to reduce saturated fats
- Total fat should range 25-30% for most cases
- Those with metabolic syndrome avoid very high fat intake also avoid very low fat intake (low HDL & high TG)
- Total fat intake can range from 30-35% if extra fat in unsaturated
- May reduce some lipid and non lipid risk factors
- Clinical judgment required

Stratton IM *et al*. *BMJ* 2000; 321: 405–412.

Smoking Cessation / Avoidance:

- A risk factor for development in children and adults
- Both passive and active exposure harmful
- A *major risk factor for:*
  - insulin resistance and metabolic syndrome
  - macrovascular disease (PVD, MI, Stroke)
  - microvascular complications of diabetes
  - pulmonary disease, etc.

Stratton IM *et al*. *BMJ* 2000; 321: 405–412.

Summary

- **Metabolic syndrome is prevalent world wide and is associated with an increased risk of mortality, particularly from cardiovascular disease.**
- **Physical activity has an important role to play in both the primary and secondary prevention of metabolic syndrome.**
- **Tight blood sugar control, Lipid control and blood pressure control reduces risk associated with this syndrome.**