

METABOLIC & ENDOCRINE CONSEQUENCES OF OBESITY STRESS-METABOLIC SYNDROME WITH PSYCHIATRY COMPONENT

Metabolic syndrome
(Syndrome X)

- Central obesity
- High blood pressure
- High triglycerides
- Low HDL-cholesterol
- Insulin resistance



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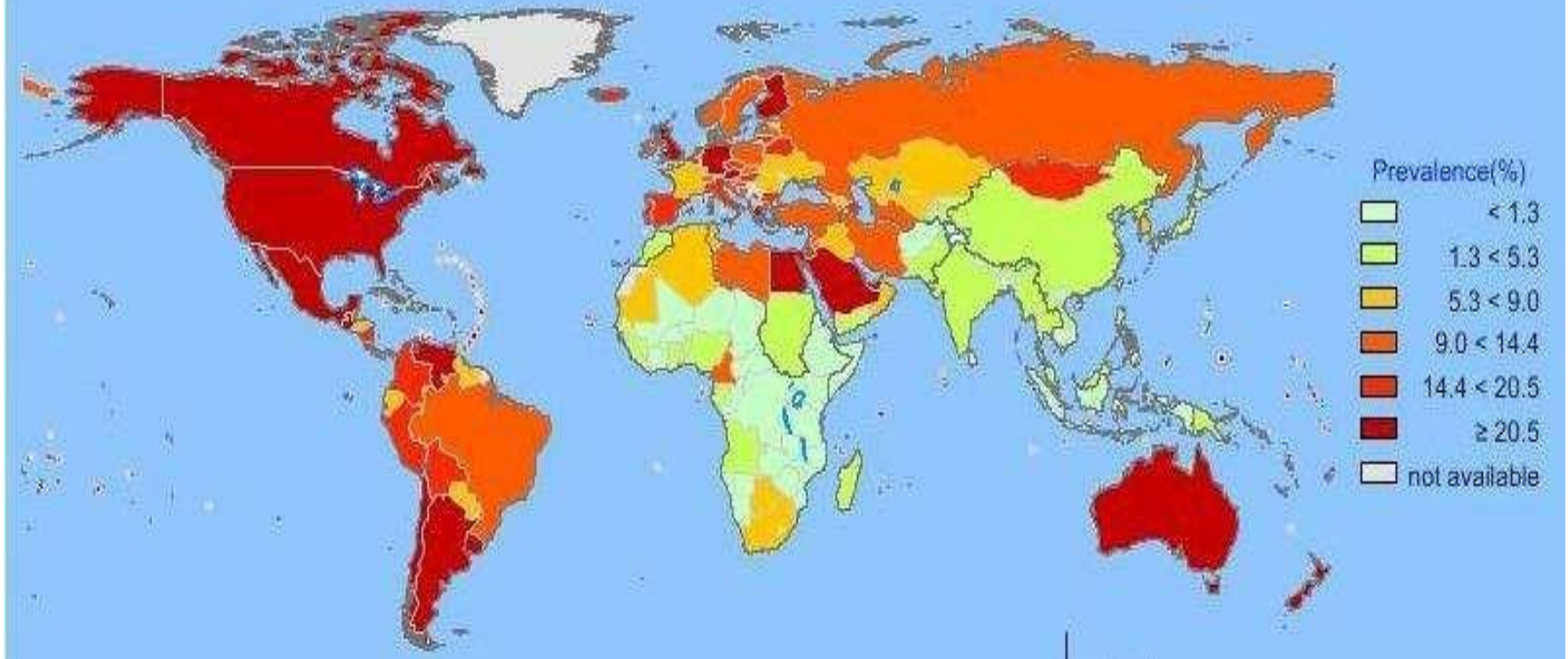
Learning Objectives

- ❖ The prevalence of obesity worldwide; The causes of obesity
- ❖ What is Metabolic Syndrome-causes of Metabolic Syndrome
- ❖ Pathophysiology of Obesity-Regional fat distribution and its relationship to the obesity health consequences -Metabolic Syndrome
 - ❖ The endocrine function of the adipose tissue
 - ❖ Insulin Resistance
 - ❖ Management

Rise of obesity

- Globally, the recent rise in **obesity and type 2 diabetes** rates has reached disturbing levels.
- This has occurred despite the fact that our knowledge about the importance and effects of diet and exercise are at an all time high.
- Overweight and obesity lead to adverse **metabolic effects** on **blood pressure, cholesterol, triglycerides and insulin resistance**.
- Risks of **coronary heart disease, ischemic stroke and type 2 diabetes mellitus** increase steadily.

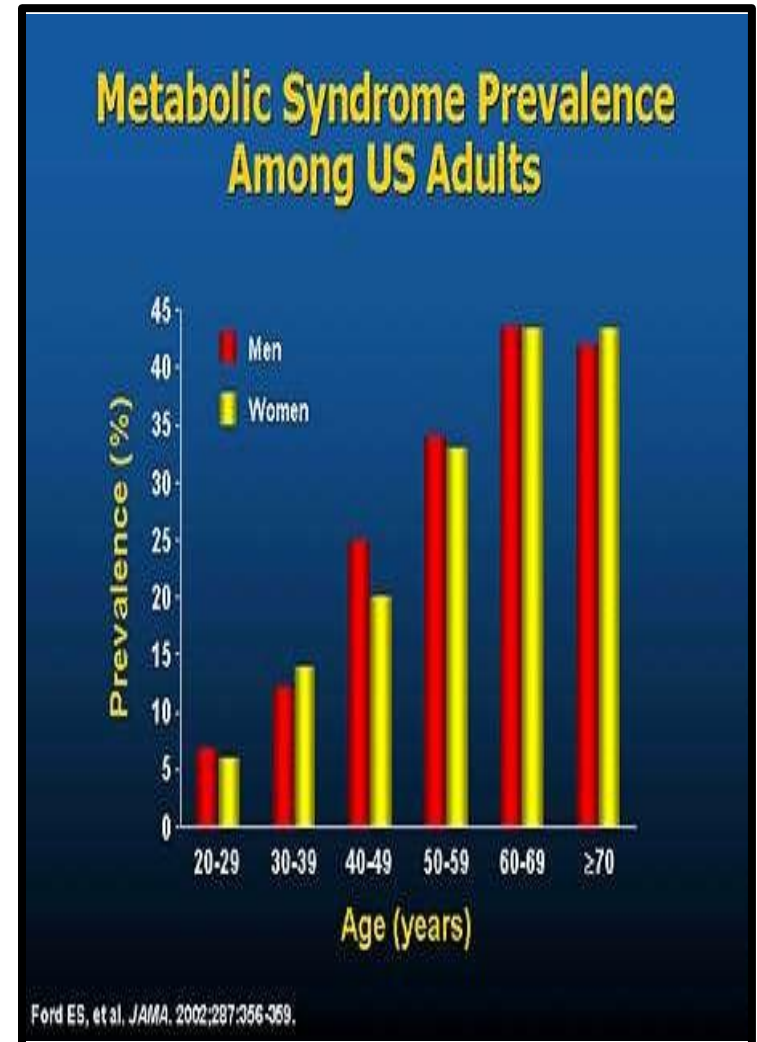
Estimated Obesity(BMI ≥ 30 kg/m²) Prevalence, Males, Aged 15+, 2010



Raised body mass index also increases the **risk of cancer** of the breast, colon, prostate, endometrium, kidney and gall bladder.

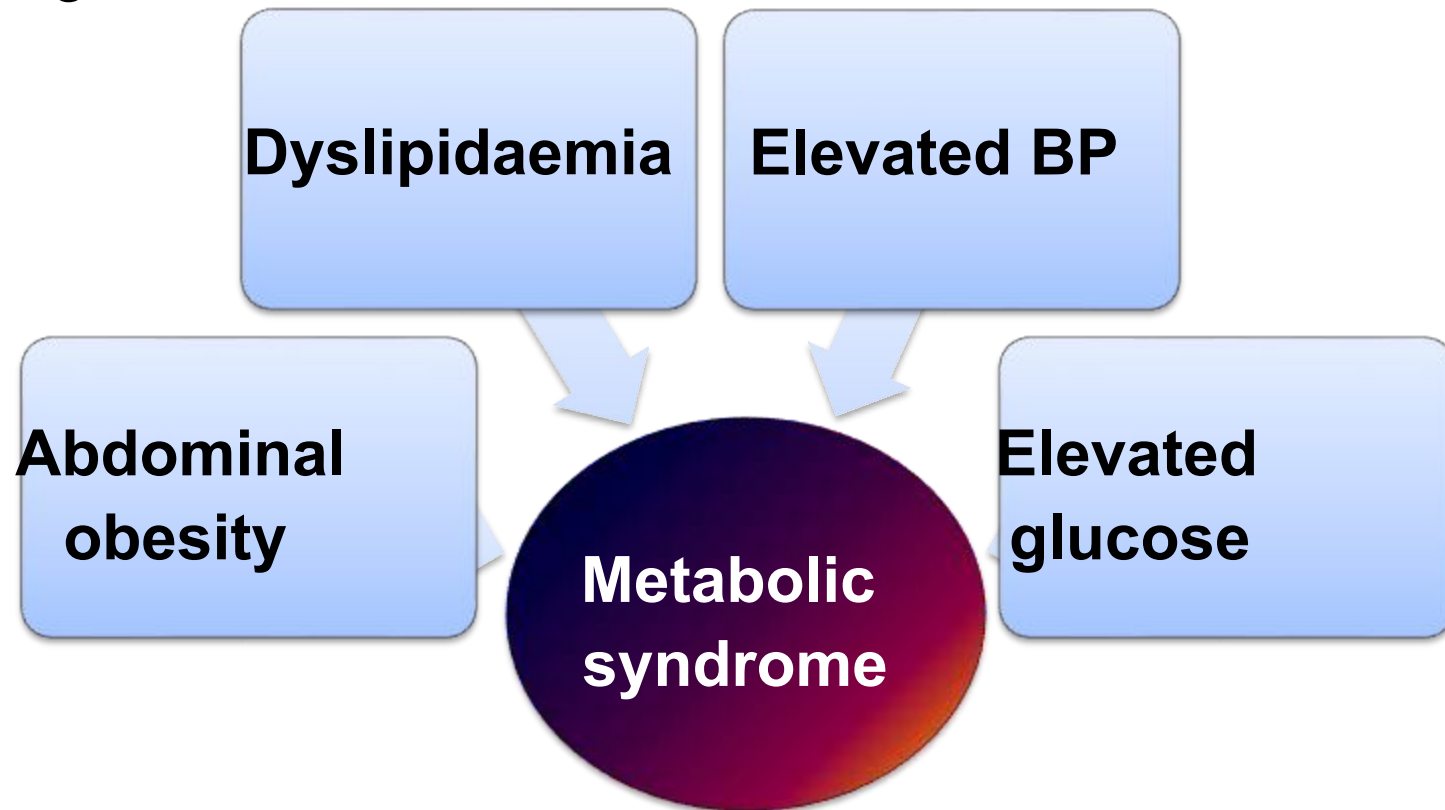
What is the global situation?

- 1/4th of adults worldwide have metabolic syndrome (similar in SL)
- People with metabolic syndrome
 - x 2 as likely to die from, x 3 as likely to have a MI or stroke
 - x 5 greater risk of developing type 2 DM
- Up to 80% of the 200 million people with DM globally will die of CVD
- Metabolic syndrome and DM are



What is metabolic syndrome?

- A true 'syndrome'
- Constellation of interrelated risk factors of metabolic origin



Associated with..

- Proinflammatory/ prothrombotic state
 - Elevated CRP
 - Endothelial dysfunction
 - Hyperfibrinogenaemia
 - Increased platelet aggregation and PAI-1
 - Microalbuminuria



Associated clinical conditions

- **Insulin resistance and type 2 DM**
- **CVD**
- Fatty liver
- PCOD
- Sleep apnoea
- Cholesterol gallstones
- Others.....

According to International Diabetes Federation, the metabolic syndrome (2006) is defined as:

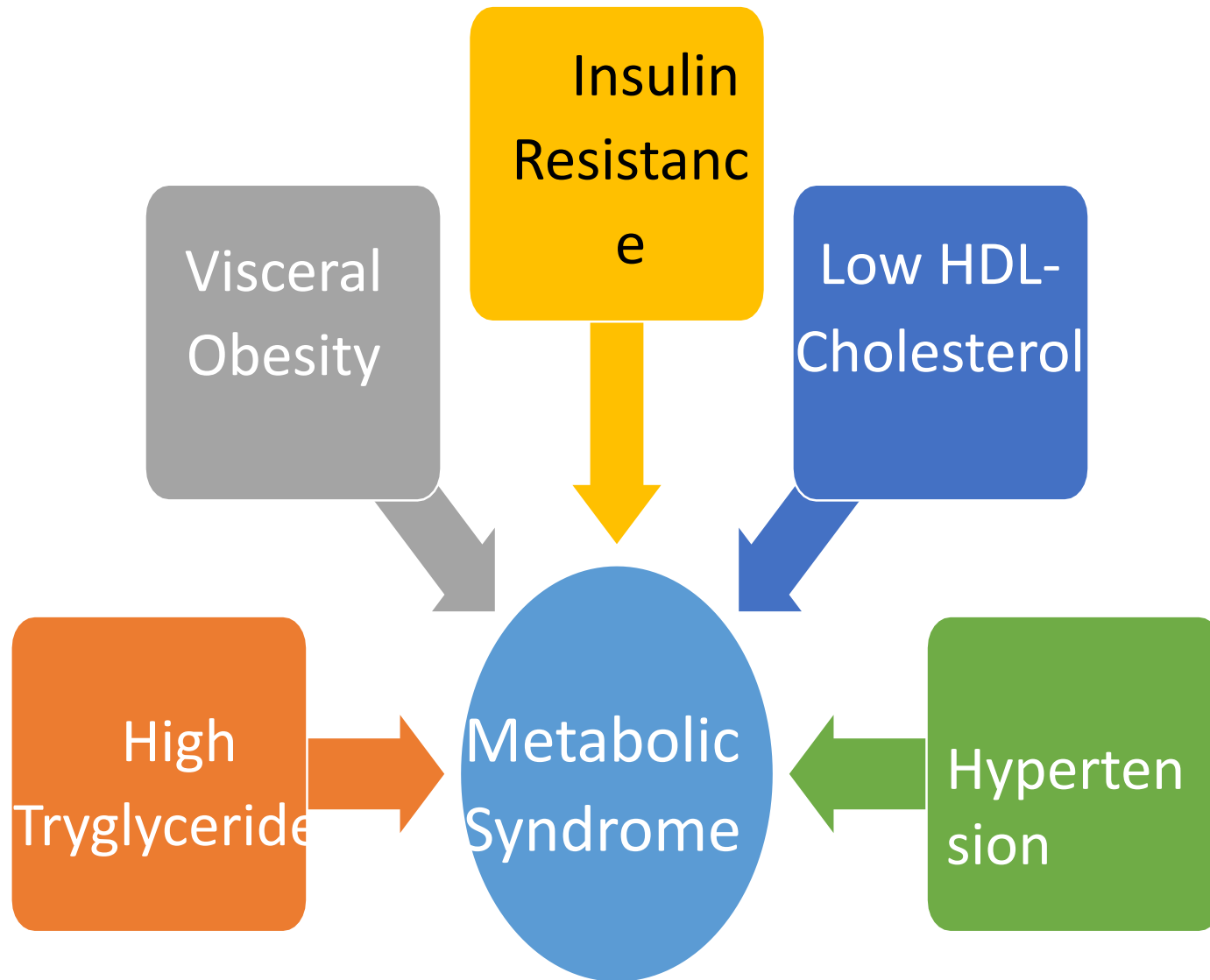
A) **Central Obesity** (Waist circumference)

and

B) **Any two** of the following:

1. **Raised triglycerides**: > 150 mg/dL
2. **Reduced HDL Cholesterol**: < 40 mg/dL in males, < 50 mg/dL in females.
3. **Raised Blood Pressure**: Systolic BP > 130 or diastolic BP > 85 mm Hg
4. **Raised fasting plasma glucose**: FBG > 100 mg/dL

- If BMI is > 30 kg/m², central obesity can be assumed and waist circumference doesn't need to be measured.



Diagnosis of metabolic syndrome

Component	ATP III (3 of the following)
Abdominal obesity (Waist circumference)	Men >102 cm (40") Women > 88 cm (35")
Hypertriglyceridaemia	≥150mg/dL (1.7mmol/L)
Low HDL - C	Men <40mg/dL (1.036mmol/L) Women <50mg/dL (1.295mmol/L)
Elevated BP	≥130/85 or use of anti HT Rx
Elevated fasting glucose	≥110mg/dL (6.1 mmol/L)

What causes metabolic syndrome?

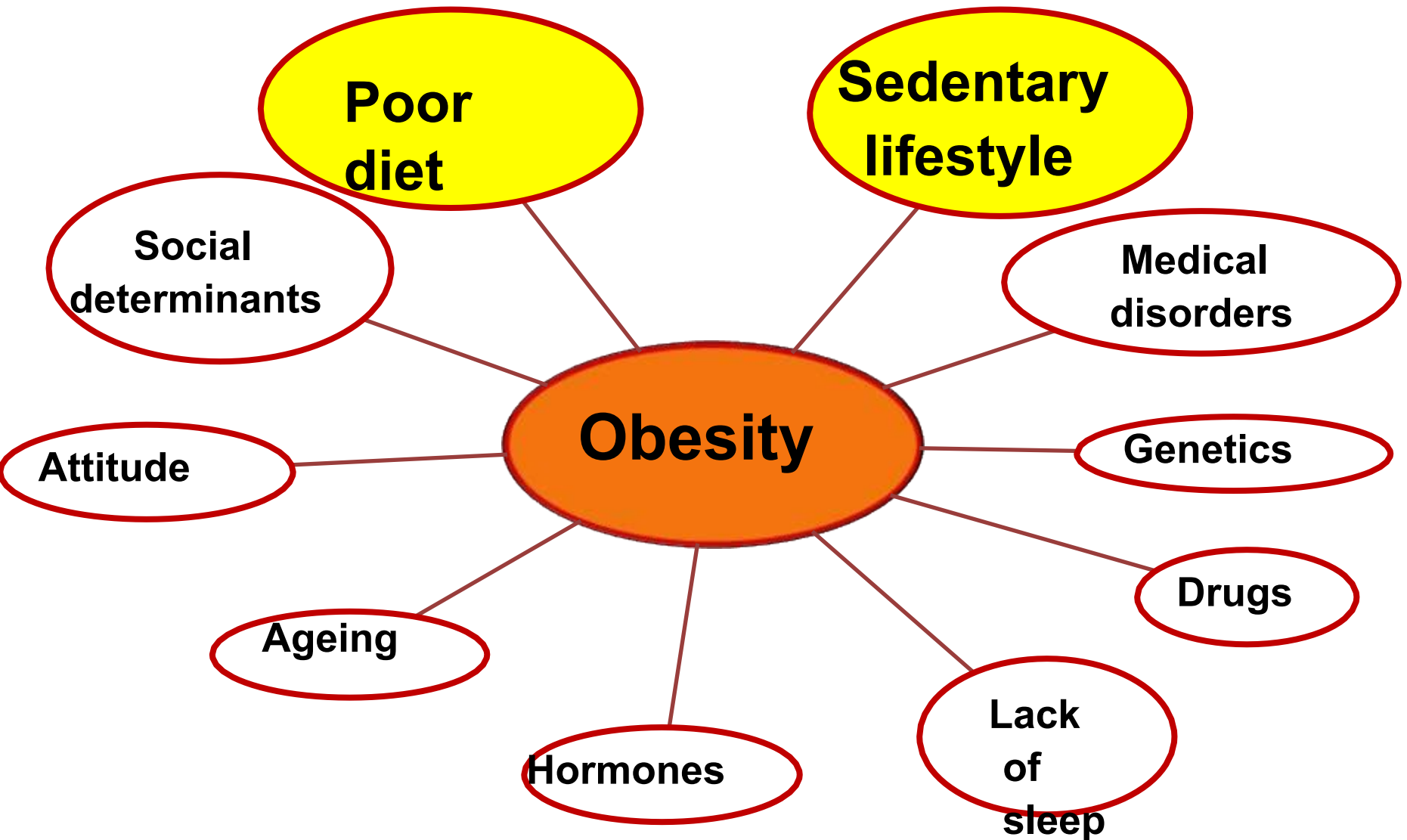
- **Abdominal obesity**
- Physical inactivity
- Ageing
- Hormonal imbalance
(eg. cortisol in chronic stress)

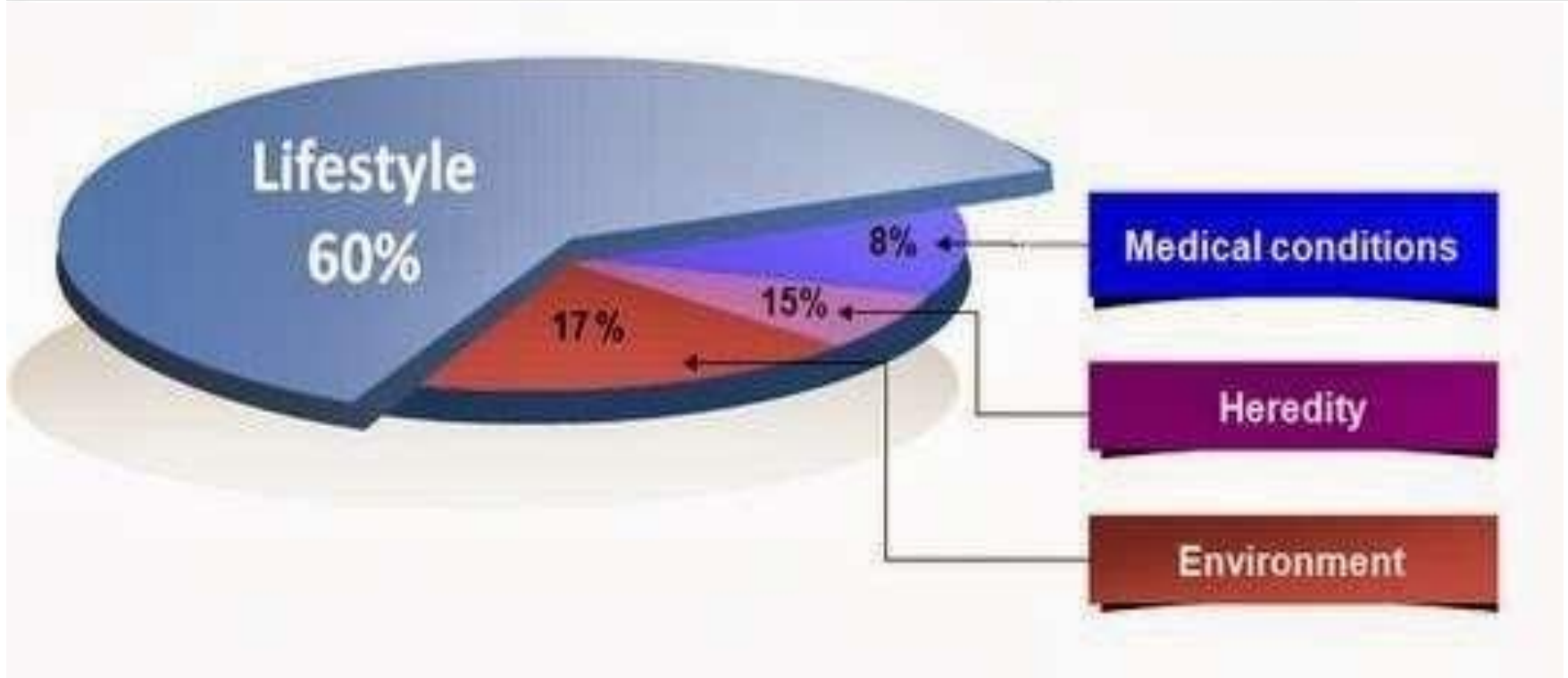


- **It's the fat – in wrong places!!!**
- Causes insulin resistance –and many other metabolic derangements
- Seen in
 - Any obese –'fat in the middle'
 - With ageing
 - South Asians
- Abdominal obesity (even in otherwise thin people) is associated with insulin resistance



What causes obesity?





Factors affecting Health

Obesogenic environment

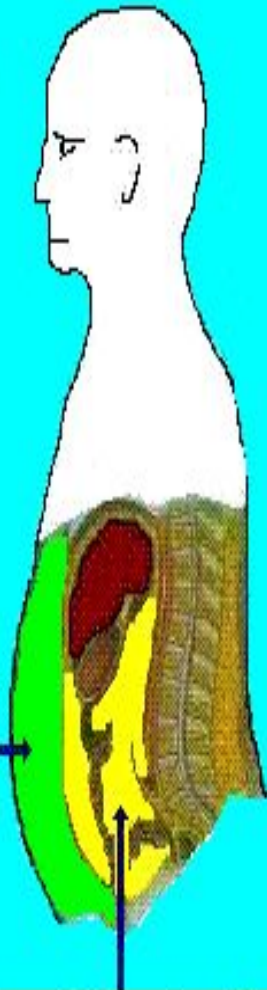
- Abundant access to energy dense food (supermarkets, vending machines, roadside food vendors)
- Food habits –holiday eating, eating out, fast foods as snacks
- Mechanization – machines have taken over
- Sedentary lifestyle –transport, movement within work and home, leisure activities
- Children –less play and more work, more comp and more TV



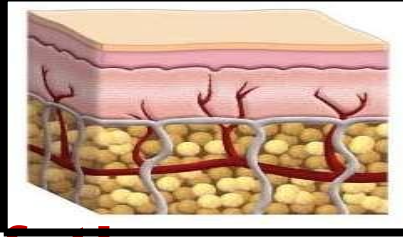
The two kinds of body fat

Subcutaneous fat
(under the skin)

Intra-abdominal fat
(around the internal organs)



How does obesity cause metabolic syndrome?



- **Adipose tissue is not only a store of fat!**

- **Immune function** (Tchkonia et al, 2006)

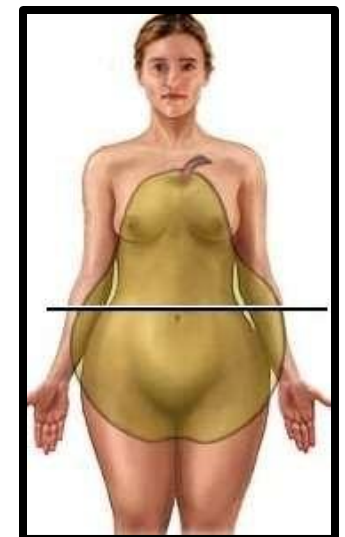
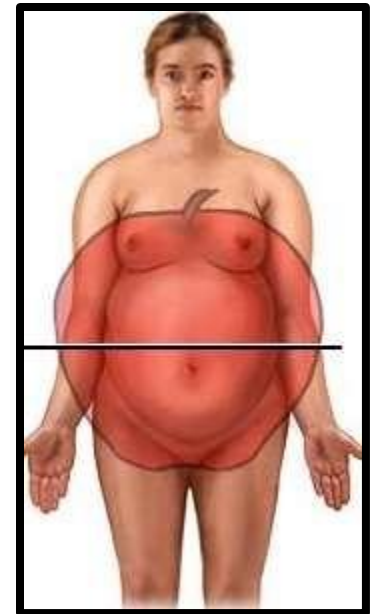
- Cytotoxic fatty acids sequestered
- Production of cytokines, complement proteins

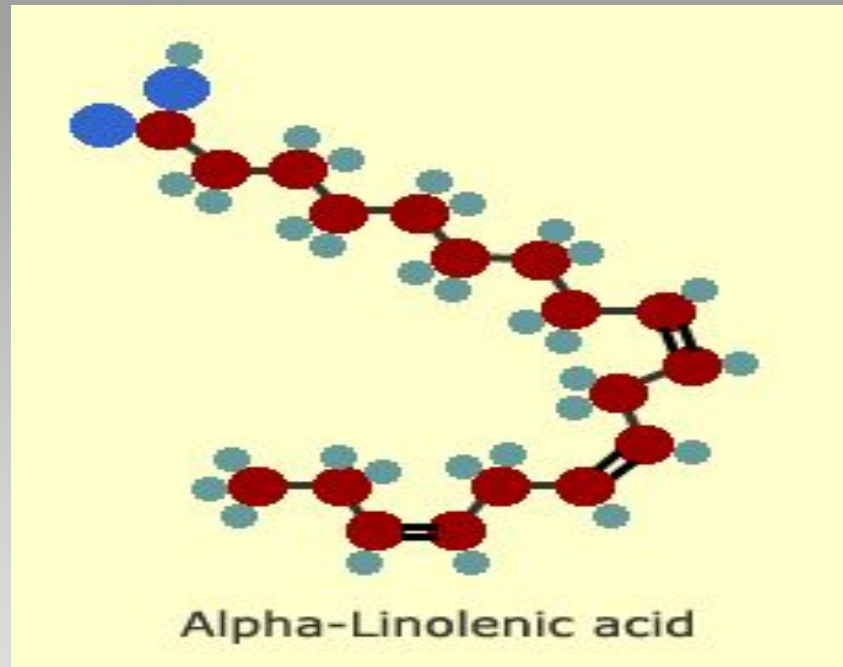
Usually no infections and no metastases in fat tissue!!

- **Largest endocrine organ** (Tchkonia et al, 2010)

- Secrete hormones (Eg. leptin, adiponectin, visfatin, angiotensin II, IGF1)
- Activates hormones (Eg. glucocorticoids, sex steroids)

- **Visceral fat** depots release inflammatory adipokines (Eg. $\text{TNF-}\alpha$, IL-1, IL-6)
- **Inflammatory adipokines** and **FFA** form the pathophysiological basis for co-morbid conditions in obesity
- Antiinflammatory and anti-atherogenic substances are also secreted (eg. adiponectin, visfatin) (Tchkonia et al, 2006)
- **Buttock fat and subcutaneous fat**—mostly storage function (Redinger, 2007)





Pathology of fats

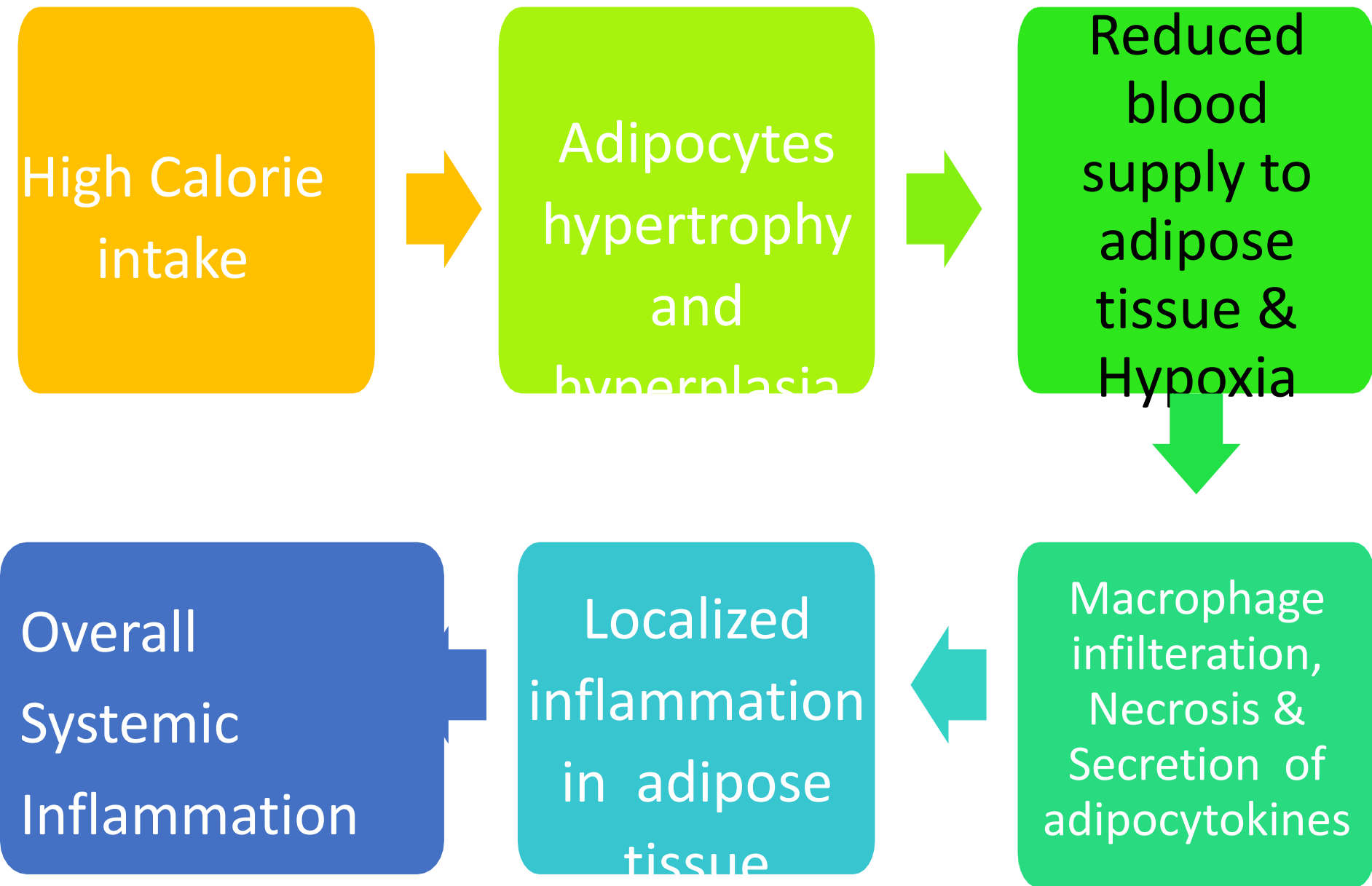
Adipose Tissue as an Endocrine Organ

- Adipose tissue is an important endocrine organ that secretes numerous protein hormones, collectively called **Adipocytokines**.
- These hormones generally influence energy metabolism, which is of great interest to the understanding and treatment of type 2 diabetes and obesity.
- Their relative roles in modifying appetite, insulin resistance and atherosclerosis are the subjects of intense research.

Obesity and Inflammation

- **Obesity is associated with a state of chronic, low-grade inflammation.**
- There is associated chronic inflammatory response characterized by **abnormal cytokine** production, increased acute-phase reactants, and activation of inflammatory signalling pathways.
- A feature of this inflammatory response is that it appears to be triggered, and to reside predominantly, in **abdominal adipose tissue**, and not in subcutaneous fat.

- Hypoxia has been proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue that leads to an overproduction of biologically active metabolites known as *adipocytokines*.
- Adipocytokines includes free fatty acids (FFA), pro-inflammatory mediators (TNF α , IL-6, PAI-1, CRP).
- These adipocytokines results in a *localized inflammation* in adipose tissue that propagates an overall systemic inflammation associated with the development of obesity related comorbidities.



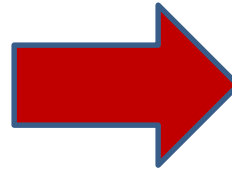
- The proinflammatory state in the adipose tissue also leads to a **local insulin resistance** including an impaired inhibitory effect of insulin on FFA release.
- The insulin resistance further supports the pro-inflammatory state because **insulin, by itself, is antilipolytic.**
- Although energy restriction leading to weight loss is the primary dietary intervention to reverse these obesity-associated metabolic disorders, other interventions targeted at alleviating adipose tissue inflammation have not been explored in detail.



Adipokine promoters	Inhibitory/ atheroprotective
Inflammatory	Anti-inflammatory
IL-1, IL-6, TNF-a, IFN-a, IFN-b, IL-8. IP-10, TGF-b, MCP-1, leptin, resistin	IL_4, IL-10, TGF-b
Hypertensive	Antihypertensive
Renin, angiotensinogen, angiotensin II	Angiotensin II receptor blockers
Insulin resistance	Insulin sensitivity
TNF-a, IL-6, resistin	Adiponectin, leptin, AgRP, MMIF, Acylation-stimulating protein
Procoagulant	Anticoagulant
PAI-I, tissue factor, TNF-a, IL-6, TGF-b	Adiponectin
Angiogenetic	Atheroprotective
Leptin, IL-8, VEGF, FGF-2, MCP-1, IP-10, VCAM, ICAM, monobutylin	Adiponectin
Lipogenetic (adipogenesis)	Lipolytic
IGF-1, angiotensinogen, angiotensin II, visfatin, acylation stimulating	TNF-a, IL-6,

What happens with ageing?

- **Fat tissue mass** increases through middle age and declines in old age
- **Fat redistribution** occurs especially during and after middle age



Waist circumference

- Most important
- Standard
 - Men >102 cm (40")
 - Women > 88 cm (35")
- But South Asians – lower cutoffs
 - **Men > 90 cm**
 - **Women > 80 cm**
- Measured at the top of iliac crest



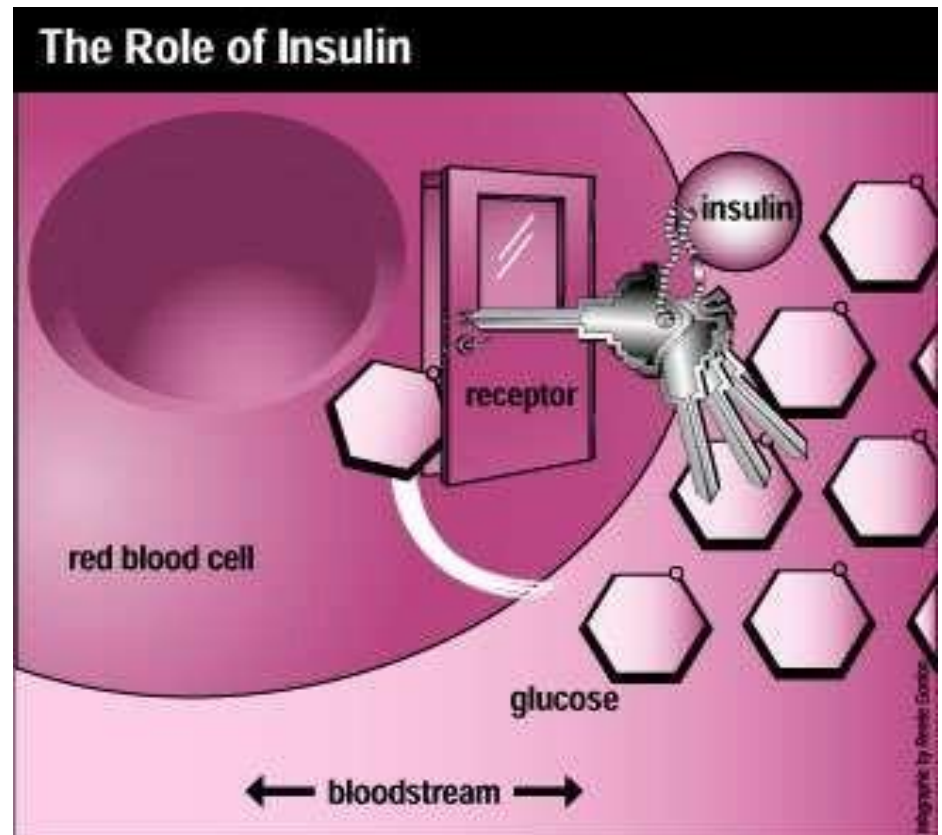
INSULIN RESISTANCE IS THE MAIN PATHOLOGY BEHIND METABOLIC SYNDROME(SYNDROME X)



How Insulin Acts

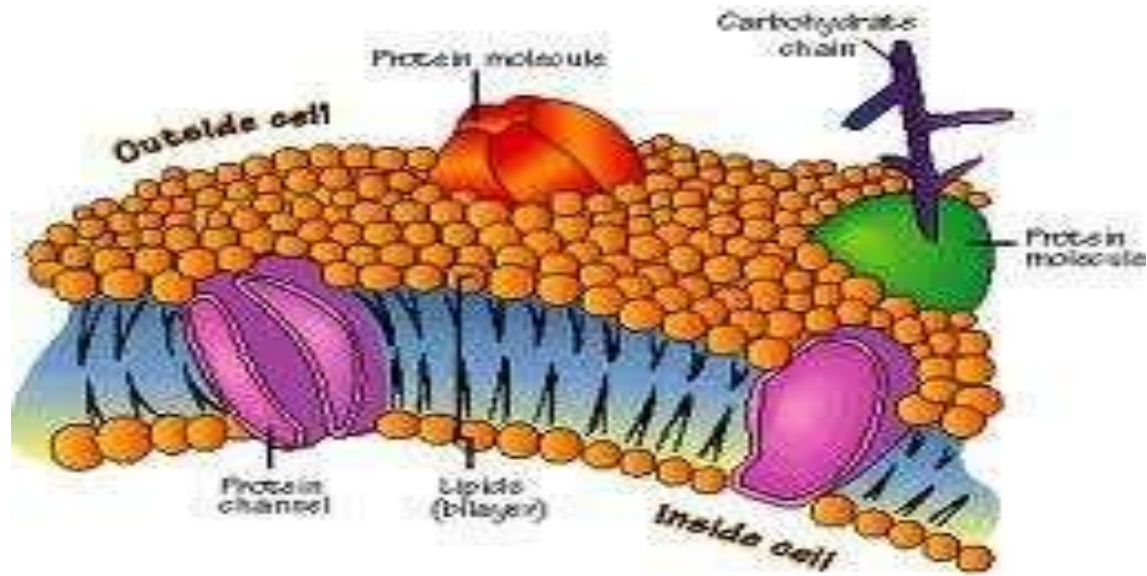
- Any food or drink containing glucose (or any digestible carbohydrates) causes blood glucose levels to increase.
- In normal metabolism, the elevated blood glucose level and **intestinal incretin** makes beta (β) cells in the Islets of Langerhans, release insulin into the blood.

- Insulin attaches to glucose-insulin receptors on cell membranes to allow glucose to be taken into the cell.
- **GLUT4** is the insulin-regulated glucose transporter that is responsible for insulin-regulated glucose translocation into the cell.



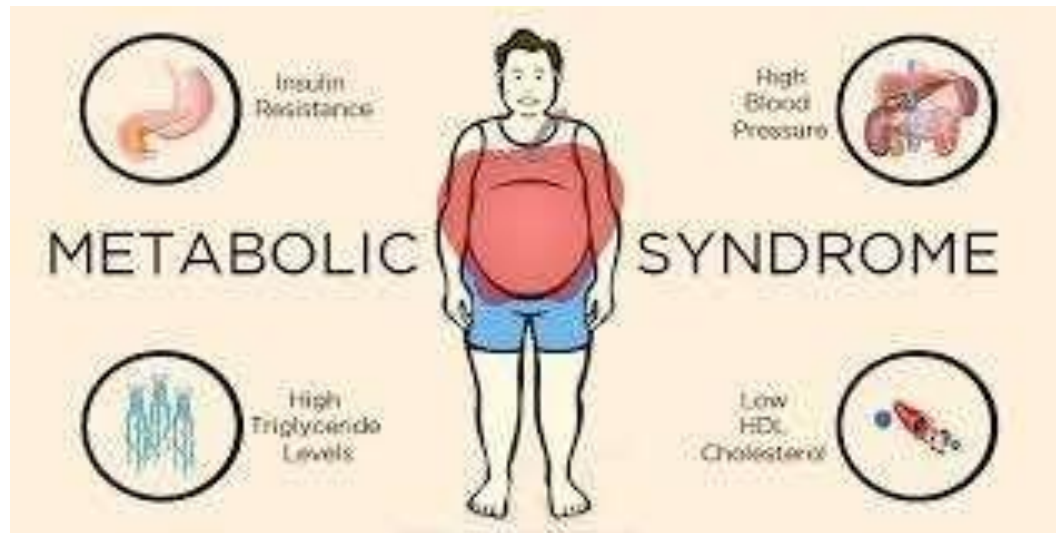
Glucose Transporter 4 Receptor

- The GLUT4 protein is expressed primarily in muscle and fat cells, the major tissues in the body that respond to insulin.
- Under conditions of low insulin, GLUT4 is sequestered in intracellular vesicles in muscle and fat cells.
- Insulin induces the translocation of GLUT4 from these vesicles to the plasma membrane.
- As the vesicles fuse with the plasma membrane, GLUT4 transporters are inserted and become available for transporting glucose.



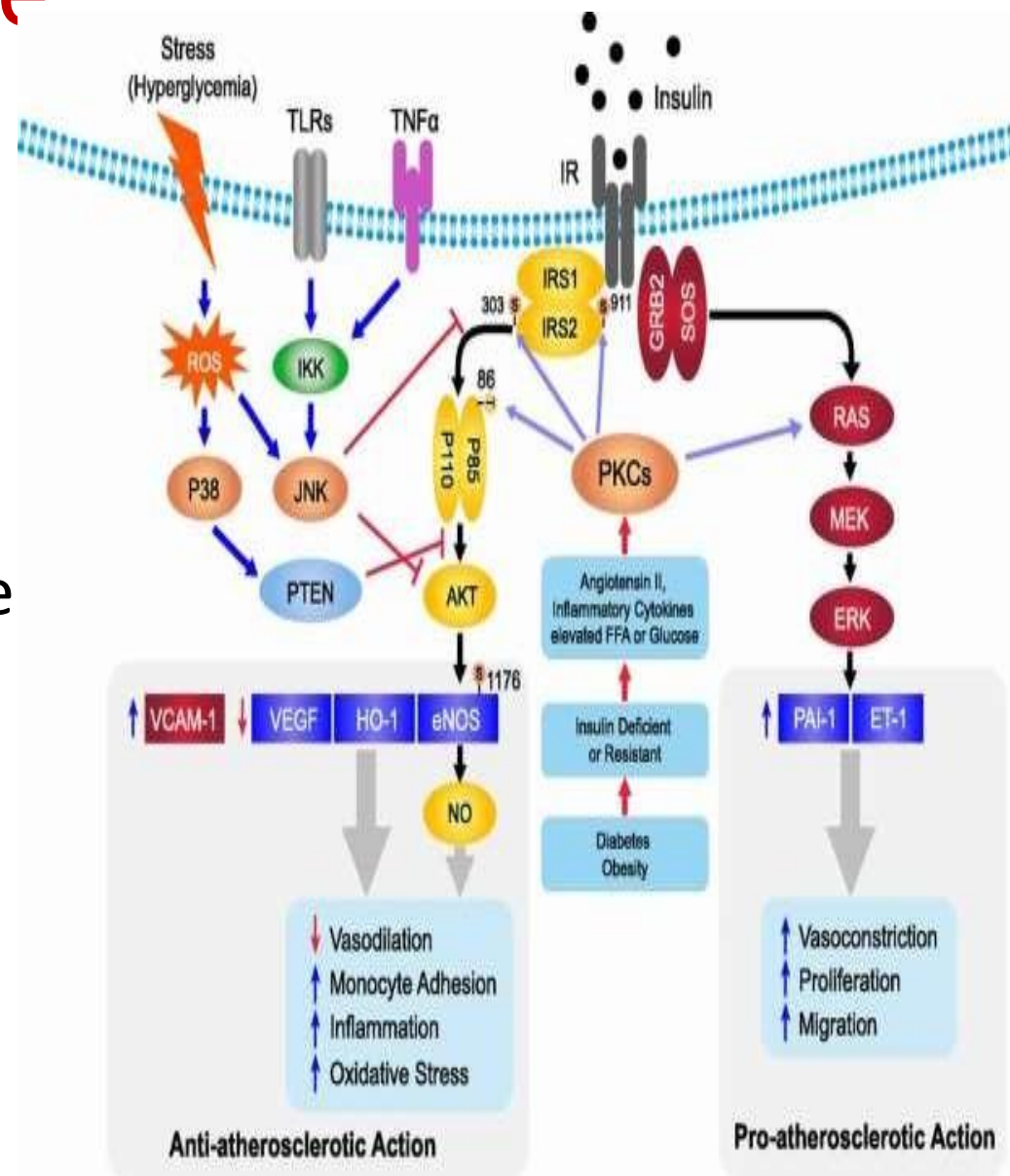
- If the cell phospholipid membrane is not “fluid” enough (i.e. its composition does not have enough PUFA), insulin receptors are disrupted.
- The insulin cannot act and glucose cannot enter the cells, and thereby lower the blood glucose level.

- Without insulin, the liver is unable to use glucose, and therefore secretes **glucagon**, which further increases blood sugar by converting liver glycogen into glucose.
- The beta cells reduce insulin output only if the blood glucose level falls.
- In IR states, insulin levels remain high, and this promotes lipogenesis.



Insulin Resistance

- Insulin resistance is the main pathology behind syndrome X.
- Insulin resistance individuals demonstrate an **impaired glucose or tolerance by an abnormal glucose** challenge, an elevated fasting glucose levels and/or overt hyperglycemia.



How Insulin Acts (in normal condition)

Elevated blood glucose level



Insulin release from beta cells

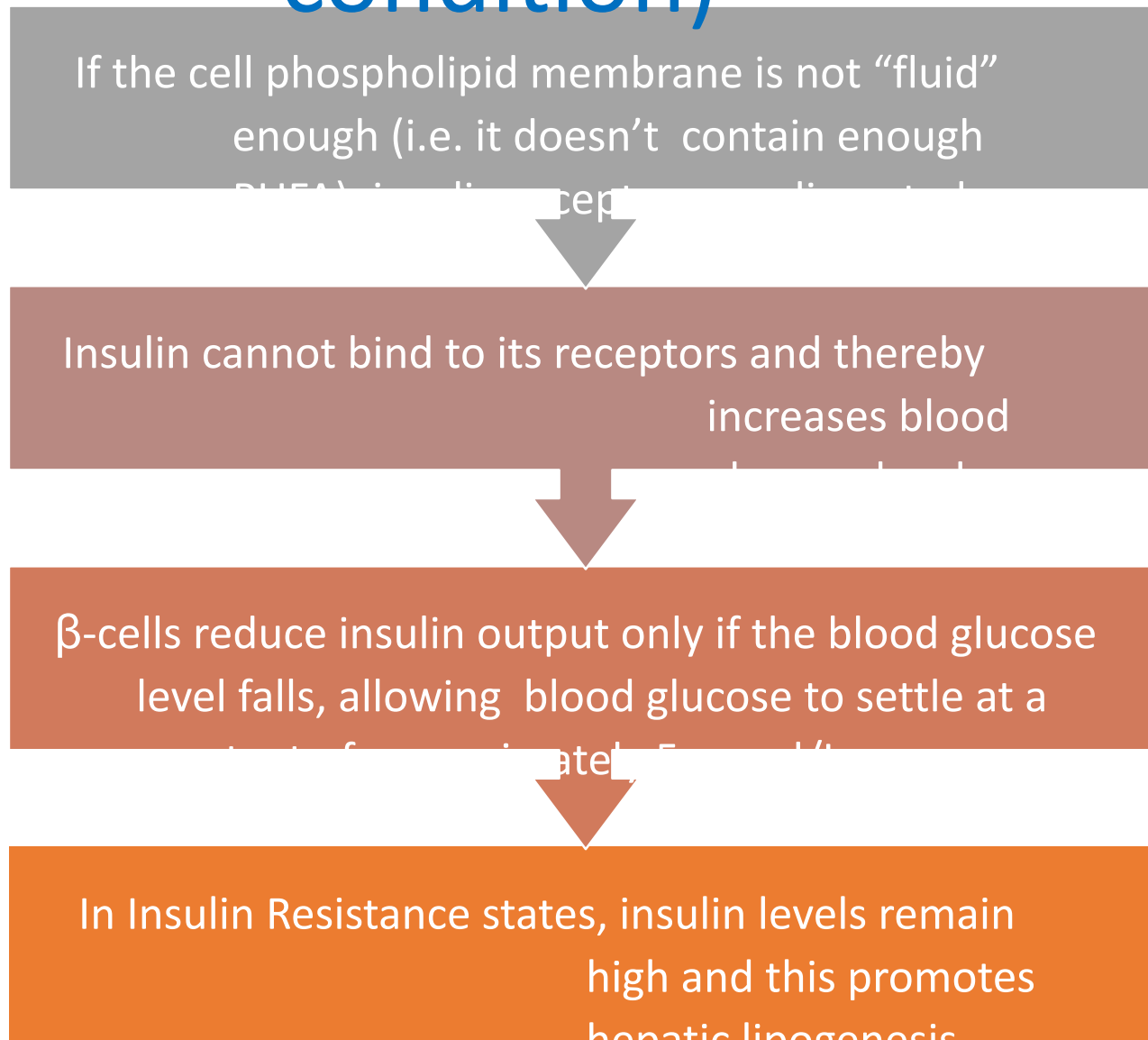


Binding to tyrosine kinase receptors



Uptake of Glucose through GLUT-4 in adipose tissues and muscles (skeletal and cardiac)

How Insulin Acts (in abnormal condition)



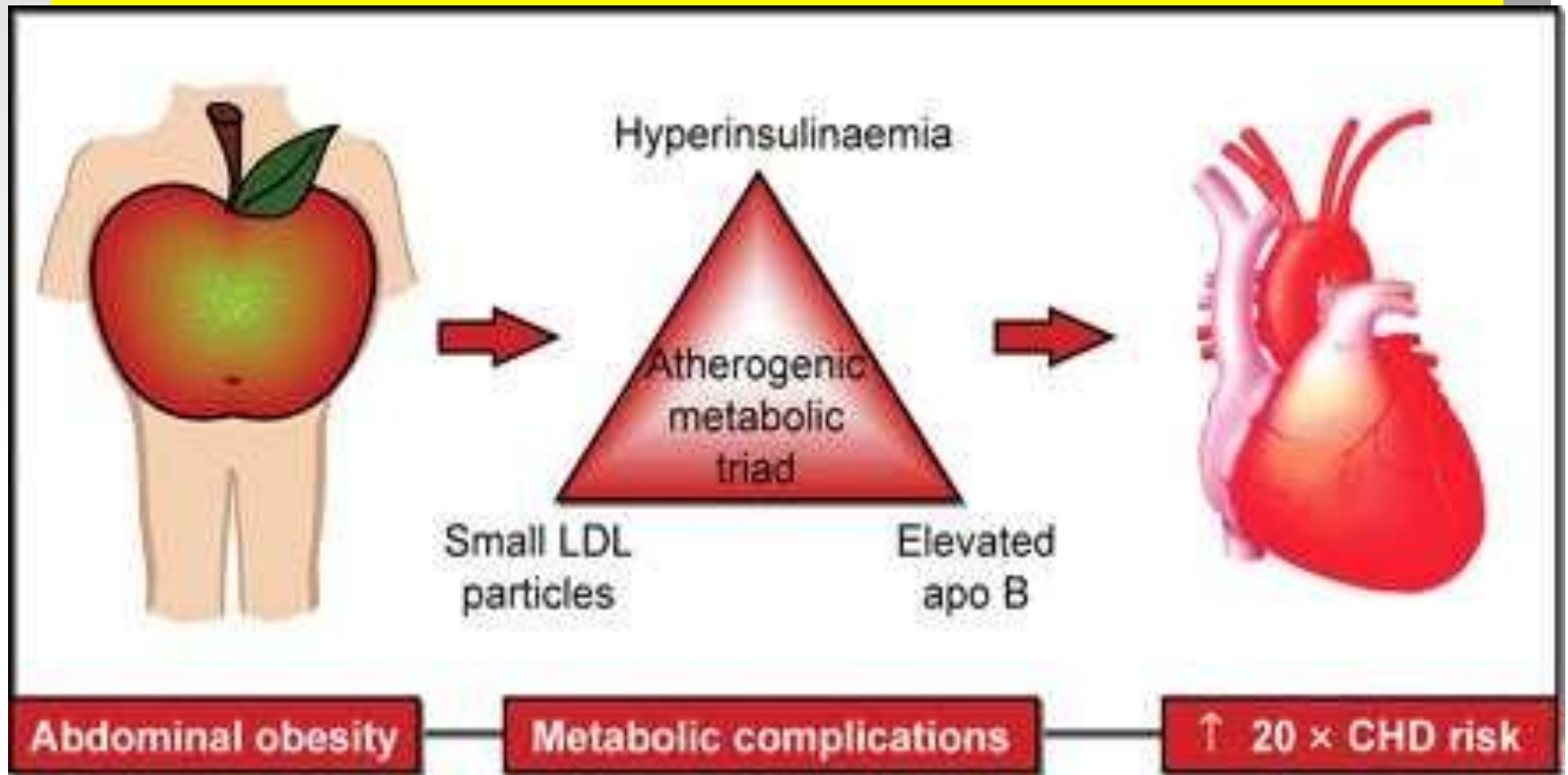
Without insulin, the muscle cells are unable to use glucose and therefore release of glucagon from pancreas

- Glucagon further increases blood sugar by converting liver glycogen into glucose.

Glucagon regulates FFA production through lipolysis

Increase in serum lipid levels leads to atherosclerosis and cardiovascular disease.

Factors influencing Insulin Resistance



Increased FFAs level in
the plasma



Increased TGs enriched VLDL secretion by
the liver



Increased Oxidative stress and
Endothelial dysfunction



Atherosclerotic disease

Diet

- It is well known that insulin resistance commonly coexists with obesity.
- Saturated fat appears to be the most effective at producing IR.
- *Being insensitive to insulin is positively correlated with fat intake, and negatively correlated with dietary fibre intake.*



CIS PUFA

- In the long term, poor diet has the potential to change the ratio of CIS polyunsaturated fats to trans phospholipids in cell membranes, correspondingly changing cell membrane fluidity.
- It is hypothesized that increasing cell membrane fluidity by increasing healthy PUFA concentration might result in an enhanced number of insulin receptors and reduced insulin resistance.

Hypertension

- Essential hypertension is frequently associated with obesity, glucose intolerance and dyslipidemia.
- Both *hyperglycemia and hyperinsulinemia activate the Renin Angiotensin System (RAS)* by increasing the expression of angiotensinogen, Angiotensin II (AT II) and the AT 1 receptor, which in concert may contribute to the development of hypertension in patients with insulin resistance.
- *Insulin resistance and hyperinsulinemia leads to Sympathetic Nervous System accumulation.* As a result, the kidney increase sodium reabsorption, the heart increases cardiac output and arteries respond with vasoconstriction resulting in hypertension.

Genetic Factors

- Some people who are not obese by traditional measures nevertheless are insulin-resistant and have abnormal levels of metabolic risk factors.
- These includes:
 - Individuals with T2D parents
 - Being black, Hispanic (Related to Spain), American Indian or Asian
- South Asian in Urban and migrant environments may be at a higher risk of CHD due to the confluence of
 1. Genetic factors that predispose to higher cholesterol levels and a possible “thrifty gene” effect

Chronic Stress and Glucocorticoid (GC) Action

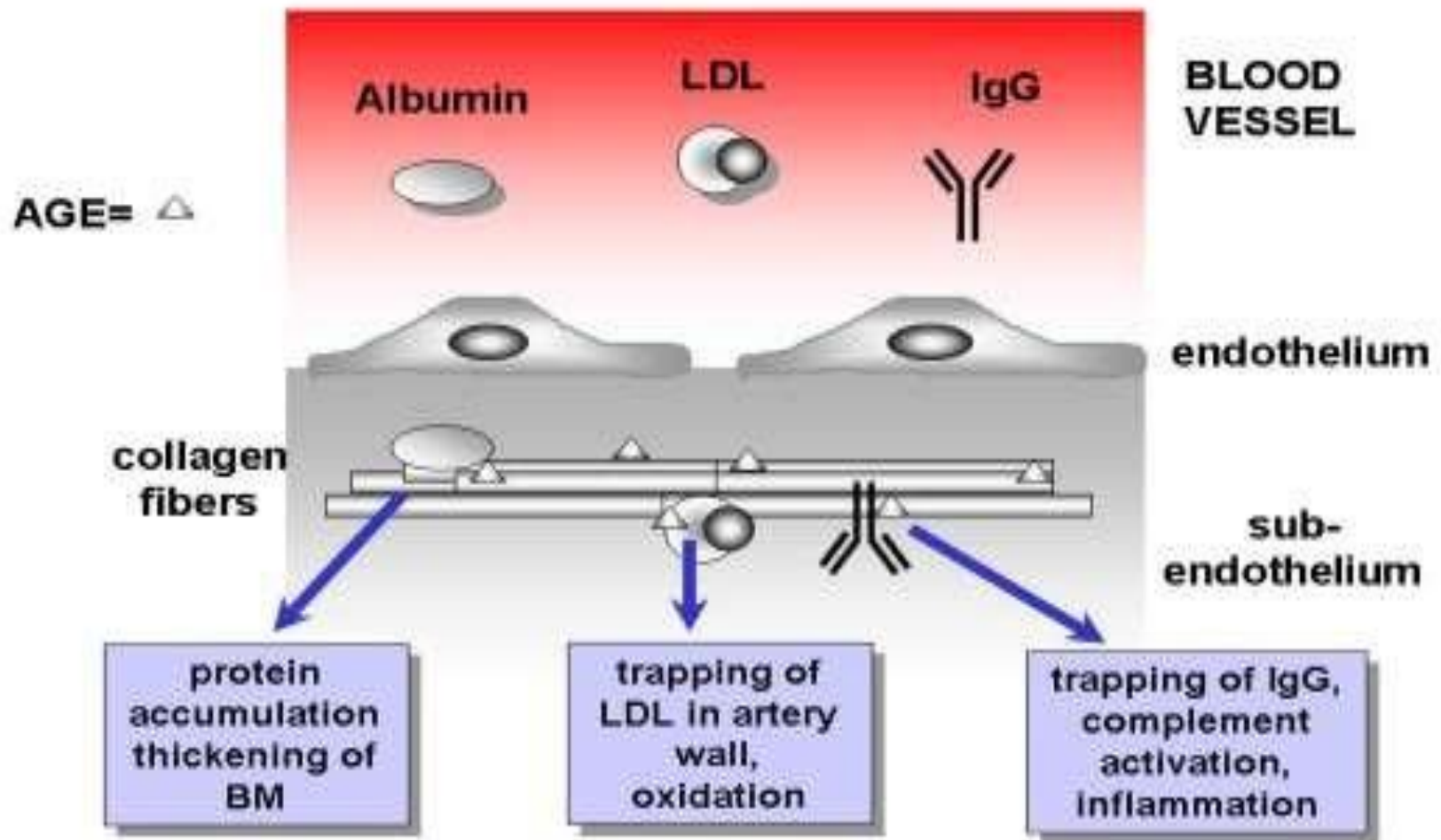
- Chronic hypersecretion of stress mediators such as *cortisol*, may lead to the **visceral fat accumulation**, low growth hormone secretion and hypogonadism.
- *GCs increase the activities of enzymes involved in fatty acid synthesis* and promote the secretion of lipoproteins; induce the hepatic gluconeogenic pathway; promote the differentiation of preadipocytes to adipocytes, which could *lead to an increased body fat mass*.
- GCs inhibit an insulin-stimulated uptake of amino acids by adipocytes and increase lipolysis which leads to **peripheral insulin resistance**.

Sedentary lifestyle

- Sedentary lifestyle increases the likelihood of development of insulin resistance.

ADVANCED GLYCATION ENDPRODUCTS

Fig 3



AGE

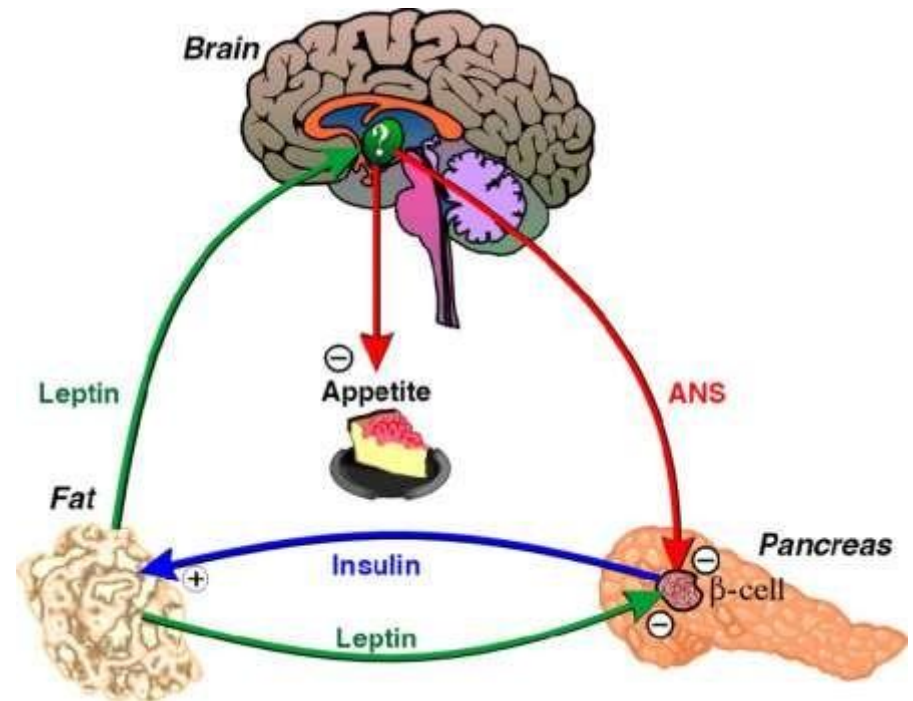
- Elevated blood levels of glucose – regardless of cause – lead to increased glycation of proteins and lipids with changes in their function throughout the body.
- These are called **Advanced Glycation End products** and contribute to the end organ damages of T2DM

Visceral fat

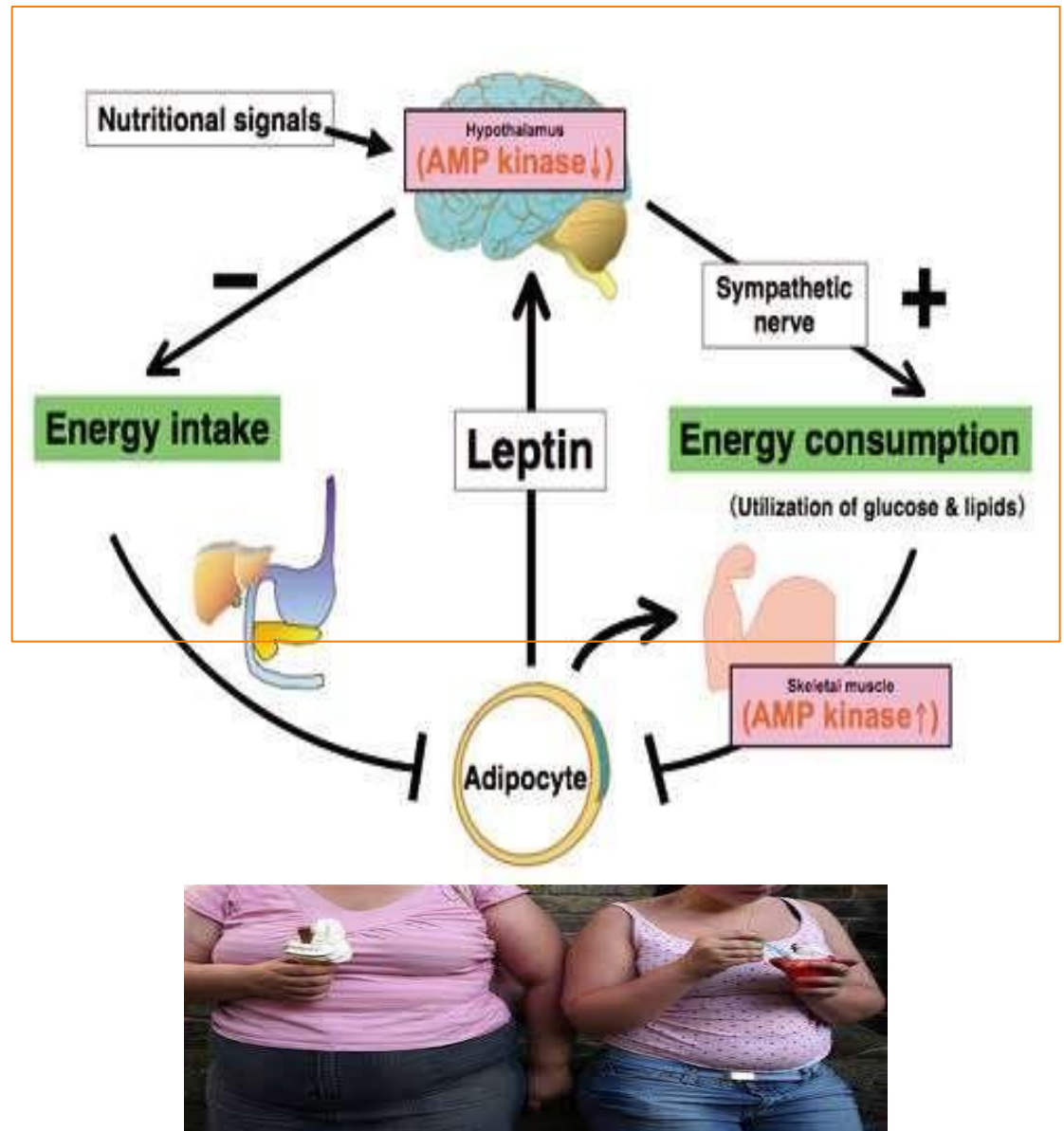
- Unlike subcutaneous adipose tissue, visceral adipose cells produce significant amounts of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF- α), Interleukins-1 and -6, etc.
- These pro-inflammatory cytokines disrupt normal insulin action in fat and muscle cells.

Role of leptin

- Yet another problem in metabolic syndrome involves the phenomenon known as leptin resistance.
- An important role of leptin is **long-term inhibition of appetite** in response to formation of body fat.



- Once leptin signalling has been disrupted, the individual becomes prone to further overeating, weight gain, and insulin resistance.



What contributes to atherosclerosis in metabolic syndrome?

- **Atherogenic Dyslipidemia**

- High TG
- High apoB
- Low HDL-C
- High LDL-C

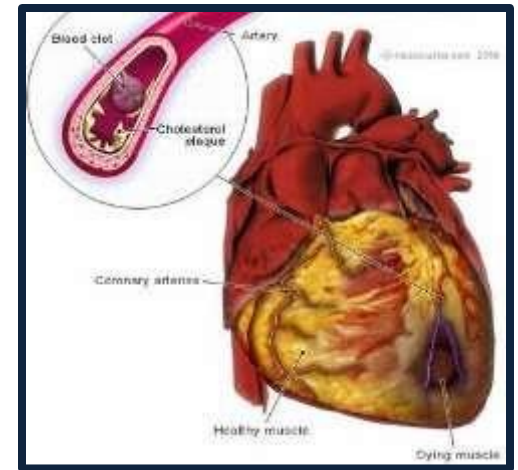
- **HT**

- **Elevated plasma glucose**

- **Proinflammatory state**

- **Prothrombotic state**

- Risk increased even when only marginally abnormal!!



Management

- Primary goal – reduce risk for CVD
- Individualized management
- Each aspect contributing to metabolic syndrome and other risk factors for CVD should be managed
- Should be continued for long - ? Lifelong
- Mostly lifestyle modifications with attitudinal changes
+/- drugs





Weight

10% of basal weight
in 6-12 months



BP

**<130/85
mmHg**

Goals



Exercise

**30-40mt/d on
3-5 d/week**

Correct blood lipids according to

CVD risk LDL <100/130 mg/dL
(2.6/3.35 mmol/L)

TG <130/160/190 mg/dL
(3.35/4.19/4.5mmol/L)



Exercise

- Skeletal muscle
 - most insulin-sensitive tissue
 - primary target for improving insulin resistance
- The impact of exercise on insulin sensitivity is **evident for 24-48 hrs**, but **disappears in 3-5 days**
- Regular physical activity necessary to improve insulin resistance



Regular Exercise

- **Walking or light jogging for 1 hr daily will produce significant loss of visceral fat (even without caloric restriction)!!**
- **Any Exercise –better than No Exercise**
- Break up the exercise
- Gradual increase in **intensity** and **frequency**
- 30-40 min/d on 3-5 days of the week



Diet

- Individualized, affordable, practical, sustainable



Reduce

- Portion size to limit calorie intake
- refined sugar/ carbohydrates
- Full fat dairy products/ red meat/ polyunsaturated fat
- Alcohol
- Salt if blood pressure elevated
- Diet very low (< 25%) in fat may increase TG and decrease HDL-C

Increase

- Whole grain
- Fruit and vegetables (5 servings/ day)
- Fish – especially in hypertriglyceridaemia

Glycemic index

- Integrated blood glucose response to a fixed quantity of carbohydrates in a meal is known as glycemic index.
- Complex carbs and foods high in fiber cause a slower rise in sugar, and reduced insulin resistance.

High GI vs Low GI Foods



Dos and Don'ts



Weight reduction

- Improves **all** aspects of metabolic syndrome
- Decreases all-cause and CVD mortality
- By **exercise** and **dietary** changes
- Aim for **BMI 20-23kg/m²**
- Even though **NO** weight loss, exercise and dietary changes
 - Lower BP
 - Improve lipids
 - Improve insulin resistance



Why is it so difficult to lose weight?



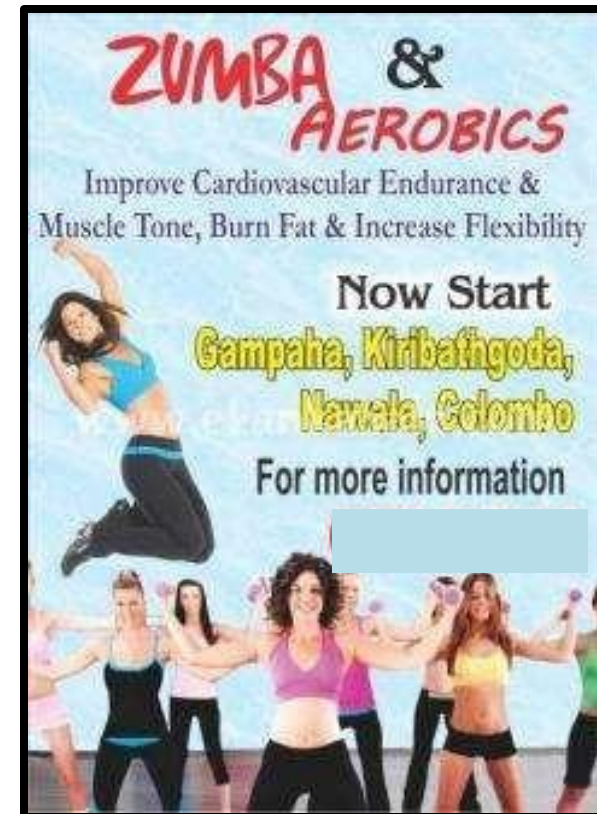
Calorie content of some foods

Food item	Quantity	Calories (Approx)
Butter / oil	1 table spoon	100 -120
Banana	1	100
Bread	1 slice	65
Chocolate cake	1 piece	340
Rice	1 cup	200
Roasted peanuts	1 cup	840
Hot dog	1	250
Samosa	1	150
Vade/ Chocolate piece	1	70
Ice cream	1 cup	350
Carbonated soft drinks	1 bottle (300 ml)	150



Calorie expenditure during activities

Exercise	Calories burned per hour (App)
Walking 4.0 mph, very brisk	300
Cycling, 12-13.9mph, moderate	475
Running, 5 mph (12 minute mile)	475
Swimming laps, freestyle, slow	400
Cricket (batting, bowling)	300
Aerobics, general	400
Stretching, yoga	250
Housework, moderate	200
Gardening, general	250
Typing, computer data entry	90
Music, playing guitar	180



Pharmacotherapy

- Needed when lifestyle changes have not improved risk factors
- Anti HT
- OHG (especially metformin)
- LDL – statin
- TG – statin/ fibrate/ nicotinic acid
- HDL - nicotinic acid/ fibrate
- ??



Pharmacological Approach:

1. Appetite suppressants (Phentermine, Sibutramine) and inhibitors of nutrient absorption (Orlistat)
2. Oral hypoglycaemics (Metformin & Glimepiride)
3. Antihypertensives (Metoprolol)
4. Statins (Atorvastatin)
5. Aspirin

Bariatric Surgery

Treatment

1. Lifestyle Modification (Smoking etc.)
2. Weight Reduction (calorie restriction e.g., 500 Kcal/d deficit)
3. Diet (PUFA)
4. Physical Activity

Summary

Metabolic syndrome is the collection of **high blood pressure, blood glucose, abdominal obesity** and **abnormal blood lipids**

It would soon be the **No 1 risk factor for DM and CVD**

Most important cause is **abdominal obesity causing a chronic inflammatory and prothrombotic state**

Lifestyle changes (**weight reduction by diet and physical activity**) are the most important management strategies

Pharmacotherapy is **added** when lifestyle changes are inadequate

Thank you

