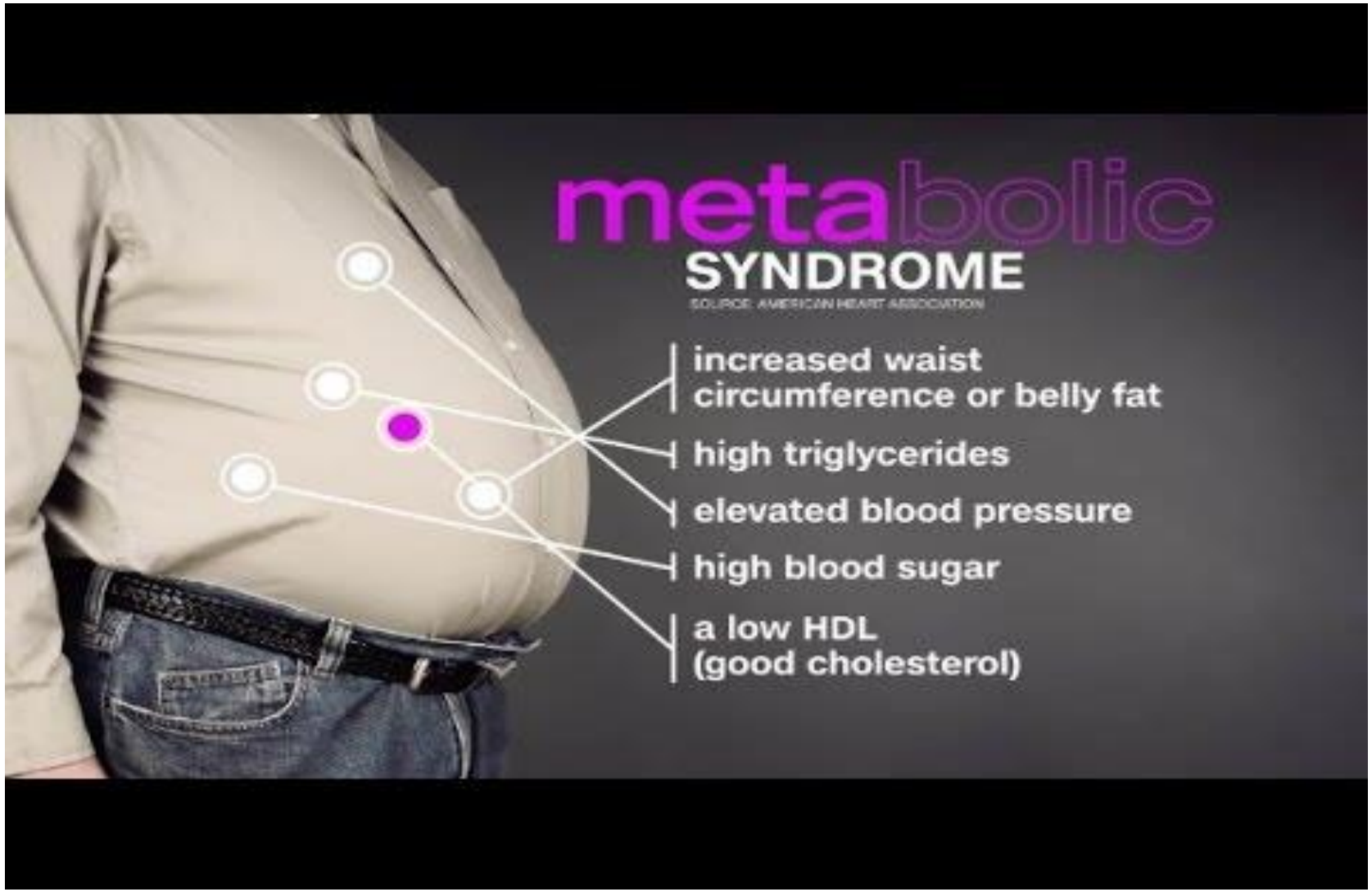
METABOLIC SYNDROME



Metabolic Syndrome or Syndrome - X

1. Introduction
2. Definition
3. Epidemiology
4. Pathophysiology
5. Treatment

1. Introduction

- The metabolic syndrome (MetS) is a major and escalating public-health and clinical challenge worldwide in the wake of *urbanization*, *surplus energy intake*, *increasing obesity*, and *sedentary life habits*.

- MetS confers a 5-fold increase in the risk of *type 2 diabetes mellitus* (T2DM) and 2-fold the risk of developing *cardiovascular disease* (CVD) over the next 5 to 10 years.

2. Definition

- MetS is defined by a constellation of an interconnected *physiological, biochemical, clinical,* and *metabolic factors* that directly increases the risk of atherosclerotic cardiovascular disease (ASCVD), T2DM, and all cause mortality.
- Unhealthy body measurements and abnormal laboratory test results include atherogenic dyslipidemia, hypertension, Impaired glucose intolerance, proinflammatory state, and a prothrombotic state.

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

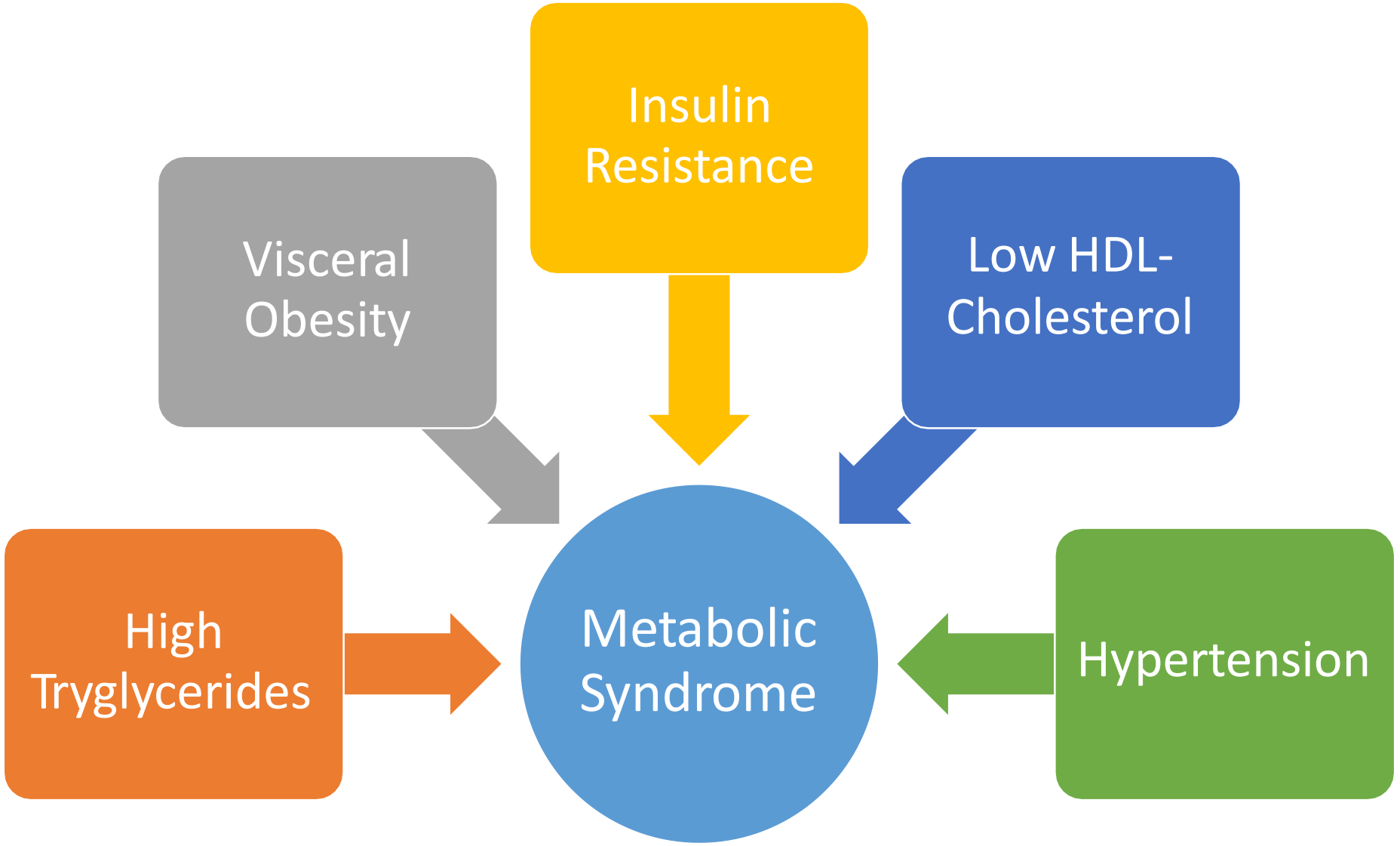
A) Central Obesity (Waist circumference)

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/m^2, central obesity can be assumed and waist circumference doesn't need to be measured.


Insulin Resistance
Visceral Obesity
Low HDL-Cholesterol
High Tryglycerides
Metabolic Syndrome
Hypertension

3. Epidemiology

- Worldwide prevalence of MetS ranges from <10% to as much as 84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population studied, and the definition of the syndrome used.

- In general, the IDF estimates that one-quarter of the world's adult population has the MetS.

- Higher socioeconomic status, sedentary lifestyle, and high body mass index (BMI) were significantly associated with MetS.

- Differences in genetic background, diet, levels of physical activity, smoking, family history of diabetes, and education all influence the prevalence of the MetS and its components.

4. Pathophysiology

- MetS is a state of chronic low grade inflammation as a consequence of complex interplay between genetic and environmental factors.

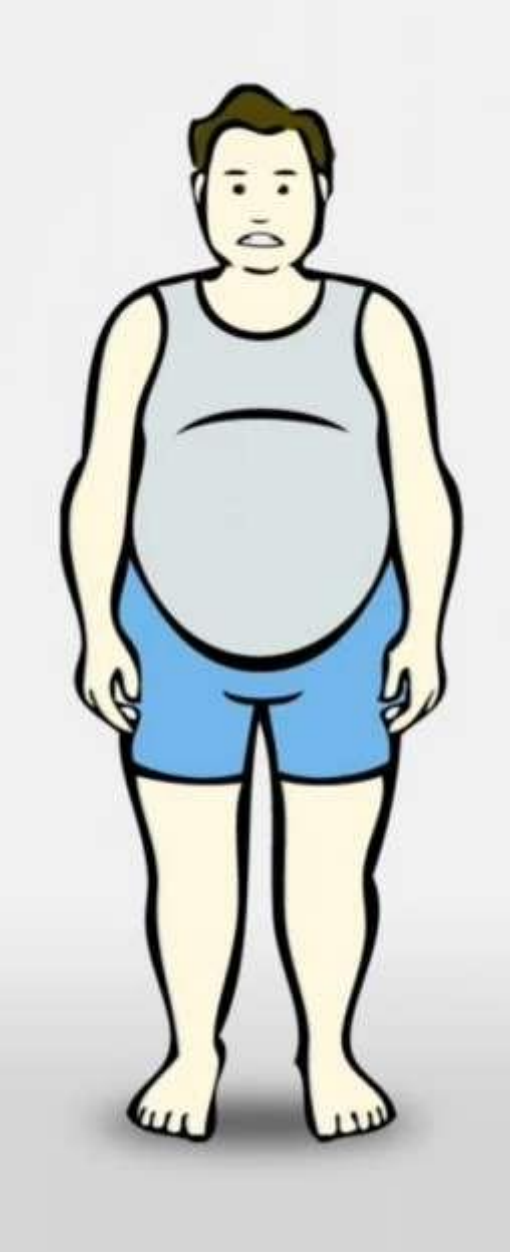
- Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state and chronic stress are the several factors which constitute the syndrome.

4.1 Abdominal Obesity

- The “obesity epidemic” is principally driven by an increased consumption of cheap, calorie dense food and reduced physical activity.

- Adipose tissue respond rapidly and dynamically to alterations in nutrient excess through adipocytes hypertrophy and hyperplasia.

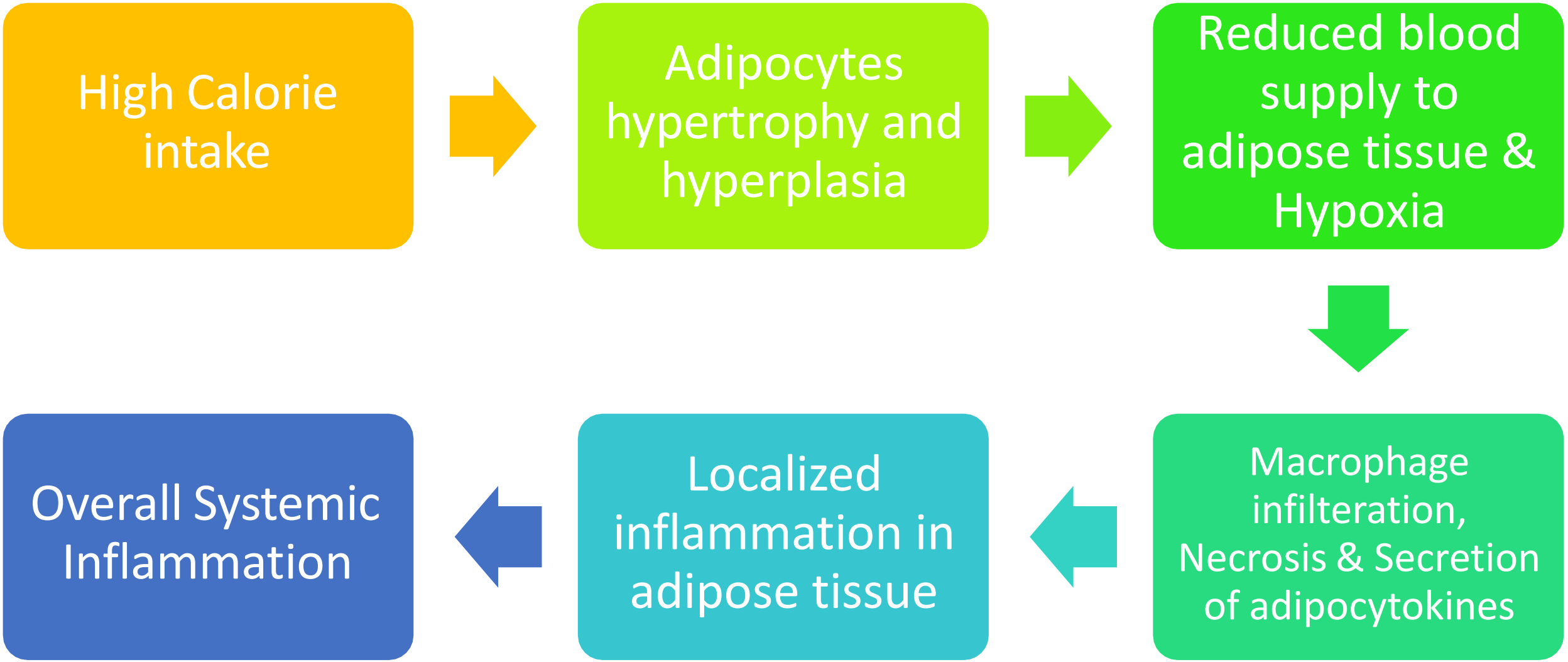
- With obesity and progressive adipocytes enlargement, the blood supply to adipocytes may be reduced with consequent hypoxia.



- 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 (TNFα, 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.


High Calorie intake
Adipocytes hypertrophy and hyperplasia
Reduced blood supply to adipose tissue & Hypoxia
Macrophage infilteration, Necrosis & Secretion of adipocytokines
Localized inflammation in adipose tissue
Overall Systemic Inflammation

4.1.1. FFA

- Splanchic FFA levels may contribute to the liver fat accumulation commonly found in abdominal obesity.
- Acute exposure of skeletal muscle to the elevated level of *FFA induces insulin resistance by inhibiting the insulin-mediated glucose uptake.*
- Chronic exposure of the pancreas to elevated FFA impairs a pancreatic β-cell function.
- FFAs increase fibrinogen and PAI-1 production.

4.1.2 TNFα

- TNF-α acts as a *paracrine mediator in adipocytes* and appears to act locally to reduce the insulin sensitivity.

- TNF-α induces adipocytes apoptosis and promotes insulin resistance by the *inhibition of the insulin receptor substrate 1 (IRS-1) signalling pathway.*

- TNF-α is positively associated with the body weight, waist circumference and triglycerides (TGs), while negatively associated with High density lipoprotein-cholesterol (HDL-C).

4.1.3 CRP

- High-sensitivity C-reactive protein (hs-CRP) has been developed and used as a marker to *predict CVD in metabolic syndrome* and it was recently used as a predictor for non-alcoholic fatty liver disease.

- CRP level is more likely to be elevated in obese insulin-resistant, but not in obese insulin-sensitive subjects.

4.1.4 IL-6

- IL-6 is *released by both adipose tissue and skeletal muscle* in humans. It has both an inflammatory and an anti-inflammatory action.
- IL-6 is also expressed in some parts of the brain such as hypothalamus, in which it controls appetite and energy intake.
- IL-6 is a systemic adipokine, which not only impairs insulin sensitivity but is also a major determinant of the hepatic production of CRP.
- IL-6 is positively associated with BMI, fasting insulin and the development of T2DM and negatively associated with HDL-C.

4.1.5 PAI-1

- A serine protease inhibitor secreted from intra-abdominal adipocytes, platelets and the vascular endothelium.

- It *exerts its effect by inhibiting the tissue plasminogen activator (tPA)* and thus is considered as marker of fibrinolysis and atherothrombosis.

- It increases the risk of an intravascular thrombus and adverse cardiovascular outcomes.

4.1.6 Adiponectin

- It *inhibits hepatic gluconeogenic enzymes* and the rate of an endogenous glucose production in the liver.

- Adiponectin is inversely associated with CVD risk factors such as blood pressure, LDL-C, TGs.

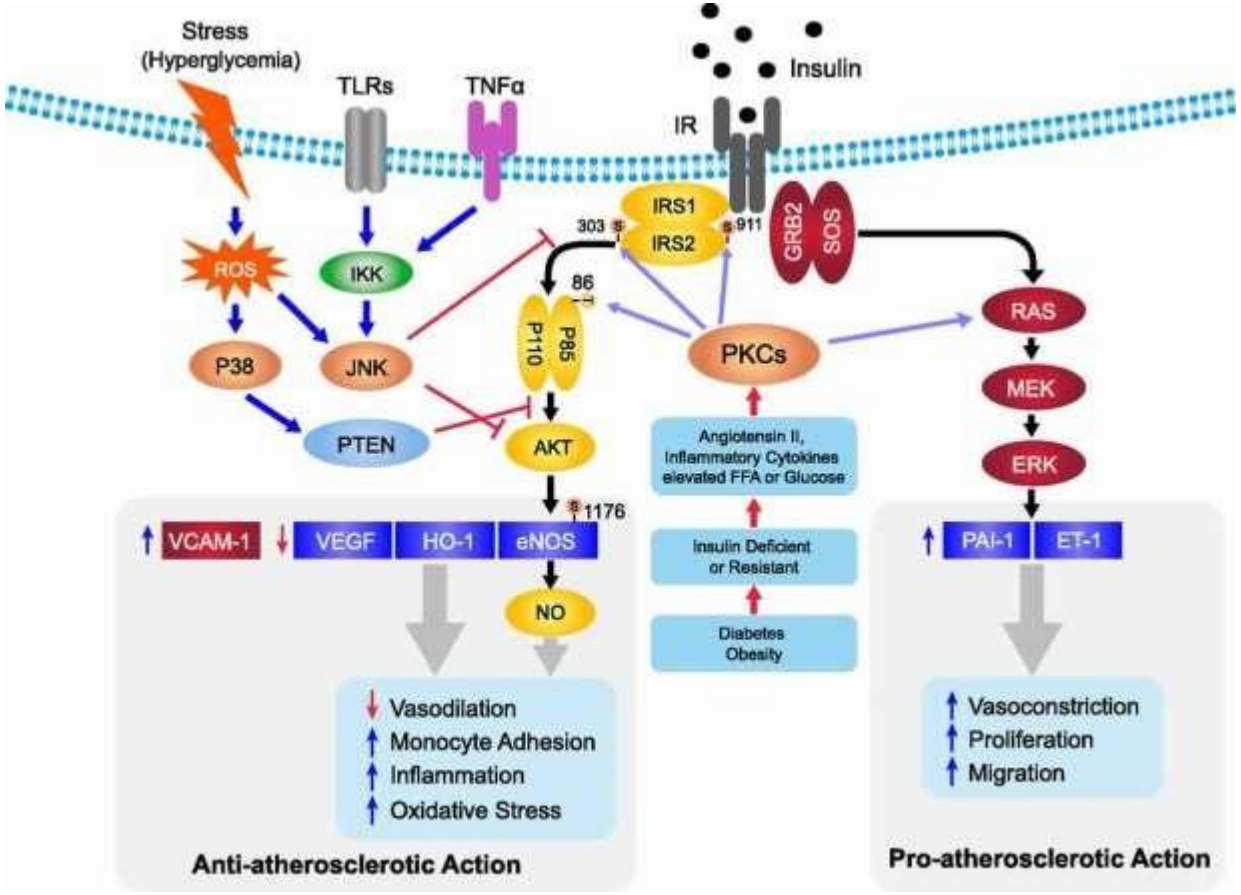
- Adiponectin expressions and secretions are reduced by TNF-α.

4.1.7 Leptin

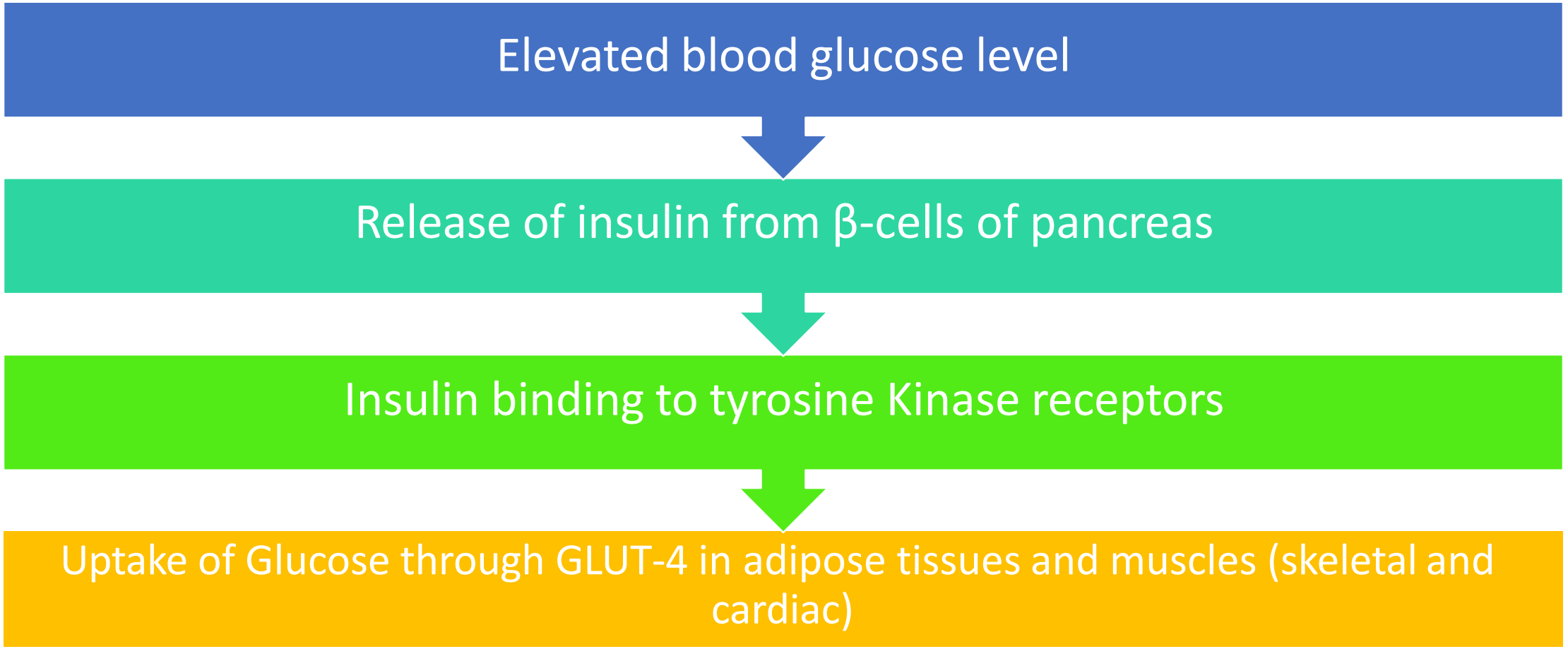
- Leptin is an adipokinin *involved in the regulation of satiety and energy intake.*
- Levels of leptin in the plasma increases during the development of obesity and decreases during weight loss.
- Leptin receptors are located mostly in the hypothalamus and the brainstem and signals through these receptors controls satiety, energy expenditure and neuroendocrine function.
- Besides, its effect on appetite and metabolism, *leptin also acts in the hypothalamus to increase the blood pressure through activation of sympathetic nervous system.*

4.2 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)



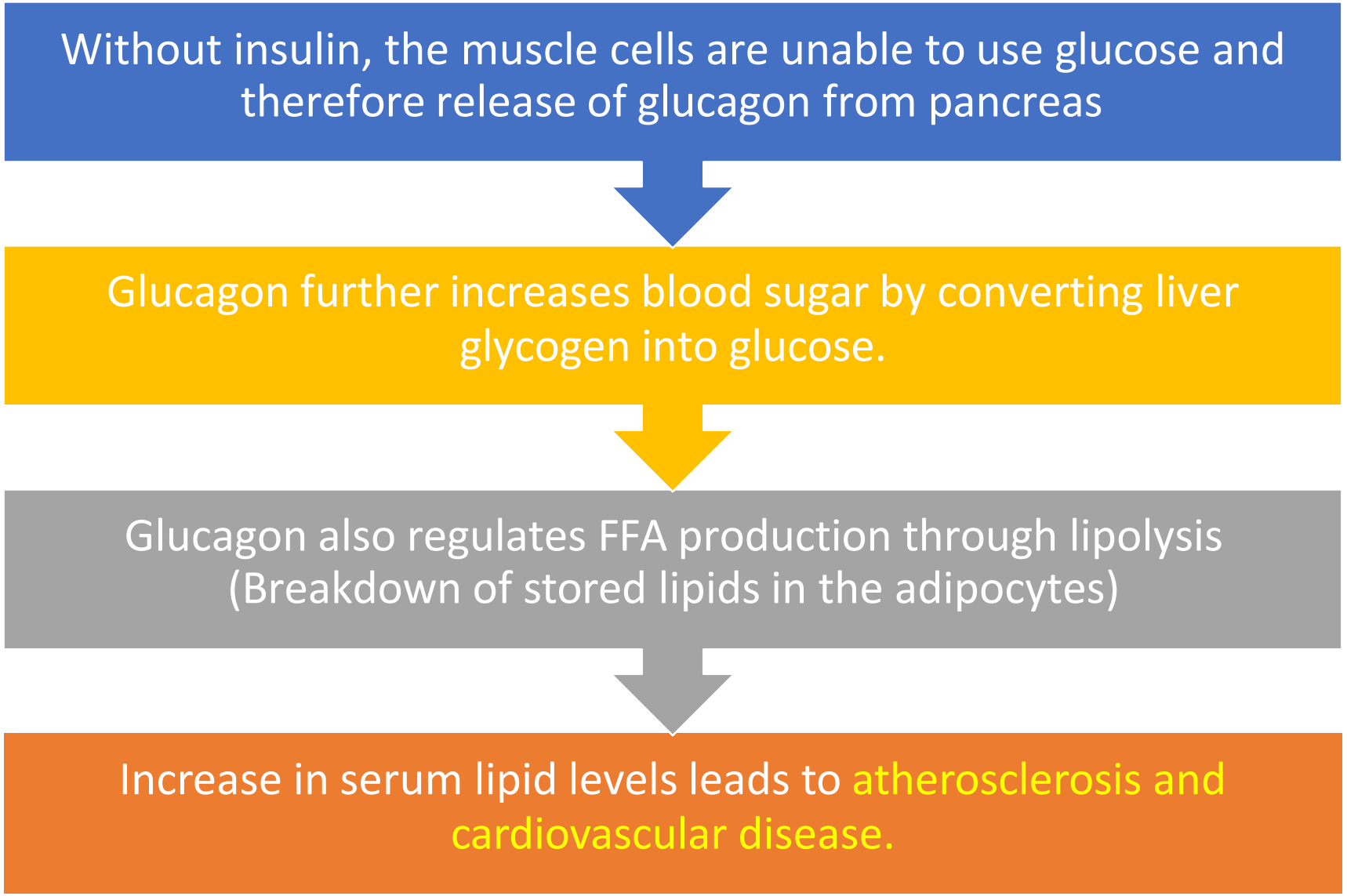
How Insulin Acts (in abnormal condition)

If the cell phospholipid membrane is not “fluid” enough (i.e. it doesn’t contain enough PUFA), insulin receptors are disrupted

Insulin cannot bind to its receptors and thereby increases blood glucose levels

β-cells reduce insulin output only if the blood glucose level falls, allowing blood glucose to settle at a constant of approximately 5 mmol/L.

In Insulin Resistance states, insulin levels remain high and this promotes hepatic lipogenesis.


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 also regulates FFA production through lipolysis (Breakdown of stored lipids in the adipocytes)
Increase in serum lipid levels leads to atherosclerosis and cardiovascular disease.

Insulin Resistant States

- In an *insulin-resistant person*, normal levels of insulin do not have the same effect in controlling blood glucose levels.

- During the *compensated phase*, *insulin levels are higher* and blood glucose levels are still maintained.

- If the compensatory insulin secretion fails, then either fasting (Impaired fasting glucose) or postprandial (Impaired glucose tolerance) glucose concentration increases.

- Eventually, type 2 diabetes occur when glucose levels become higher throughout the day as the resistance increases and compensatory insulin secretion fails.

- The elevated insulin levels have additional effects that cause further abnormal biological effects throughout the body.

Factors Influencing Insulin Resistance

Diet

- It is well known that insulin resistance commonly coexist with obesity.
- Saturated fat appears to be the most effective at producing insulin resistance.
- High fat diet has the tendency to result in calorie intake that is far in excess from our energy needs, resulting in rapid weight gain.
- IR is positively correlate with fat intake and negatively correlated with dietary fibre intake.

PUFA

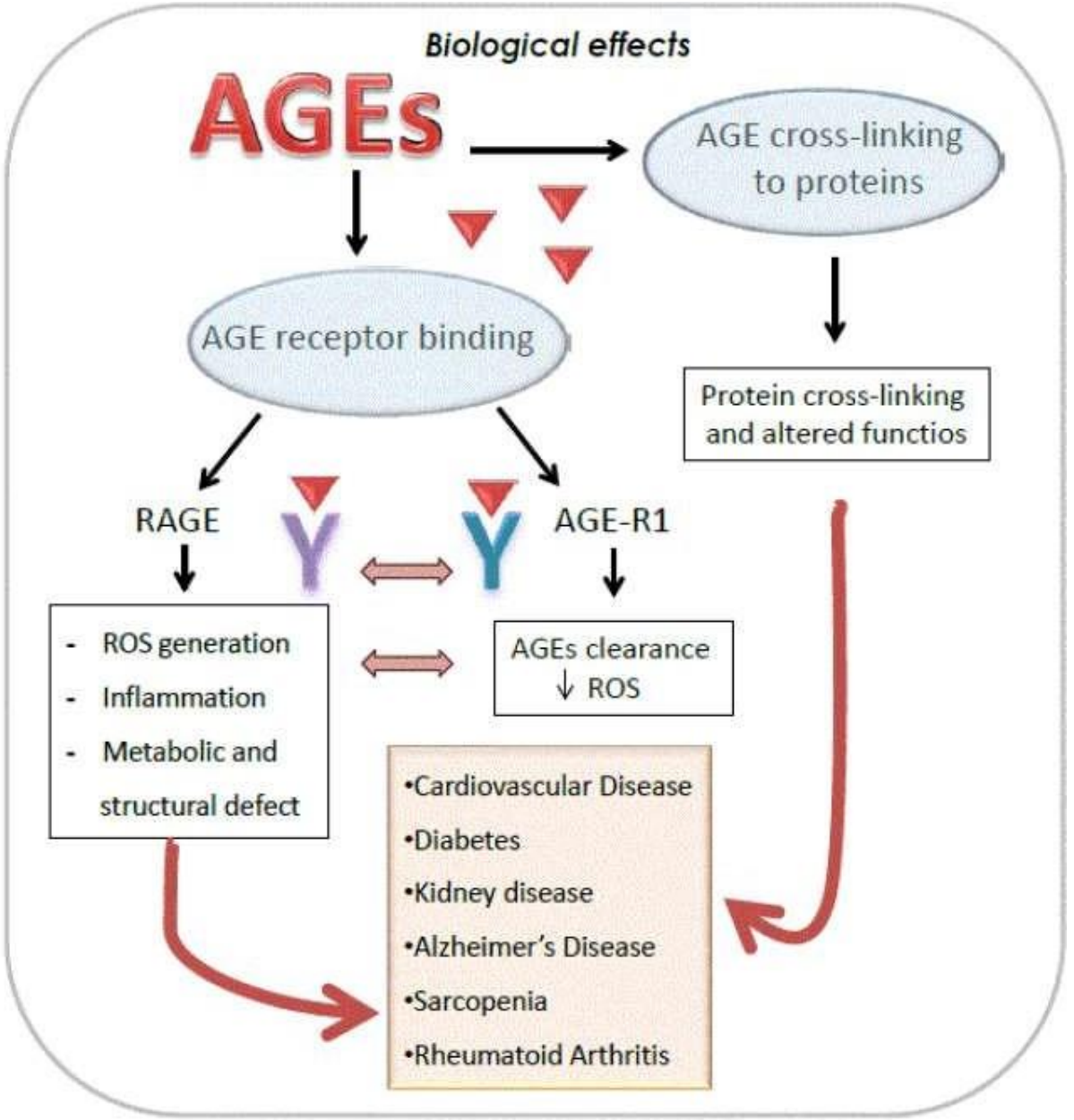
- In the long term, diet has the potential to change the ratio of polyunsaturated to saturated phospholipids in cell membrane, correspondingly changing cell membrane fluidity.

- It is hypothesized that increasing cell membrane fluidity by increasing PUFA concentration might result in an enhanced number of insulin receptors and reduced insulin resistance.

Advanced Glycated End Products

- AGE: Elevated blood glucose levels leads to increased glycation of proteins with changes in protein function throughout the body.

- These are called Advanced Glycated End products and contribute to the end organ damages of T2DM.



4.3 Dyslipidemia

- *Insulin normally suppresses lipolysis in adipocytes*, so an impaired insulin signalling increases lipolysis resulting in increased FFA levels. In the liver, FFAs serve as a substrate for the synthesis of TGs.

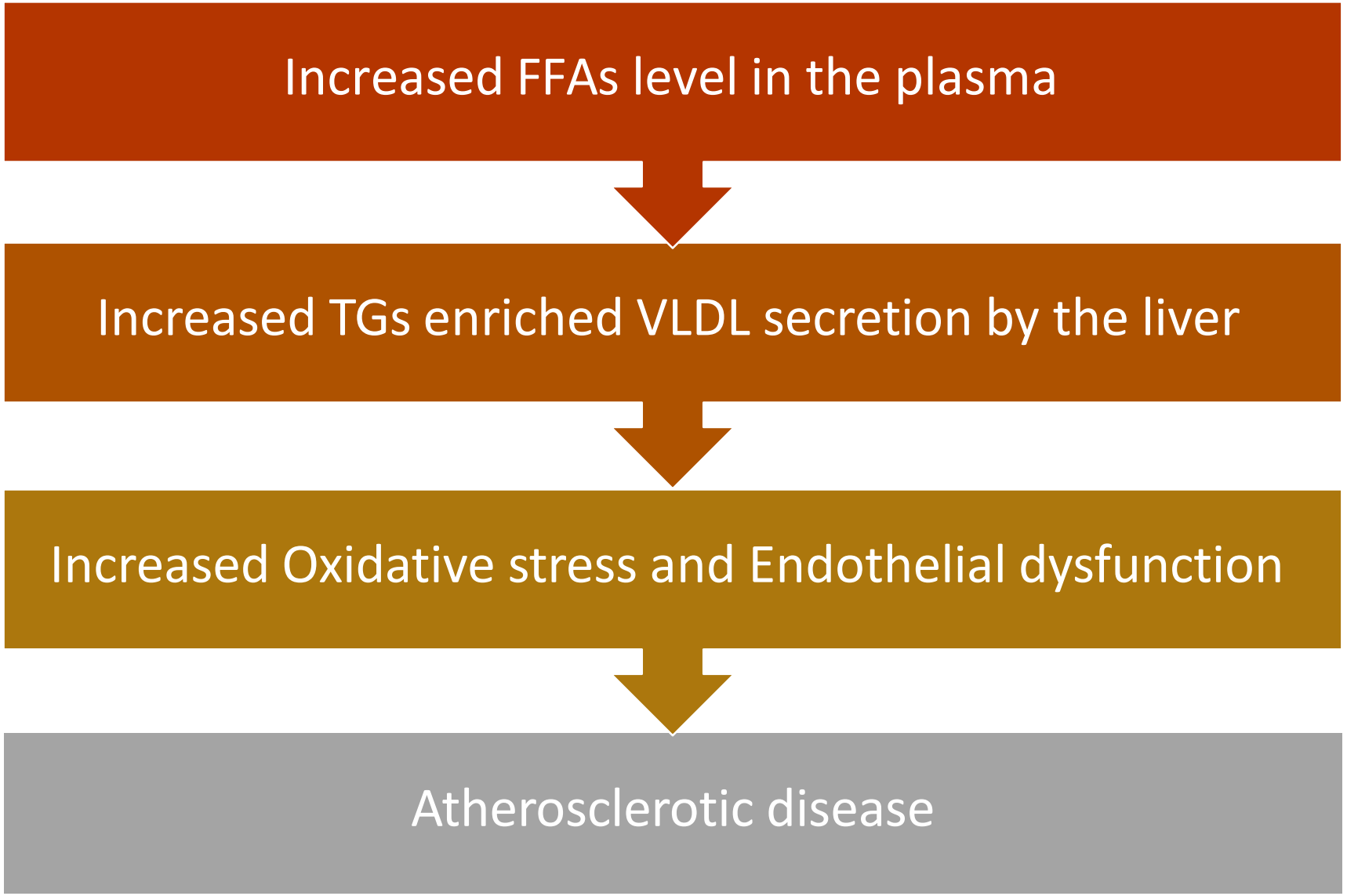
- *Insulin normally degrades apoB through PI3K-dpendent pathway*, so an insulin resistance directly increases VLDL production.

- *Insulin regulates the activity of lipoprotein lipase*, the rate limiting and major mediator of VLDL clearance. VLDL is metabolized to remnant lipoproteins and small dense LDL, both of which can promote atheroma formation.

- The TGs in VLDL are transferred to HDL by cholesterol ester transfer protein (CETP) in exchange for cholesteryl esters, resulting in TG-enriched HDL and cholesteryl enriched VLDL particles.

- TG-enriched HDL is a better substrate for hepatic lipase so it is rapidly cleared from the circulation, leaving a few HDL particles to participate in a reverse cholesterol transport from the vasculature.

- It is believed that dyslipidemia associated with insulin resistance is a direct consequence of increased VLDL secretion by the liver.


Increased FFAs level in the plasma
Increased TGs enriched VLDL secretion by the liver
Increased Oxidative stress and Endothelial dysfunction
Atherosclerotic disease

4.4 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.

4.5 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.
  2. Environmental influences that lead to weight gain.

4.6 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.

4.7 Sedentary lifestyle

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


Thank You!