Metabolic syndrome and Diabetic heart disease

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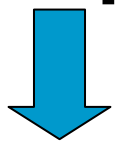
Causes:

genetic and environmental, stress and inflammation, physical inactivity, obesity, aging, endothelial dysfunction, drugs (eg. alpha or beta blockers, antidepressant, antihistamine), endocrinopathies, cirrhosis, hepatitis, renal failure, cytokines, transcription factors etc.



Impaired insulin action in insulin-sensitive peripheral tissues such as fat, muscle, liver, as:

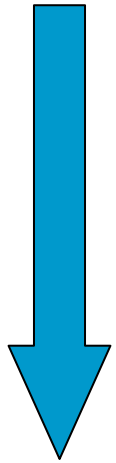
- **Impair endothelial function, increase vascular inflammation and thrombosis**
- **Abnormality in glucose and fatting acid metabolism in skeletal muscle and myocardium**
- **Decrease adipogenesis and increase lipolysis causing release of free fatty acid in adipose tissue**
- **Increase hepatic gluconeogenesis, abnormality in lipid metabolism and dyslipidemia**
- **Loss of neural weight control function of insulin**

insulin resistance

compensatory hyperinsulinemia

(=compensatory mechanism required to maintain normal glucose level)

decompensate if pancreatic beta-cell impairment



impaired glucose tolerance

hyperglycemia

type 2 diabetes mellitus

Major contributing factors to insulin resistance = obesity, physical inactivity, advancing age

- Insulin resistance → increase plasminogen activator inhibitor 1 (PAI-1) → impaired fibrinoloysis → endothelial function

- Insulin resistance = hallmark of metabolic syndrome, most important predictor of type 2 diabetes mellitus and precedes overt hyperglycemia and type 2 diabetes mellitus by 10-20 years

Metabolic syndrome (=syndrome of insulin resistance)

- **Insulin resistance associated with cardiovascular risk factors (clinical and biochemical abnormalities such as: hypertension, obesity, dyslipidemia, hypercoagulability, reduced vascular compliance,increased inflammatory markers, hyperuricemia etc) = “metabolic syndrome” → atherosclerosis, endothelial dysfunction → diabetic heart disease (coronary atherosclerosis, diabetic cardiomyopathy, diabetic autonomic neuropathy)**

Manifestation of metabolic syndrome

- **Insulin resistance targets many tissues eg. adipose tissue, vasculature, musculature, myocardium, pancreas, liver, brain with metabolic, vascular, proinflammatory and oxidant effects, as:**
- **Dyslipidemia (disturbance in lipid homeostasis) and atherosclerosis**
- **Hypertension (due to genetic factors, sodium retention, hyperinsulinemia → renal sodium and water retention, sympathetic nervous system activation)**
- **Cardiomyopathy and heart failure (due to neurohormonal, endothelial, metabolic and inflammatory disturbances)**

- Coronary artery disease, peripheral and cerebrovascular disease (due to vascular inflammation, atherogenic dyslipidemia, hypercoagulability eg. Increased fibrinogen, von Willebrand factor, plasminogen activator inhibitor (PAI-1), platelet adhesion and aggregation
- Fatty liver
- Glucose intolerance and type 2 diabetes mellitus
- Malignancy (impairment of immune response, impact of adipose tissue on hormone levels, systemic trophic effects of hyperinsulinemia)
- Frailty
- Dementia and Alzheimer's disease
- Nephropathy, retinopathy, neuropathy

Management of metabolic syndrome

- ***Lifestyle modification:*** **exercise, diet control, weight loss, stop smoking**
- ***Medications:***
- **Aspirin – antioxidant, antiinflammatory and antithrombotic effects**
- **Lipid-lowering drugs**
- **Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB)**

= first-line agent for treating hypertension in patients with insulin resistance and metabolic syndrome

- **antioxidant, antiinflammatory, antithrombotic effects**
- **improve endothelium function, insulin sensitivity and glucose metabolism**
- **decrease microvascular complication, microalbuminuria, proteinuria and delay diabetic nephropathy and retinpathy**

- Aldosterone antagonist eg. Spironolactone
- Beta blocker – reduce cardiovascular events.
  Adverse effects=affect blood glucose and lipid levels, decrease peripheral blood flow → worsen claudication
- Alpha blocker – lack of adverse metabolic effects
  - decrease insulin resistance, improve glucose tolerance, reduce lipid
  - side effects = orthostatic hypotension
- Diuretics – low dose useful in volume overload diabetic patients. High dose → detrimental metabolic effects (dyslipidemia, hyperinsulinemia, hyperuricemia)
- Calcium blocker – not affecting blood glucose and lipid

- **Insulin-sensitizing therapy eg. thiazolidinediones or glitazones**
  - **activate peroxisome proliferator-activated receptors (PPAR) = transcriptor factor → enhance insulin sensitivity, improve carbohydrate and lipid metabolism**
  - **antioxidant, antiinflammatory and vasculoprotective effects**
- **Biguanides eg. Metformin**
  - **inhibit hepatic gluconeogensis**
  - **small peripheral insulin-sensitizing effect**
  - **decrease cardiovascular risk and delay onset of type 2 diabetes mellitus**