On the Haematological Risk Factors for Coronary Heart Disease
Coronary Heart Disease

- One of the most frequently encountered multifactorial disorder.
- The most common cause of morbidity and mortality worldwide*.
- Aetiological factors:
  - Genetic susceptibility--- (polygenic).
  - Environmental factors.
- Gene-environment interactions essential for CHD development.

The Framingham Study*
(Initiated in 1948)

• Recently reached its 50 years legacy.

• Provided insight into prevalence, incidence, full clinical spectrum and predisposing factors for coronary diseases.

• Coined the term ‘Risk’ factors and listed the “Traditional Risk Factors” for CHD development.

Risk Factors for CHD

- Traditional (Established) Risk Factors
- Non-Traditional (Novel) Risk Factors
Traditional risk factors fail to explain the high incidence of CHD in different populations.

Extensive studies are searching for novel risk factors for CHD.
Traditional (Established) Risk Factors for CHD

1. Age ≥ 45 years for men; ≥ 55 years for women.
2. Family history of CVD.
3. Smoking.
4. Hypertension (BP ≥ 140/90 mmHg).
5. Hypercholesterolaemia.
6. LDL-C (≥ 160 mg/dl; ≥ 4.1 mmol/l) with < 2 risk factors.
7. LDL-C (130-159 mg/dl; 3.4-4.1 mmol/l), with ≥ 2 risk factors.
8. HDL-C (35 mg/dl; 0.9 mmol/l).
10. Diabetes mellitus.
Novel (Non-Traditional) Risk Factors for CHD

- Left ventricular hypertrophy.
- Hyper homocysteinemia.
- Lipoprotein(a) excess.
- Hypertriglycerideamia.
- Oxidative stress.
- Infectious agents (e.g. *chlamydia pneumoniae*, *Helicobacter pylori* and CMV)
- Markers of inflammation (e.g. CRP and serum amyloid A).
- Hyperfibrinogenemia.
- Procoagulant substances (e.g. plasminogen, factor VII, plasminogen activator inhibitor, von Willebrand factor, etc).
Haematological Genetic Risk Factors for CHD
Contribution of systemic risk factors to Thrombosis

- Lipids
- Hormonal factors
- Hyperglycaemia
- Others

Hemostasis

Platelet & Leucocyte function

Fibrinolysis

Abnormality:

Increased Thrombogenicity (Hypercoagulable state)

Local Thrombotic Occulsions → CHD
Defects in Hemostasis → CHD
Hemostasis

A property of the blood circulation system that maintains the blood in a fluid state within the vessel walls in combination with an ability to prevent excessive blood loss when injured.

Due to balanced interaction between:

- Blood vessel walls
- Circulating platelets
- The plasma coagulation factors
- The fibrinolytic factors

Any defect in these may lead to thrombus formation.
Thrombophilia

* An increased tendency to thrombosis.
* Due to:
  - An ongoing stimulus to thrombosis.
  - Defect of natural anticoagulant or fibrinolytic mechanism that predisposes to thrombus.
Inherited Molecular defects in thrombophilia

- ATIII deficiency.
- Protein C deficiency.
- Protein S deficiency.
- Dysfibrinogenemia.
- Activated protein C resistance.
- Plasminogen deficiency.
- ↓ Plasminogen activator activity.
- ↑ Increased PA inhibitor.

Approx. 20-60% of patients with thrombophilia have APC resistance & the other defects are present in approx. 10%.
Genetic Prothrombotic Risk Factor* for CHD

- Elevated Fibrinogen
- Deficiencies of:
  - Protein C
  - Protein S
  - Antithrombin
  - Plasminogen
- Factor V Lieden Mutation
- Plasminogen activator
- Prothrombin (G20210A) mutation
- Plasminogen activator inhibitor
- Elevated homocysteine
- Elevated Lp(a) >30mg/dl

*Methylenetetrahydrofolate reductase TT677 genotype

*Etiological factors in familial thrombophilia
Clotting Factors and CHD

Increased levels of clotting factors → Increased Coagulation → CHD
Clotting Factors & their Defects
Fibrinogen

- Major protein in blood plasma (200-400 mg/dl)
- Important clotting factor

Synthesised in the liver

During clotting:

thrombin

Fibrinogen → Fibrin

Clot ← (Polymer)

Affects:
- Blood
- Coagulation
- Rheology
- Platelet aggregation
- Vascular walls
- Acute-phase reactant
Fibrinogen in CHD

- Elevated fibrinogen increases risk of:
  - CHD
  - Stroke
  - MI
  - Peripheral arterial disease

Increase of 1 mg/dl Fibrinogen → correlates with nearly 2-fold increase in probability of death within 6 years

Involved in:
- Pathogenesis of arterial disease
- Strong independent predictor of death*
- Pathogenesis of atherosclerosis**

> 350 mg/dl Independent risk factor for infarction of brain and heart

*Banerjee et al, 1992 **Lassila et al, 1993
Risk factors that elevate fibrinogen

- Cigarette smoking
- Age
- Sedentary lifestyle
- Race
- Gender (higher in females)
- Oral contraceptive use
- Stress
- Inflammation
- Diabetes mellitus
- Obesity
Factors effective in reducing fibrinogen

Diets rich in Omega-3 and Omega-6 fatty acids

Exercise

Smoking cessation

Weight reduction

Stress management
<table>
<thead>
<tr>
<th>Elevation of</th>
<th>Independent Risk for CHD</th>
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</thead>
<tbody>
<tr>
<td>Factor II</td>
<td>Not significant</td>
</tr>
<tr>
<td>Factor V</td>
<td>Significant (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Significant (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Factor X</td>
<td>Significant (p = 0.005)</td>
</tr>
</tbody>
</table>

*In several studies.*
Clotting activity of coagulation factors II, V, VII and X in MI patients and controls

<table>
<thead>
<tr>
<th>Factor</th>
<th>Synonym</th>
<th>Patients</th>
<th>Control</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>F II(%)</td>
<td>Prothrombin</td>
<td>96</td>
<td>95</td>
<td>0.979</td>
</tr>
<tr>
<td>F V(%)</td>
<td>Proaccerleriin</td>
<td>111</td>
<td>103</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>F VII(%)</td>
<td>Prothrombin conversion accelerator</td>
<td>118</td>
<td>100</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>F X</td>
<td>Stuart-Prower factor</td>
<td>108</td>
<td>99</td>
<td>0.005*</td>
</tr>
</tbody>
</table>
### Relative Risk of MI in patients with elevated coagulation factors

<table>
<thead>
<tr>
<th>Elevated Factor</th>
<th>RR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>F II</td>
<td>1.0</td>
<td>0.4 - 1.7</td>
</tr>
<tr>
<td>F V</td>
<td>3.3</td>
<td>1.8 - 6.6</td>
</tr>
<tr>
<td>F VII</td>
<td>5.2</td>
<td>2.4 - 11.2</td>
</tr>
<tr>
<td>F X</td>
<td>2.2</td>
<td>1.03 - 4.52</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>5.4</td>
<td>2.5 - 11.9</td>
</tr>
</tbody>
</table>
Prothrombin 20210 G→A allele

Increase prothrombin activity.
Increase Prothrombin level.

*2.7 fold increase risk of venous thrombosis.
*4.0 fold increase of risk of MI.
Factor V Leiden Allele, 1691A-G

Nucleotide 1691

A → G

Factor V

506 Arg → Gln

Activated protein C resistance

Increased risk of CAD
Activated Protein C Resistance

- Autosomal Dominant Disorder.

- Results from several genetic defects:
Von Willebrand Factor

- Marker of endothelial cell dysfunction
- Promotes platelet adhesion and aggregation
- Binds to Factor VIII
  - Has procoagulant activity
  - Stabilises procoagulant activity
Intermediate derived from methionine:

\[ \text{Met} \rightarrow \text{Homocys} \downarrow \text{CH}_3 \]

Normal fasting plasma level: 5-15 mmol/l

Homocystinuria:
- Rare, AR disorder
- Deficiency of cystationine \(\beta\)-synthase.
- Elevated homocyst in blood and urine.

- Atherosclerosis
- Thrombotic vascular disease
- MR
- Skeletal defect
Hyperhomocysteinemia associated with*:

- CAD
- MI
- Peripheral vascular disease
- Cerebrovascular disease
- Stroke
- Death from CAD

Role of homocysteine in vascular disease

- Promotes endothelial dysfunction
- Induces endothelial cell injury
- Reduces the protective effect of endothelium-derived relaxing factor
- Induces proliferation of smooth-muscle cells
- Has procoagulant effect
- Enhances thromboxane A2 formation and platelet aggregation
- Increases binding of Lp(a) to fibrin
Homocysteine (conti.)

- Increase of fasting homocysteine by 5 mmol/l increases the incidence of coronary disease by 1.6-1.8 fold*.

- However, some prospective studies failed to show relation between homocysteine level and coronary heart disease**.

- Why the controversial results???

???? Genetic variability.

Factors reducing homocysteine in hyperhomocysteinemia

Supplementation with:
- Folate
- Vit. B12
- Vit. B6

Use of oral estrogen in men and postmenopausal women
→ 11-14% reduction in homocysteine level
Fibrinolysis
The Fibrinolytic Pathway

Extrinsic Activation Organ Tissues
- Vascular endothelium

Intrinsic Activation
- Kininogen
- Kallikrein
- Factor XIIa

Extrinsic Activators
- Streptokinase
- Thrombin

Plasminogen

Plasmin

Antiplasmins
- Alpha1-Antiplasmin
- Alpha-2-Microglobulin
- Alpha-1-AT
- Antithrombin III
- C1 inactivator

Fibrin

Fibrin degradation products (Fibrinolysis)
Plasminogen Activator Inhibitor Type I (PAI1)

Inhibits conversion of plasminogen to plasmin

Inhibits Fibrinolysis

Inhibits dissolution of Thrombus
Steps towards Control & Prevention of CHD
The Healthy Heart Program

- Increase anti-oxidants in diet (e.g. vit.C, vit.E, beta-carotenes, flavonoids etc)
- Reduce obesity & excess calorie intake.
- Decrease sugar & other carbohydrates in diet.
- Increase exercise.
- Decrease smoking.
- Maintain Blood glucose level.
- Decrease salt.
- Increase sea food and fish oil in diet.
- Decrease stress in life.
THANK YOU FOR LISTENING