I. Overview of Diabetes Mellitus (DM):

1. Systemic disease process

2. **Cardiovascular risk associated with DM is equivalent to that of having had a previous myocardial infarction**

3. More often patients with DM have multi-vessel, diffuse disease with a higher incidence of left main

4. Diagnosis of DM
   - Based on fasting plasma glucose $> 7.0$ mmol/L
   - **OR** casual plasma glucose $> 11.1$ mmol/L with associated symptoms (polyuria, polydipsia, unexplained weight loss)
   - **OR** oral glucose tolerance test 2 hour plasma glucose $> 11.1$ mmol/L

5. Risk Factors of DM
   - 1st degree relative
   - Ethnicity
   - History of impaired glucose tolerance (IGT); impaired fasting glucose (IFG), or gestational DM
   - Polycystic ovary disease
   - Acanthosis nigricans
   - Schizophrenia
   - Vascular disease
   - Presence of nephropathy, neuropathy, or retinopathy
   - Metabolic Syndrome
     - Abdominal obesity
       - $> 102$ cm in males; $> 88$ cm in females
     - Hypertension
       - Systolic blood pressure $> 130$ mmHg
       - Diastolic blood pressure $> 85$ mmHg
     - Dyslipidemia
       - HDL $< 1.0$ mmol/L in males; $< 1.3$ mmol/L in females
       - TG $> 1.7$ mmol/L
     - Insulin resistance/glucose intolerance
II. Myocardial Infarctions (MI) in the Diabetic Patient:

1. Increased complications
   - Recurrent infarction
   - Shock
   - Electrical disturbances
   - Heart failure
   - Myocardial rupture

2. Increased morbidity given the following:
   - Transmural infarcts
   - Anterior territory infarcts
   - Previous myocardial infarctions
   - Female
   - Previous Insulin Therapy
   - Obesity

3. Considerably higher short-term and long-term mortality following MI compared to non-diabetics
   - Hospital mortality reported to be 25% - 40%
   - Based on Framingham data
     - Men have 2X > mortality
     - Women have 4X > mortality

III. DM Under a Microscope:

1. Multiple metabolic derangements
   - Hyperglycemia and hyperinsulinemia
   - Dyslipidemia
   - Increase endothelin secretion
   - In the heart
     - Hypertrophy
     - Fibrosis and basement membrane thickening
     - Abnormal Ca\(^+\) shifting
     - Microaneurysms

2. Alterations to the coagulation cascade
   - Platelets
     - Relatively activated
     - Decreased lifespan
     - Increased size/weight
     - Increased glycoprotein IIb/IIIa receptor sites
   - Increase in D-dimer, fibrinogen, thrombin, PAI-1, TxA2
   - Increase in Factor VII
3. Alterations to the vascular function
   - Neuropathic changes ➔ Sensory and autonomic
     - Unopposed sympathetic tone
     - Increased plaque instability
     - Increased arrhythmogenicity
     - Worsening heart failure
     - Atypical anginal symptoms
   - Changes to vasoreactivity
     - Attenuation of NO production
     - Increased NO scavenging
     - Blunted vasomotor reactivity

4. Alterations in metabolism
   - Normal rates of glucose oxidation in the myocardium ~ 40%, even as the only exogenous supply for oxidative metabolism
   - Normally, long-chain fatty acids (FA) are preferred to carbohydrates in the aerobic hearts and supply ~ 60% - 70% for oxidative metabolism
   - In DM there is inappropriate free FA metabolism

5. Alterations in metabolism secondary to ischemia
   - In states of ischemia glucose is the chief fuel source
   - In myocardial ischemia there is a catecholamine surge which decreases insulin
   - Insulinopenia favours lipolysis, ketones, and free FA metabolism
   - Free FA metabolites become toxic to cells due to inability of mitochondria to manage products of oxidative metabolism
   - Oxidative products ➔ inhibit glucose movement
   - In states of anoxia and ischemia oxidative metabolism decreases, but makes alterations to pathways to predominate as ATP supplier
   - Ischemia impairs mitochondrial function ➔ ATP supply decreases
   - FA do not have an anaerobic metabolic pathway ➔ ATP yield declines much more rapidly
   - Metabolism of FA ➔ increased oxygen demand, metabolites accumulate which further inhibit oxidative metabolism, direct toxic effects ➔ potentiate myocardial ischemic injury
IV. The Evidence for Use of Insulin During an Acute Myocardial Infarction:

1. Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI)
   - Malmberg et al. (1995) conducted a randomized trial in 19 Swedish CCU’s that demonstrated the benefits of insulin therapy in patients who presented with an acute MI and a random blood glucose greater than 11.0 mmol/L.
   - With a sample size of 620, patients were randomized to receive either 24 hours of insulin infusion therapy and then a minimum of 3 months QID subcutaneous insulin therapy or control which involved treating patients according to standard coronary care unit practice and did not receive insulin unless deemed clinically necessary.
   - Patients were stratified into four groups: Those with or without ≥ 2 high risk features (age > 70 years, history of previous MI or heart failure, or ongoing treatment with digitalis); and those with or without previous insulin therapy.
   - At the end of one year there was a statistically significant decrease in mortality in all four groups (26.1% vs 18.6% in the control group vs the insulin group, respectively, p = 0.0273, relative reduction of 31%).
   - Those largest benefit was seen the lowest risk group (no high risk features or prior insulin use) with a 52% risk reduction in one-year mortality (18.0% vs 8.6%, in the control group and insulin group, respectively, p = 0.020).
   - High incidence of hypoglycemia 15% in the insulin group and 0% in the control group.
   - Long-term follow-up (average of 3.4 years) saw a statistically significant relative risk reduction of 28% in all groups and a 51% relative risk reduction in the lowest risk group.

2. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2):
   - Malmberg et al conducted a multi-center trial between 1998 and 2003 randomizing 1253 into 3 different glycemic management strategies (group 1 – insulin-glucose infusion followed by long-term insulin; group 2 – insulin-glucose infusion followed by standard glucose control; group 3 – routine metabolic management according to local practices.
   - With similar inclusion and exclusion criteria to DIGAMI 1, this study did not show a mortality benefit with a 2.1 year follow-up between the three groups with 23.4% in group 1, 21.2% in group 2; and 17.9% in group 3, with a and overall mortality of 18.4%.
Patients in groups 1 and 2 had better glycemic control compared to group 3, with a slightly lower incidence of hypoglycemia compared to DIGAMI 1 in group 1. Did show that hyperglycemia is an important prognostic predictor of short and long-term mortality. Limitations of the study include slow recruitment, lack of adherence to study protocols, and lack of power in study.

V. Intervention:

1. Patients admitted with an acute coronary syndrome and DM and/or a random blood glucose ≥ 10.9 mmol/L should be initiated on insulin (intravenous/sliding scale) therapy for a minimum of 24 hours.
2. Insulin therapy should be titrated for a blood glucose between 7 mmol/L to 10.9 mmol/L.
3. Following 24 hours of insulin therapy patients should be assessed for transition to subcutaneous QID insulin therapy.
4. Assess short and long-term glycemic management.
5. Referral to Endocrinology.
6. Referral to Diabetic Nurse Educator.

References:


