Review Article

Metabolic syndrome, cardiovascular disease and type - 2 diabetes
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Abstract
The Metabolic Syndrome, a highly prevalent entity is a clustering of risk factors of metabolic origin that are accompanied by increased risks of cardiovascular disease and type - 2 Diabetes Mellitus. These risk factors are atherogenic dyslipidaemia, elevated blood pressure, raised plasma glucose, a prothrombotic and a proinflammatory states. Two major underlying risk factors for the metabolic syndrome are obesity and Insulin resistance; exacerbated by physical inactivity, advancing age, endocrinal and genetic factors. The condition is progressive and in many patients eventually culminates in type - 2 Diabetes, which further enhances the risk of cardiovascular disease.

Primary treatment for the metabolic syndrome is lifestyle therapy i.e. weight loss, increased physical activity and antiatherogenic diet. As the condition progresses, drug therapies may be required to ameliorate the individual risk factors. Ultimately, it may be possible to develop drugs that will simultaneously modify all the risk factors. However, they are under development and so far have not reached the level of clinical practice.

Introduction
The National Cholesterol Education Program (NCEP) Adult Treatment Panel - III (ATP - III), in 2001 introduced the metabolic syndrome as a risk partner to elevated Low-Density- Lipoproteins (LDL) in cholesterol guidelines1 in response to the increasing prevalence of obesity and it's metabolic consequences in the USA. The term metabolic syndrome (MS) was applied to the constellation of risk factors that often accompany obesity and are associated with increased risks for both Atherosclerotic Cardiovascular Disease (ASCVD) and type-2 diabetes. The advantage of identifying this particular cluster of risk factors is that it should bring together the fields of cardiovascular disease and diabetes mellitus for a concerted and unified effort to reduce the risk for both conditions simultaneously. Moreover, cardiovascular disease is the foremost killer of patients with diabetes and this is of interest to both fields.2
Nomenclature and concept of metabolic syndrome (MS)

The understanding of metabolic syndrome stems from epidemiological studies meant for cardiovascular disease and type-2 diabetes mellitus. The naming of risk factor grouping as syndrome largely came from the diabetes field. Reaven coined the term "Syndrome X" to the constellation of risk factors associated with Insulin resistance, which as he contends is the dominant underlying risk factor for the syndrome. In accord, other diabetologists have conferred the name Insulin resistance syndrome.

Obesity has been viewed as an exacerbating factor. Among the diabetologists, some have used the term metabolic syndrome as a more generic name for the collection of metabolic risk factors. Epidemiological studies have established a strong association of obesity with ASCVD and type-2 diabetes. Obesity induced risk factors called the metabolic complications of obesity (i.e. plasma cholesterol, elevated blood pressure and diabetes) are strongly related with increased incidence of cardiovascular disease. The ATP III guidelines followed suit and employed the name "Metabolic Syndrome (MS)" because it seemed to be widely used to describe risk-factor aggregation. The syndrome has been assigned international classification of disease (ICD-9) code 277.7) as the dysmetabolic syndrome.

Pathophysiology

The risk factors of MS are of metabolic origin and comprise of atherogenic dyslipidemia, elevated blood pressure, glucose intolerance, a prothrombotic and proinflammatory states. Atherogenic dyslipidemia includes elevation of lipoproteins containing apolipoprotein B, elevated triglycerides, increased small particles of LDL and low levels of high density lipoproteins (HDL). Elevated plasma glucose falls in the range of either prediabetes or diabetes. A prothrombotic state signifies anomalies in procoagulant factors i.e. an increase in fibrinogen and factor VII as well as antifibrinolytic factor (plasminogen activator inhibitor), platelet abrasions and endothelial dysfunction. A proinflammatory state is characterized by elevated circulating cytokines and acute phase reactants (e.g. C. reactive protein).

The pathogenesis of MS is multifactorial. The major underlying causes are obesity and Insulin resistance. Obesity is best identified by increased waist circumference (abdominal obesity). Insulin resistance can be secondary to obesity but it can have genetic components. Several other factors exacerbate the syndrome: physical inactivity, advancing age, endoerinal dysfunction and genetic aberrations affecting individual risk factors. The increasing prevalence of metabolic syndrome worldwide seems largely to be due to obesity exacerbated by sedentary lifestyle. Insulin resistance, which is the key phase of metabolic syndrome follows deactivation of Nuclear peroxisome proliferator activated receptors (PPAR) mainly because of obesity. There are two principal pathways of the development of Metabolic Syndrome:-

a. The B-cells of pancreas are preserved resulting in insulin hypersecretion to compensate for insulin resistance. This mainly leads to the macrovascular complications of MS.

b. Massive damage to B cells of pancreas leading to reduced insulin secretion and hyperglycaemia. This pathway leads to both microvascular and macrovascular complications.

It is suggested that PPAR based appraisal of metabolic syndrome and type-2 diabetes mellitus may improve the understanding of these diseases and may set basis for a comprehensive approach to their treatment.

The factor that dominates in obesity is the permanent elevation of plasma free fatty acid (FFA) and predominant utilization of lipids by the muscles inducing a diminution of glucose uptake and insulin resistance. People who develop type-2 Diabetes pass through the phases of excessive adipogenesis (obesity), whereas PPAR modulation, insulin resistance, hyperinsulinemia, pancreatic B cell stress and damage leads to progressive decrease of insulin secretion and impaired post parandial and fasting glucose.

Further more, adipose tissue plays an important role in whole - body energy homeostasis both in terms of fat storage and release as well as through the effects of adipocyte cytokines. Leptin deficiency is associated with hyperphagia, lack of satiety and also increased body fat. Infusion of insulin and glucose in humans to maintain euglycaemia increases leptin levels after 3 hours and decreases level of adiponectin. Adiponection has insulin sensitizing action, anti-inflammatory effects on vascular endothelium and increases HDL-cholesterol. Its levels increase with weight loss and thiazolidinediones. Thus there are acquired as well as genetic causes of metabolic syndrome and the discovery of nuclear PPARS have further improved the understanding of the pathogenesis of this condition.

Clinical Outcome and Natural History

The relative risk of atherosclerotic cardio-vascular disease (ASCVD) ranges from 1.5 to 3.0 among patients with MS depending upon the stage of progression. When diabetes is not yet present, risk of progression to type-2 diabetes is about five fold than compared with those who
don't have MS. Once diabetes has developed, cardiovascular risks increase even more.

Most individuals who develop the syndrome first acquire abdominal obesity without risk factors. But with the passage of time, multiple risk factors begin to emerge. Initially these are elevated to a small extent, but later in many individuals they are categorically raised. In some, syndrome culminates in type-2 diabetes with all its consequent complications. If ASCVD develops complications like cardiac arrhythmias, and heart failure, then thrombotic episodes ensue. When ASCVD and diabetes coexist, the risk of subsequent cardiovascular morbidity and mortality is very high. The syndrome runs a progressive course with advancing age causing worsening of obesity and physical inactivity.

Patients with MS can manifest a variety of other conditions such as fatty liver, gallstones, sleep apnea and gout. Presence of several or all of these outcomes leads to the use of multiple medicines (polypharmacy) which carry the risk of drug interactions, interfere with compliance and imposes a prohibiting cost burden.

**Diagnosis and Risk Assessment**

In 1998, a diabetes working group of the World Health Organization (WHO) proposed a set of criteria for a clinical diagnosis of the metabolic syndrome. These include clinical evidence of insulin resistance such as impaired glucose tolerance, impaired fasting glucose or type-2 diabetes as necessary for the diagnosis. Shortly afterward European group for study of Insulin Resistance (EGIR) proposed the same criteria. The ATP III simplified the WHO criteria by requiring three of the five simple clinical measures: increased waist circumference, elevated triglycerides, reduced HDL, elevated glucose and elevated blood pressure.

The International Diabetes Federation (IDF) replaced WHO criteria with those closer to ATP III. Waist circumference threshold were made ethnic specific and abdominal obesity was required for diagnosis. Thus the ATP III update and the IDF report harmonize the clinical diagnosis of MS when at least three of the following criteria are present:

1. Central obesity as defined by ethnicity specific values of waist circumference ≥ 90 cm in men and ≥ 80 cm in women for South Asians and South East Asians.
2. Elevated triglycerides ≥150mg/dl (1.7m mol/L) or specific treatment for lipid abnormality.
3. Reduced HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women.
4. High blood pressure ≥130/85 mm Hg or treatment of previously diagnosed hypertension.
5. High fasting blood glucose (FPG) ≥ 100mg/dL and <120 mg/dL or previously diagnosed type 2 diabetes.

Importantly, the MS is not a reliable tool for global risk assessment for ASCVD in short term (i.e. 10 years) as it does not include all risks i.e. age, gender and smoking, total cholesterol etc. All patients with MS deserve global risk assessment whether by risk factor algorithms or by atherosclerosis imaging in order to identify persons for preventive medications.

**Management**

Once a person is found to have the syndrome, lifestyle therapy should be introduced, reinforced and monitored. Drug therapy is a secondary consideration that should be guided by global risk assessment.

The ATP III recommended lifestyle therapy that includes weight reduction, increased physical activity and an anti-atherogenic diet. Smoking cessation is mandatory. Over the past century there is an evidence of approximately 15% weight increase among the USA population. A 5% - 10% weight loss is the goal. Weight loss follows low fat diet, exercise for 60-90 minutes per day and regular meals. Carbohydrate restriction will be effective in improving the atherogenic phenotype. Life style intervention unfortunately is often neglected in routine practice.

**Drug Therapies**

The idea of reducing multiple risk factors with a single drug or a combination is attractive and needed. At present, the only drugs approved for treatment are those that target the individual risk factors. Lipid lowering agents, anti hypertensive and hypoglycaemic drugs, anti platelet and weight loss agents. For the treatment of risk factors of MS, the physician should follow current treatment guideline of the NCEP, the sixth joint national commission (JNC-IV) for blood pressure treatment, the American Diabetes Association, the American Heart Association and the National Institute of Health obesity Initiative.

Pharmacological therapies for the two underlying risk factors for the syndrome i.e. obesity and insulin resistance are under development. They nonetheless hold promise for adding benefit for delaying progression of the condition and to reduce the risk for ASCVD and / or diabetes. The drugs include weight reducing agents, peroxisome proliferator activated receptor (PPAR) alpha agonists (fibrates), PPAR- gamma agonist (Thiazidinediones [TZDS]), and dual PPAR agonists.

Two weight loss drugs - Sibutramine and orlistat are already FDA approved. They improve all of the metabolic
syndrome risk factors but produce only moderate weight loss. A new promising weight loss drug is a selective cannabinoid receptor-1 (CB1) antagonist called Rimonabant. Endocannabinoids activate G-protein coupled CD, in hypothalamus and limbic forebrain, thus accentuating hyperphagia. Rimonabant suppresses endogenous activation of the endocannabinoid system. The drug causes 5% to 10% weight loss up to two years and may have systemic effects to reduce MS risk factors.

Clinical trials show that fibrates independently reduce risk of ASCVD by treating atherogenic dyslipidemia and possibly because of anti-inflammatory properties. TZD lessen insulin resistance and moderately reduce metabolic risk factors. A recent clinical trial strongly suggests reduction of cardiovascular outcomes with one TZD, pioglitazone. Dual PPAR (combined alpha and gamma) agonists such as Tesaglitazar have favourable effects on several metabolic risk factors. Inspite of promise, all these drugs have outcome hurdles to mount before they can be approved for routine use in patients with MS.

In conclusion, the metabolic syndrome is a cluster of risk factors of metabolic origin that together are associated with higher risk for ASCVD and Type - 2 Diabetes involving approximately one fourth of adults. It is accompanied by Insulin resistance and its increasing prevalence is due to escalating obesity and physical inactivity. The syndrome is a progressive condition that worsens with advancing age and increasing obesity often culminate in type-2 Diabetes mellitus which carries particularly high risk for both cardiovascular events and other complications. However, MS itself is not a robust risk assessment tool for estimating absolute 10 years risk. Primary intervention is lifestyle therapy particularly weight reduction and increased exercise. Drug therapies may help control the various risk factors of MS and thus ASCVD and type-2 Diabetes.

References
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Case Report

Deep vein thrombosis - a rare post transplant complication
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Abstract

Deep vein thrombosis (DVT) is a rare post transplant multifactorial disease and often results from a combination of risk factors causing venous stasis. Venography and doppler ultrasound are reliable and accurate procedures for detecting venous thrombosis. Once DVT has been established, these patients should be treated with anticoagulants atleast for a limited duration particularly in high risk post transplant patients with previous episodes of thrombotic events.

We report here a case of a 7 years old boy with B-thalassaemia major, who developed deep vein thrombosis at 04 month post SCT. He was treated with low molecular weight heparin and oral warfarin sodium and INR was stabilized between 2.5 - 3.0. Two months later, he presented with bleeding diathesis and died of intracranial haemorrhage. Excessive unchecked anticoagulation was the cause of death. It is recommended that patients on anticoagulation therapy require strict monitoring with PT/INR to avoid bleeding complications related to unchecked over anticoagulation.

Introduction

Deep vein thrombosis (DVT) is a rare post transplant complication. It is a multifactorial disease and often results from a combination of risk factors like venous stasis due to prolonged immobilization, vascular endothelial damage by preparative regimens/use of indwelling catheters, prolonged glucocorticoids therapy for GVHD and hypercoagulability states including factor V Leiden, deficiency of natural anticoagulant proteins (C and S) and anti thrombin III deficiency.1,2 DVT either involves one or both legs and it is characterised by painful swelling with normal or raised local temperature and dilation of superficial veins.3 Because clinical diagnosis is unreliable, accurate diagnostic tests are required when DVT is suspected. Venography is the most accurate and reliable technique for assessing the presence of venous occlusion. Doppler ultrasound is also a reliable, non-invasive procedure for detecting venous thrombosis.4 If the patient has a proven venous thrombosis, it is necessary to exclude thrombophilic conditions. Once DVT has been established, these patients should be treated with anticoagulants atleast for a limited duration (3 months), particularly in high risk patients with previous episodes of thrombotic events.5,6

Case Report

A 7 years old boy with B-thalassaemia major, had received multiple irregular transfusions along with chelation therapy was eventually subjected to splenectomy for massive splenomegaly. Liver biopsy showed bridging fibrosis. On the basis of pre-transplant Pesaro risk group classification criteria, he was placed in Pesaro risk class III. He was conditioned with Hydroxy urea, 30 mg/kg daily (day - 45 till day -11), Azathioprine, 3 mg/kg daily (day - 45 till day -11), Fludarabine, 20 mg/m² daily (day - 17 till day - 13) followed by Busulphan, 4 mg/kg daily for 4 days and Cyclophosphamide 40mg/kg daily for next 4 days. He received allogeneic stem cell transplant (allo-SCT) from his HLA matched sibling brother in March 2004. After successful early engraftment, he was discharged from the hospital on day + 20 post - SCT. There after patient was on regular follow up in out patient department. His post transplant period remained uneventful for four months post-SCT, when he developed painful swelling of right calf and popliteal region. Ultra sound