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## Symposium 5A: Metabolic syndrome

### S5A-1. Metabolic syndrome: its significance and application in clinical practice

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The Metabolic Syndrome (MetS) or cardiometabolic syndrome is recognized as a constellation of risk factors that increase CVD risk as well as progression to type 2 diabetes mellitus (T2DM). It has long been known that these risk factors cluster in susceptible individuals. The definition of MetS and its clinical significance is fraught with problems as there is no unified consensus. The ATP III definition for MetS requires 3 or more of the following:

- Type 2 diabetes / Impaired fasting glucose (IFG)  $\leq 5.6$  mmol/L
- Hypertension  $> 130/85$  mmHg
- Fasting triglyceride  $\geq 1.7$  mmol/L
- HDL-cholesterol  $< 1.03$  (men) /  $< 1.29$  (women) mmol/L
- Waist circumference (Asian cut-point) -  $>90$ cm (men) /  $>80$ cm (women)

The WHO-IDF (2005) made one change to the above, making the waist circumference obligatory for the diagnosis of MetS. The recent controversy regarding its clinical implications has also caused barriers to its clinical application and subsequent management. Criticisms aimed at the MetS state that it does not predict increased atherosclerotic CVD risk beyond the sum of its risk factors and that use of other Risk engines ie Framingham or UKPDS are superior. Others feel that a simple practical tool to assess future CVD risks in people with this cluster of risk factors can help identify these high risk individuals. Therefore for the day-to-day practice of a Clinician, such a simple tool will be easy to apply in identifying the MetS in an individual. There is no specific therapy for the MetS, but upon identification of its presence, aggressive management of the individual risk parameters is required. The general therapeutic approach involves modifying diet and lifestyle change. Dietary modification that reduces weight in obese individuals or those with pre-diabetes, by an average of 4 kilograms in ~ 4 years has been shown to successfully decrease progression from impaired glucose regulation to overt Type 2 diabetes in the well known landmark trials such as the Diabetes Prevention Program and the Finnish Prevention Study. Pharmacological therapy is a critical step in the management of patients with metabolic syndrome when lifestyle modifications fail to achieve the therapeutic goals. If central obesity is considered as the driving force of the Metabolic Syndrome, the appropriate management would be to address management of overweight / obesity. Other than weight loss, there is no single best therapy and treatment should consist of treatment of the individual components of the metabolic syndrome. Specific targets include glycaemic control, blood pressure reduction and management of dyslipidaemia. The targets for control depend on whether the patient is diabetic – targets being lower and more aggressive for these individuals. With respect to prevention, public health initiatives are long overdue. They are absolutely essential if one is to stem the increase in prevalence and adverse impact of the Metabolic Syndrome!

**S5A-2. Modification of HDL – Implication in cardiovascular disease**

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According to WHO, 16.7 million people die every year because of Heart diseases. However the major risk factors used in predicting future events of heart attacks are associated with only a maximum of half of the patients. While all these risk factors positively correlate with the risk, the only factor that negatively correlates is HDL. Observational studies like the Framingham study and the Randomized controlled studies have all shown the benefits of increasing HDL levels in the blood. The cardio protective functions of HDL are two fold, first, it is involved in reverse cholesterol transport and thus inhibits the formation of new plaques and also stabilizes the existing plaques, preventing their rupture. Second, HDL is an antioxidant molecule and is also anti proliferative. It decreases the expression of cell adhesion molecules and maintains the integrity of vascular endothelium. These properties of HDL are attributed to HDL associated proteins. It is now increasingly recognized that HDL can also undergo modification transforming it from an anti-inflammatory molecule to a pro inflammatory molecule. In vitro studies have demonstrated that though HDL is an anti oxidant molecule itself can undergo oxidative modification rendering it inactive in its antioxidant properties. We have shown the oxidation and glycation inactivation of HDL associated protein Paraoxonase in vitro. Paraoxonase has also been reported to be significantly lower in inflammatory diseases like diabetes and cancer which are characterized by increased oxidative stress. Thus it seems reasonable to hypothesize that oxidative and other modifications could also inactivate the other cardio protective functions of HDL. We have shown that modification of HDL did not affect its quantitative determination by the conventional diagnostic procedures. This suggests that the current assay procedures do not distinguish between functional and non functional HDL molecules. Thus a clinical test based on the functionality of HDL rather than the total HDL-C may be a better marker of cardiovascular risk.

**S5A-3. Body fat distribution – its link with diabetes and metabolic syndrome**

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Several epidemiological studies suggest that obesity is strongly linked to diabetes and metabolic syndrome. Obesity is considered to be the link between insulin resistance and metabolic abnormalities. Population based studies from India have shown that obesity is strongly associated with type 2 diabetes and metabolic syndrome. The Chennai Urban Rural Epidemiology Study (CURES). However, it is now becoming increasingly clear that regional distribution of fat plays a major contributory role for metabolic abnormalities. Research during the last decade has suggested that the distribution of adiposity is important in understanding the association of obesity with metabolic abnormalities. Abdominal obesity as measured by the waist circumference was found to be more appropriate than generalized obesity defined using Body Mass Index. This is more so in certain ethnic groups like the Asian Indians who have decreased rates of generalized obesity, but higher prevalence of abdominal obesity, type 2 diabetes and coronary artery disease. Developments in the imaging techniques have enabled the investigators to look further into the role of different components of abdominal fat in relation to diabetes and related metabolic abnormalities. The intra-abdominal or visceral component of abdominal fat was shown to have a stronger correlation with glucose intolerance and insulin resistance. Several studies have shown that the visceral accumulation of fat is more atherogenic, diabetogenic and hypertensiogenic compared to subcutaneous accumulation. It was reported that visceral fat was the best variable predicting insulin sensitivity that explained 54% of the variance in insulin sensitivity. Among Japanese, it was found that visceral fat strongly associated with glucose intolerance even

after adjusting for total and subcutaneous fat. Studies from India also have supported the hypothesis that visceral fat is more deleterious than subcutaneous fat. The CURES suggested that visceral fat as measured by CT scan and central abdominal fat assessed by DEXA were significantly higher in type 2 diabetic subjects. It was also shown that the visceral, but not subcutaneous fat was associated with hypertension and metabolic syndrome in individuals with normal glucose tolerance. Although the exact pathogenic mechanisms behind the association of visceral fat with diabetes is still unclear, it is widely believed that the visceral adipose tissue is more “active” and may be the main source of adipokines, which are known to influence glucose and lipid metabolism. Several studies have shown that visceral fat was significantly associated with serum levels of adiponectin, a protective adipokine. A recent study from India has shown that visceral, but not subcutaneous fat was associated with serum visfatin. Further, the anatomical site of visceral fat with direct drainage into portal venous system is also important as direct release of free fatty acids into the liver may cause derangement of metabolic processes. Selective reduction of visceral fat has shown to improve insulin resistance. Recent studies from India have also shown that certain genetic polymorphisms could influence increased adiposity. The Thr394Thr polymorphism of the PGC1 alpha gene was found to be associated with excessive adiposity in South Indians. These evidences suggest that abdominal obesity, particularly visceral fat is strongly associated with type 2 diabetes and metabolic syndrome.