

Metabolic Syndrome: An Overview

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Metabolic Syndrome (MetS) has emerged as a leading public health problem worldwide. As researchers try to unravel the mystery of MetS, it appears that the terminology encompasses much more than what was initially thought and it seems that we are far from getting out of this maze in the near future. What started out as a disease complex of adiposity with hypertension, a predisposition to diabetes, dyslipidemia and atherosclerotic cardiovascular disease (ASCVD), also has a prominent hepatic overtone and is a pro-inflammatory state. In addition the gonadal effects in both genders add to the complexity of this disease complex. With childhood onset adiposity, problems of somatic and sexual development add yet another dimension to this syndrome. The typical dyslipidemia with low HDL-C, high TG and raised small dense LDL-C contributes to increased ASCVD and its ensuing complications¹. Increased risk of certain types of cancers has also been established. The clustering of these cases in families definitely points to a genetic aetiology, compounded by an adverse lifestyle and eating patterns.

Insulin resistance (IR) and hyperinsulinemia are considered to be the key factors underpinning this disorder. Dysregulation of the fuel-sensing enzyme AMP-activated protein kinase (AMPK) may play an important role in Insulin resistance and offer a significant target for treatment². Strategies aimed at more effectively activating AMPK may provide future therapeutic answers in improving insulin sensitivity. Exercise in any form is known to increase AMPK activity and so do all the anti-diabetic drugs that are weight neutral or induce weight loss.

It is now well known that NAFLD/NASH have the potential of progressing to end stage liver disease as well as hepatic cancer. Plentiful consumption and sedentary lifestyle contribute to hepatic steatosis along with somatic adiposity. The triggering role of high fructose consumption in processed food may be one of the key factors in hepatic steatosis³. With NAFLD/

NASH affecting a large proportion of the population of patients with MetS, it is not feasible to subject all of them to liver biopsies in order to evaluate disease severity as well as to assess progression. Many imaging techniques employing MRI with radio-labelled compounds, blood tests measuring fibrosis and even breath tests, have been developed and are in advanced stages of clinical evaluation to assess inflammation and fibrosis^{4,5}. These will hopefully replace the need for invasive, impractical and painful liver biopsies. The standard liver function tests do not provide much information with regards to hepatic steato-hepatitis, as seen in the study published in this issue.

The association of obesity with Polycystic Ovary Syndrome (PCOS) has been well described in over 70% of patients thus affected, even though it is still not one of the defining features of PCOS. However, the classical obese PCOS patient has all the features of MetS⁶. The impact of hormonal truncal adipose aberration caused by the hormones produced and cross talk between them in the expanded compartment, of the MetS patient is as yet largely uncharted. Non-obese patients labeled as PCOs by current diagnostic criteria may well have a completely different pathogenesis than obese PCOS patients⁷.

The association of obesity and insulin resistance with male hypogonadism is well established. Increasing BMI is associated with declining testosterone levels with all its attendant issues⁸. The sex hormone disturbances in MetS in both sexes has a negative impact on fertility⁹. Delay in puberty in the obese pre-pubertal male child is also an increasingly recognized entity, especially when the insulin resistance is high. This is compounded by the development of gynecomastia and nipple pigmentation in the same young boys due to excess estrogen being generated from the fat compartment¹⁰. The counterpart in female pre-pubertal obese child is precocious puberty due to the hyperestrogenism and insulin resistance, followed by the evolution of classical features of PCOS¹¹.

The risk of certain cancers has been shown to be increased in MetS, including colorectal, endometrial, pancreatic, breast, liver, bladder in men and gall bladder^{12,13}. The role of high insulin level in promoting cancer in these individuals is highly plausible.

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The possible cause and effect role of Vitamin D in MetS is far from clear. Vitamin D levels have been reported to be inversely related to rising BMI. Lower vitamin D levels are associated with increased risk of MetS and insulin resistance¹⁴.

Obstructive Sleep Apnoea (OSA) is prevalent in 74-85% of MetS patients. OSA and its management with CPAP mitigate many of the metabolic consequences of MetS. A cause and effect relationship is yet to be established¹⁵.

Prevention and treatment of MetS is currently reliant on promoting healthy lifestyles and eating patterns, as well as promoting insulin sensitivity with a limited range of drugs¹⁶. We need better, affordable and effective prevention and treatment strategies for this complex problem with myriad implications.

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