

Metabolic Syndrome and HIV Infection **Abhijit Swami**

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Introduction

In the present day world, morbidity and mortality from infectious diseases has taken a backseat which can be attributed to the better understanding of the disease process and the resultant more effective treatment. Instead, non-communicable diseases like Metabolic Syndrome (MetS) has become a public health concern round the globe. It has posed a great challenge to global health planners due to its implications in multiple lifestyle disease. And in a world of affluence with sedentary lifestyle, increasing obesity and a taste for not so healthy food items the challenge posed by MeTS is only going to be greater. Metabolic syndrome is a complex of interrelated risk factors for Cardiovascular Disease (CVD) and diabetes. These factors include dysglycemia, raised blood pressure, elevated triglyceride levels, low high-density lipoprotein cholesterol levels, and obesity (particularly central adiposity).

The associations and clustering of these factors have been known for decades. Several scientists, starting as early as almost 90 years ago, have described the common coexistence of the various components of the syndrome, including hypertension, and some of them gave several names to this clustering. The name of Syndrome X was given by the Reaven in the 1988 Banting lecture where he described a cluster of risk factors for diabetes and cardiovascular disease [1].

Though the health implications of MeTS have been known, there have been no uniform diagnostic criteria for diagnosis. Multiple diagnostic criteria have been proposed over the years by different organizations with significant differences between them.

The diagnostic criteria as suggested by different organizations are different probably reflecting the increasing knowledge of the subject accumulated over time. Questions have been raised about adding the word 'Syndrome' to MeTS as it is considered to be a mixture of unrelated phenotypes. IDF and AHA/NHLBI have attempted to resolve the differences between the different definitions of MeTS.

Epidemiology

Since its initial description and formulation of various diagnostic criteria, MeTS have been reported from all countries around the globe though with varying prevalence rates. In general, it is a disease of the affluent class with sedentary lifestyle and a food habit dominated by junk food coupled with smoking as addiction and a family history of diabetes mellitus. NHANES data 2003-

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2012 have shown a prevalence rate of 18.3% among those aged 20 to 39 years which increased to 46.7% among those aged 60 years or older with a higher incidence noted among women [2-9]. Even in the developing countries of South Asia which incidentally has high incidence of Type 2 DM, MeTS has shown an increasing prevalence among all age groups with an additional component of being a more urban rather than rural phenomenon [10].

Pathogenesis of Metabolic Syndrome

Metabolic syndrome is now thought to be the result of a complex interplay between environmental and genetic factors. The initial event is believed to be development of abdominal obesity, which is now known to cause insulin resistance. Adipose tissue in the abdomen is known to be metabolically active and produce a variety of cytokines – adipocytokines which includes glycerol, Free Fatty Acids (FFA), proinflammatory mediators (Tumor Necrosis Factor Alpha (TNF α) and Interleukin-6 (IL-6)), Plasminogen Activator Inhibitor-1 (PAI-1), and C-Reactive Protein (CRP) [11]. Increased production of free fatty acids, inflammatory cytokines, and adipokines and mitochondrial dysfunction contribute to impaired insulin signaling, decreased skeletal muscle glucose uptake, increased hepatic gluconeogenesis, and β cell dysfunction, leading to hyperglycemia. In addition, insulin resistance leads to the development of hypertension by impairing vasodilation induced by nitric oxide.

Though obesity has been linked to environmental and genetic factors, several recent studies have opened a new dimension into our understanding of obesity and metabolic syndrome. Chronic low grade inflammation of multiple etiologies– both infectious

and non-infectious has been linked to development of obesity in susceptible individuals which again is further compounded by using of disease specific medications.

Of particular interest have been the recent observations that chronic infectious diseases like HIV and chronic hepatitis B and C are associated with MeTS. High blood levels of pro-inflammatory cytokines like CRP have been found in these conditions indicating enhanced inflammation. Chronic Hepatitis B and C patients have high level of several coronary disease markers though these diseases have not been conclusively linked to coronary artery disease [12,13]. However, the infectious disease which has been conclusively linked with MeTS for more than two decades has been HIV infection even if the patient has responded to antiretroviral therapy. The high prevalence of MeTS in HIV infection has added entirely new dimensions in the pathogenesis of MeTS.

The initial description of MeTS was made in HIV patients few years after initiation of protease inhibitor chiefly ritonavir plus saquinavir combination based antiretroviral therapy. The unquestionable success of ART has lead to a wider availability of the drugs around the globe thereby bringing to notice an unanticipated aspect of drug therapy of HIV. Though the actual numbers of MetS in HIV populations are still debatable, reported prevalence for MetS in the HIV population can be regarded as high, ranging from 11.2% up to 45.4% [14].

Since its initial description about three decades back, our understanding of HIV has increased exponentially. With effective therapy, the infection has been converted from a disease with profound immune suppression and often terminal, fatal opportunistic infections to a disease associated with disordered lipid metabolism, dysglycemia and high blood pressure with increased proinflammatory cytokines. And as HIV patients live longer, this aspect of HIV infection is now an important global health concern.

The pathogenesis of MeTS is not completely understood. The metabolic changes in HIV infections begin early in the course of infection. Due to selective targeting of the immune system by the virus and the consequent progressive deterioration of the immune system, the individual becomes susceptible to multiple opportunistic infections and some neoplasm. Targeting of the immune system by the virus causes profound disruption of the cytokine network from the earliest stages of HIV infection. Cytokines like hS-CRP, tumor necrosis factor, IL-6, IL-1 β , urokinase plasminogen activator receptor (suPAR) and IL-6 are increased in the initial stages of HIV infection and these not only contributes to viral replication but also initiates the earliest changes leading to development of metabolic syndrome in future [15]. Some genes responsible for suppressing inflammation like tyrosine kinase RON are downregulated in HIV infection leading to continuing inflammatory response and increased HIV transcription [16]. Even after institution of HAART (Highly Active Antiretroviral Therapy) with HIV levels below detectable range, the blood levels of these cytokines remain elevated. In the SMART trial, participants

bearing ≤ 400 copies/mL of HIV RNA also had elevated hsCRP and IL-6 levels in 38% and 60%, respectively, in comparison to normal individuals form cohorts for cardiovascular outcomes [17].

The earliest changes in the treatment naïve HIV patients are probably dyslipidemia with plummeting of HDL levels. As the disease progresses, LDL-C decreases followed by an increase in triglycerides, apolipoprotein levels and VLDL in the advance course of the disease. Hypertriglyceridemia may be due to decreased clearance of triglycerides and increased production of VLDL [18].

Once the patients are initiated on HAART, the impact on the components of MeTS is more pronounced. Some of the initial changes found in the early stages of HIV infection get exacerbated with addition of more components. These changes depend on the medications on the HAART regime. Hypertriglyceridemia in general worsens with Ritonavir based PI regime with an increase up to 83% in one study and could be due to effect of Ritonavir on inhibitory effect on degradation of apolipoprotein B [19].

Insulin resistance can occur in HIV patients on therapy, but probably the mechanism is different from the general population. Multiple antiretroviral drugs – zidovudine, lamivudine, stavudine, efavirenz and most of the protease inhibitors have been found to have influence on glucose metabolism though by different mechanisms some of which are still not well understood. Studies have shown that PIs selectively inhibit glucose transport in adipocytes without affecting early insulin-signaling events or translocation of intracellular GLUT4 transporters to the cell surface [20].

The resultant effect of HIV infection with or without therapy lead to a state of immune dysfunction with profound influence on lipid metabolism, body habitus and vascular architecture leading to a prothrombotic state thereby enhancing the risk of cardiovascular diseases manifold (Table 1 and Figure 1) [21].

Fat Distribution and Metabolic Syndrome

The most visible effect of metabolic syndrome in HIV patients is the development of lipodystrophy which includes facial lipoatrophy (fat loss), increased upper trunk fat (buffalo hump), lipoatrophy of the arms and legs, and abdominal obesity. HIV patients also experience increase prevalence of ectopic fat distribution in liver and muscles [22]. This is not seen in treatment naïve HIV patients, but more common once HAART is initiated with PI based regimes and also with stavudine, which mercifully is now rarely used. Central obesity as a consequence of lipodystrophy is a component of MeTS. Also these patients have abdominal subcutaneous lipoatrophy more pronounced in the abdomen with consequent loss of hip circumference and spuriously elevated waist hip ratio. This makes inclusion of waist hip ratio an unreliable component in the diagnosis of HIV induced metabolic syndrome (Table 2).

Hypertension

The link between HIV infection and development of hypertension is at best tenuous. Epidemiological studies have not found an increased incidence of hypertension in treatment naïve HIV patients [23]. However, use of effective antiretroviral therapy

Table 1: Diagnostic criteria for the clinical diagnosis of the MetS [2-8].

Clinical measures	WHO (1998)	EGIR (1999)	ATPIII (2001)	AACE (2003)	IDF (2005)
Insulin resistance	IGT, IFG, T2DM, or lowered insulin Sensitivity plus any 2 of the following	Plasma insulin >75th percentile plus any 2 of the following	None, but any 3 of the following 5 features	IGT or IFG plus any of the following based on the clinical judgment	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI > 30 kg/m ²	WC ≥ 94 cm in men or ≥ 80 cm in women	WC ≥102 cm in men or ≥ 88 cm in women	BMI ≥ 25 kg/m ²	Increased WC (population specific) plus any 2 of the following
Lipids	TGs ≥ 150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TGs ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TGs ≥ 150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥ 150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥ 150 mg/dL or on TGs Rx. HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
Blood pressure	≥ 140/90 mm Hg	≥ 140/90 mm Hg or on hypertension Rx	≥ 130/85 mm Hg	≥ 130/85 mm Hg	≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)	IGT or IFG (but not diabetes)	≥ 100 mg/dL (includes diabetes) ^b

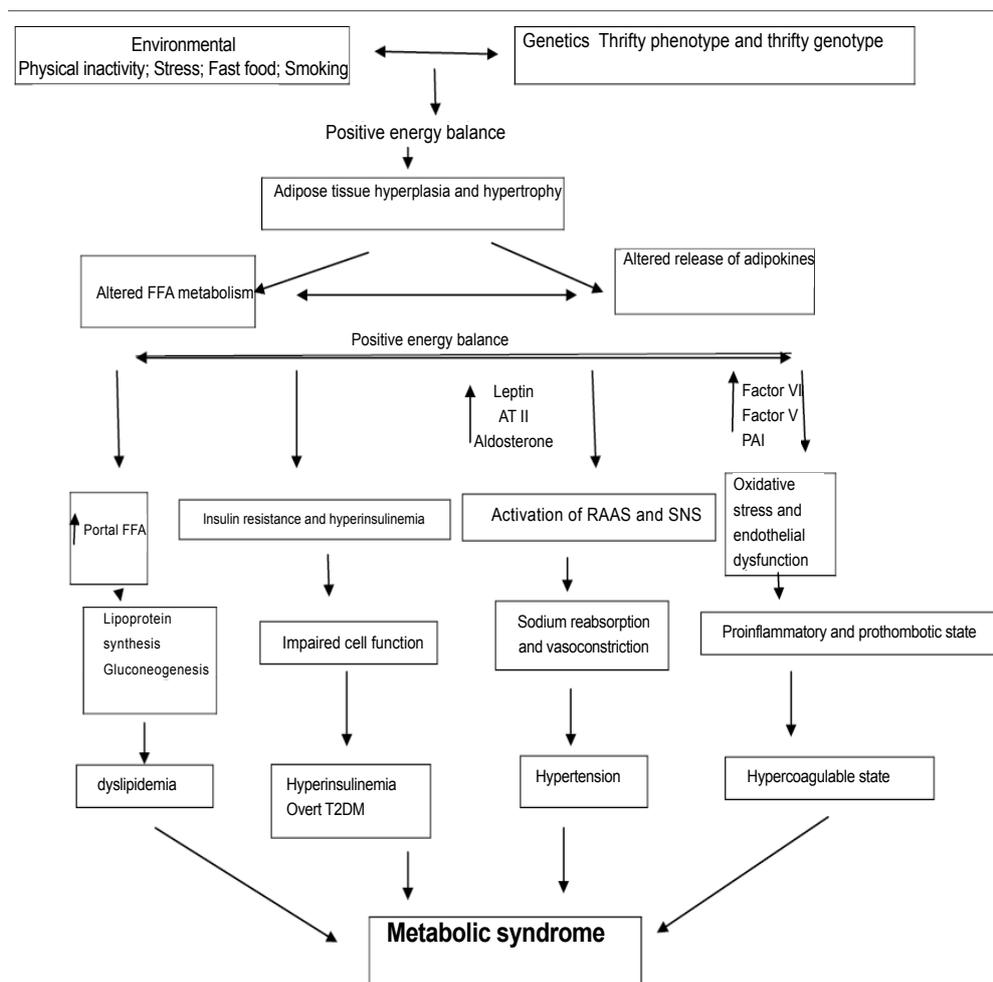


Figure 1 Schematic presentation of MetS (FFA: Free Fatty Acid, ATII: Angiotensin II, PAI-1: Plasminogen Activator Inhibitor-1, RAAS: Renin Angiotensin Aldosterone System, SNS: Sympathetic Nervous System) [2].

Table 2: Harmonized definition [3].

Measure	Categorical Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥ 100 mg/dL
Presence of any 3 of 5 risk factors constitutes a diagnosis of metabolic syndrome	

has been linked to development of hypertension though some reports have implicated protease inhibitors as the cause [24]. Increase in BMI after effective antiretroviral therapy has been postulated as the cause of hypertension.

Therapy for Metabolic syndrome in HIV

Advances in therapeutics have converted HIV from an invariably fatal disease to a chronic disease where a patient has less chance of succumbing to opportunistic infections, but at the cost of development of metabolic syndrome. The disease itself along with the drugs used to treat the disease are the main causes with smoking and limited physical activity contributing to the process.

Cessation of smoking is the single most important and the easiest therapy MeTS in HIV patients without any side effects. HIV infected patients are more likely to be smokers and cessation of smoking was associated a reduction of cardiovascular diseases in the DAD study [25]. Management of dyslipidemia should include non-drug measures like dietary modifications to attain ideal body weight and increased physical activity depending upon the

general condition of the patient. Routine aerobic activity and muscle conditioning exercise improved trunk adiposity and lipid parameters in HIV infected patients [26]. Dietary modifications at diagnosis even before initiation of Anti-retroviral therapy prevented development of MeTS [27]. In the management of dyslipidemia, lipid lowering drugs are indicated but, drug-drug interaction should be considered when combined with PI based HAART. Older statins like lovastatin and simvastatin are better avoided while newer ones like atorvastatin and rosuvastatin are to be used with caution. Combined use of statins with antiretroviral drugs may lead to clinically relevant drug-drug interactions including reduced lipid lowering effects due to enhanced metabolism of statins and increased risk of potentially fatal rhabdomyolysis [28]. Some older anti-retroviral drugs like stavudine could be substituted with more lipid friendly drugs of the same class though mere switching to another regime may not alone produce the desired response. Nutritional supplementation of omega fatty acids may also help.

Switching of antiretroviral therapy is generally not indicated in HIV patients only for MeTS as the sole indication. Patients initiated on protease inhibitor based regime with complications of MeTS can be switched over to NNRTI based regimes if no contraindication exists. Alternatively, older PIs like Nelfinavir can be substituted with newer PIs like Atazanavir though the existing cosmetic changes are unlikely to reversed.

Conclusion

As HIV patients live longer, health care workers are more likely to treat patients with components of metabolic syndrome. However, the presentation of MeTS in HIV patients may not be the same as general population. With better understanding about the pathophysiology of chronic inflammation and endothelial dysfunction in HIV infection, it may become possible to initiate measures that can target the inflammatory pathways active in HIV infection. Future ART drugs may be developed with lesser impact on insulin resistance and lipid metabolism. As of now, the knowledge regarding this aspect of HIV infection is still in the early stages.

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