Tobacco and metabolic syndrome

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ABSTRACT
Tobacco is a leading contributor to morbidity and mortality globally. Metabolic syndrome is a constellation of abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance (with and without glucose intolerance), pro-inflammatory state, and pro-thrombotic state. Tobacco use is associated with various core components of metabolic syndrome. It has been found to play a causal role in various pathways leading on to development this condition, the current article discusses various facets of this association.

Key words: Metabolic syndrome, second-hand smoke, tobacco

INTRODUCTION
Adverse impact of tobacco products on health has been well established for more than 50 years.[1] Consumption of tobacco is a risk factor for six of the world’s eight leading causes of death.[2] Projected to kill around 1 billion people in this century, it remains the commonest preventable and modifiable contributor to morbidity and mortality globally. Apart from the direct tobacco smoke, exposure to second-hand tobacco smoke (SHS) causes illness, disability, and death from a wide range of diseases.[3] In fact, it contributes to about 1% of the total global disease burden.[4]

Contrary to popular belief the problem of tobacco use hits developing countries the hardest. By 2030, tobacco is projected to take a toll of 8 million lives per year, with 80% of these deaths occurring in low and middle income countries like India.[5]

In India, the National Family Health Survey (NFHS-3) conducted in the years 2005–2006 puts the prevalence rate of current tobacco use at 57% and 10.8% among males and females aged 15–49 years.[6] A more recent Global Adult Tobacco Survey (GATS) reported that more than one-third (35%) of adults in India use tobacco in some form or the other. Among them, 21% adults use only smokeless tobacco, 9% only smoke and 5% smoke as well as use smokeless tobacco. The prevalence of overall tobacco use among males and females was found to be 48% and 20%, respectively.[7]

Metabolic syndrome remains an evolving concept with different work groups presenting varied criteria for this condition. The state of controversy is reflected in the fact that the American Diabetes Association and the European Association for the Study of Diabetes made a joint statement in 2005 that no existing definition of this condition meets the criteria of a syndrome.[8] However, abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance (with and without glucose intolerance), pro-inflammatory state, and prothrombotic state continue to remain core features of different definitions of metabolic syndrome.[9] Table 1 presents the 2009 consensus criteria proposed by International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation International Atherosclerosis Society, and International Association for the Study of Obesity.[10]

Metabolic syndrome predicts the development of type 2 diabetes mellitus and cardiovascular disease.[11] It has also

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been identified as a pre-disease state of fatty liver disease,\textsuperscript{[12]} chronic kidney disease (CKD),\textsuperscript{[13]} and chronic lung disease [Box 1].\textsuperscript{[14]}

Studies exploring the prevalence of metabolic syndrome have come up with varied findings, primarily due to differences in cut-off points for various components of the syndrome. It is estimated that around 20–25% of the world’s adult population has metabolic syndrome.\textsuperscript{[15]} General population based studies from India have reported variable prevalence rates of 11.2%\textsuperscript{[16]} 13\%,\textsuperscript{[17]} 24.6\%,\textsuperscript{[18]} and 41\%\textsuperscript{[19]} for metabolic syndrome. This wide variation in prevalence is partially explained by the different diagnostic criteria used across these studies. Additionally, the differences in population characteristics, specially the place of residence, have also contributed to this variation. The prevalence rate of metabolic syndrome has been consistently found to be higher in urban setting.

**Tobacco and Metabolic Syndrome**

Association between tobacco and metabolic syndrome has been well established. Exposure to tobacco, direct as well as indirect, has been found to play a causal role in emergence of various core components of this condition.

**Epidemiological Findings**

Tobacco use has been associated with an increased risk of developing metabolic syndrome.\textsuperscript{[20,21]} It acts at multiple levels in the etiopathogenesis of metabolic syndrome. There is a positive dose–response relationship between the daily number of cigarettes smoked and the risk of metabolic syndrome.\textsuperscript{[22]} Both the former and current smoking are associated with an increased incidence of metabolic syndrome.\textsuperscript{[23]} In fact the risk has been shown to persist for up to 20 years after quitting tobacco use.\textsuperscript{[24]} A national nutrition examination survey in USA reported an increase in risk of development of metabolic syndrome among women (OR, 1.8; 95% CI: 1.2–2.6) and men (OR, 1.5; 95% CI: 1.1–2.2) who were current smokers compared with those who never smoked.\textsuperscript{[25]} Exposure to tobacco smoke is associated with a 4-fold increased risk of development of metabolic syndrome among adolescents who are either overweight or at risk for overweight.\textsuperscript{[26]}

The prevalence rate of smoking among patients diagnosed with metabolic syndrome tends to vary across studies. One of the major limitations of most of these studies is the reliance on self-report on tobacco use as it might underestimate the prevalence rates. Takeuchi et al., reported the smoking rate of 40% among individuals diagnosed with metabolic syndrome. The rate of smoking was found to be 71% among individuals with metabolic syndrome in a Columbian study.\textsuperscript{[27]} A recent study from urban India found the rate of smoking to be 26% and 3% among males and females diagnosed with metabolic syndrome.\textsuperscript{[28]}

**Type of Tobacco Exposure and Metabolic Syndrome**

Exposure to tobacco smoke in all forms has been associated with metabolic syndrome. The strongest evidence base linking tobacco and metabolic syndrome is for smoking. Smoking has been found to play a causal role in emergence of core components of metabolic syndrome. Although the evidence base is much wider and stronger for the smoking, even the smokeless forms have been associated with increased prevalence of metabolic syndrome. Additionally exposure to SHS (also called environmental tobacco smoke, ETS) has been found to contribute to increased prevalence of this syndrome.\textsuperscript{[29]}

**Association of Tobacco Use and Core Components of Metabolic Syndrome**

The various pathways of etiopathogenesis of metabolic syndrome include increased adiposity, insulin resistance,
leptin resistance, low-grade systemic inflammation, endothelial dysfunction, and autonomic dysfunction. Tobacco use is associated with all these cascades and hence could contribute to development of metabolic syndrome through multiple mechanisms.

Smoking has been associated with an increased waist circumference (and increased waist–hip ratio, WHR), increased triglycerides, and reduced HDL cholesterol. WHR is positively associated with the number of pack-years of smoking and there is a dose–response relation between WHR and the number of cigarettes smoked. The association among smoking amount and high triglyceride level and low HDL level has also been reported to be dose-dependent. It has been associated with endothelial dysfunction and a hypercoagulable state. Interestingly, smoking is associated with a reduced prevalence of hypertension as compared to non-smokers. However, the methodological issues have been carted as reasons behind this observation. Although smoking increase blood pressure, recordings taken after a few hours of gap in smoking reflect lower blood pressure as compared to non-smokers.

The use of smokeless tobacco has received relatively lesser attention in the scientific literature as compared to smoking. However, the use of smokeless forms of tobacco is not uncommon. In fact while there is a decline in smoking rates in many developed countries, prevalence of smokeless tobacco use continues to rise. In India prevalence of use of smokeless tobacco among adult males and females is 33% and 18%, respectively.

Smokeless tobacco use has been associated with various metabolic and hemodynamic derangements associated with metabolic syndrome. These include hypertension, dyslipidemia, and impaired glycemic control. Role of smokeless tobacco in platelet dysfunction and derangement of factors of coagulation cascade has not been well established.

**Tobacco and Insulin Resistance**

Insulin resistance has been postulated to play a significant role in development of metabolic syndrome. Insulin resistance directly contributes to other metabolic risk factors as well. Increased insulin resistance might underlie the metabolic and hemodynamic abnormalities contributing to metabolic syndrome. Tobacco use has been associated with reduced insulin sensitivity and development of insulin resistance. Even a short-term tobacco use also leads to development of insulin resistance. Smoking increases the circulating levels of hormones such as cortisol, catecholamines, and growth hormone which have insulin antagonistic actions. High circulating levels of free fatty acids also interfere with insulin mediated glucose uptake. Autonomic dysfunction as reflected in the increased heart rate has also been associated with insulin resistance. Additionally, the heart rate has been found to be linearly associated with an increased risk of metabolic syndrome.

A higher heart rate has also been found to be an independent risk factor for hypertension. Tobacco use is associated with increased heart rate.

Smokeless tobacco use has been associated with hyperinsulinemia. However, the mechanism of insulin resistance induced by smokeless tobacco use might be different from that of smoking as the level of growth hormone (an insulin counter-regulatory hormone) has not been found to be raised among users of smokeless tobacco forms.

**Tobacco and Dyslipidemia**

Smoking leads to increase in triglyceride levels and reduction in HDL cholesterol by increasing sympathetic activity. Smoking causes higher fasting plasma cortisol concentrations, resulting in an increase in visceral adipose tissue.

Studies assessing the impact of smokeless tobacco use on lipid profile have come up with contradictory findings. While higher blood cholesterol, higher triglyceride and lower high-density lipoprotein levels have been reported in some studies, others have failed to find such associations.

**Tobacco and Adiposity**

As mentioned above smoking is related to high WHR in a dose-dependent manner. Smokers tend to have a higher waist and lower hip circumference compared to non-smokers. Waist circumference is closely related to the visceral adipose tissue distribution. The visceral adipose tissue distribution, in turn, is influenced by the serum cortisol and sex hormone concentrations (low estrogen and testosterone). Low levels of total and free testosterone have been associated with development of
visceral obesity and metabolic syndrome. Testosterone facilitates lipolysis and inhibits fatty acid formation. The effect of testosterone on metabolic syndrome is independent to that of risk of obesity. Smokeless tobacco use has also been shown to lead to obesity development.

**Tobacco and Hypertension**

Smoking as a hypertension risk factor is not well established. Smoking leads to an acute increase in blood pressure. Nicotine acts as an adrenergic agonist, mediating local and systemic catecholamine release. Additionally, it causes release of vasopressin. Smoking also causes an increase in the heart rate. A higher heart rate has also been found to be an independent risk factor for hypertension.

However, several epidemiological studies have found that blood pressure levels among cigarette smokers are the same as or lower than those of non-smokers. This observation has been attributed to the methodology employed in these studies. The studies assessing 24-h ambulatory blood pressure monitoring have found that smokers tend to maintain a higher mean daytime ambulatory systolic blood pressure than nonsmokers. The use of smokeless tobacco has been associated with an increase in blood pressure consequent to its effect on sympathetic system. These findings have been reported in studies from India as well. High sodium content, nicotine and licorice present in smokeless tobacco are responsible for this effect. Users’ age, level of physical activity, and total duration of effect seem to mediate the long-term effect on blood pressure. Also, it is associated with an increase in the heart rate.

Similarly acute response of blood pressure to environmental tobacco smoke exposure is uncertain with studies reporting either an increase or no effects following the passive smoking.

**Tobacco and Proinflammatory State and Prothrombotic State**

Smoking has been associated with increased levels of inflammatory markers such as C reactive protein and fibrinogen. It triggers an immunologic response to vascular injury, which is associated with increased levels of inflammatory markers. These markers have a dose-dependent and temporal relationship to smoking and smoking cessation.

Smoking alters the coagulation–fibrinolysis system in favor of thrombosis. It influences coagulation–fibrinolysis cascade at many levels. Its primary action is on endothelium, platelets, and fibrinogen.

**Persistence of Effect of Tobacco Use on Metabolic Syndrome**

Tobacco use cessation lowers the risk of developing metabolic syndrome. However, the increased risk of metabolic syndrome among smokers tends to persist for years after quitting. This risk is reduced as compared to the risk during smoking years, but is still higher than those who have never smoked. The possible underlying mechanisms for the long-lasting effects of smoking on insulin resistance include vascular changes leading to decreased glucose uptake by skeletal muscle, proinflammatory effect (as evidenced by increased circulating white blood cell count, cytokines) and decreased plasma levels of adiponectin.

**Management of Tobacco Use**

Effective management of tobacco use requires an individualized comprehensive intervention plan. All users should be advised to quit. Those who have not yet started should be advised not to initiate. All patients seeking medical help should be asked about their tobacco use—both smoking and smokeless forms. Additionally, they should be assessed about the exposure to SHS. Severity of tobacco dependence can be assessed using the Fagerstrom Test for Nicotine Dependence (FTND) scale. Separate versions are available for smoking and smokeless forms.

Various pharmacological and nonpharmacological interventions are available for treatment of tobacco dependence. The medications approved for treatment of tobacco dependence include the Nicotine Replacement Therapy (NRT), bupropion-sustained release (bupropion-SR), varenicline, clonidine, and nortryptiline.

NRT is one of the most commonly used first-line therapy for tobacco dependence. It prevents the withdrawals associated with abstinence from tobacco products and addressed craving. It avoids the harmful consequence of the non-nicotine ingredients of tobacco products. It is freely available as a gum. Other delivery forms include patch, inhaler, lozenges, and nasal spray. The dose of nicotine is determined by the amount of tobacco product used by the individual.

Bupropion-SR acts by blockade of reuptake of dopamine and norepinephrine in the central nervous system. Its use is preferred if there is co-morbid depression. Additionally, it has been found to be effective for quitting associated weight gain. Varenicline is a partial agonist at the nicotinic cholinergic receptors. Recently, there are some reports about cardiovascular adverse effects associated with its use.
Clonidine and nortriptyline constitute the second-line therapies that are not frequently used. Along with the medications each individual should be offered nonpharmacological interventions. It has been shown that a combination of pharmacological and nonpharmacological interventions is associated with best results for tobacco dependence treatment.\textsuperscript{[69]} Some of the nonpharmacological interventions commonly used include motivation enhancement therapy, brief intervention, and relapse prevention.

**Impact of Smoking Cessation on Metabolic Syndrome**

Tobacco use cessation lowers the risk of developing metabolic syndrome. It has been associated with a reduction in the triglyceride level and improved HDL level.\textsuperscript{[34]} It improves insulin sensitivity as well.\textsuperscript{[70]}

However, increase in body weight subsequent to quitting tobacco use could contribute to the increase risk of metabolic syndrome. The possible mechanisms of weight gain after quitting tobacco use include increased energy intake, decreased resting metabolic rate, decreased physical activity, and increased lipoprotein-lipase activity.\textsuperscript{[71]} Additionally, nicotine, through its antiestrogenic effects, induces lipolysis by stimulating the sympathetic nervous system.\textsuperscript{[72]} An imbalance between lipid intake and lipid oxidation consequent to smoking cessation can also contribute to increased body fat. NRT has been reported to be associated with hyperinsulinemia and insulin resistance. This association has been found to be independent of the postcessation weight gain among these individuals.\textsuperscript{[73]}

However, the potential benefits of tobacco use cessation are multiple. Hence, it is important to advise all users to quit. An appropriate dietary and exercise schedule should be formulated for those interested in quitting tobacco use to address quitting associated weight gain.

Exposure to tobacco—smoking, smokeless forms and SHS—is a contributor to the various core components of metabolic syndrome. Tobacco acts at multiple levels in the etiopathogenesis of metabolic syndrome. Appropriate management of tobacco use and prevention of exposure to SHS can help reduce the risk of metabolic syndrome.

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