CHAPTER 5

Moving Beyond Metabolic Syndrome: Assessing Diabetes and Cardiometabolic Risk

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Abstract: Association of metabolic abnormalities including glucose intolerance, hypertension, central obesity and dyslipidemia comprise what is called "Metabolic Syndrome (MS)". It is known that MS is a risk factor for both diabetes and cardiovascular disease (CVD). Non-alcoholic fatty liver disease (NAFLD) has also emerged as an important metabolic disease which is associated with both diabetes and cardiovascular disease. South Asian countries and particularly India have very high prevalence rates of MS and NAFLD. Moreover, the prevalence of type 2 diabetes and premature coronary artery disease is very high. However, the link between MS, NAFLD and CVD are not very well defined. This chapter reviews in detail the association of MS with CVD and also NAFLD and CVD. It also discusses the controversies with MS and highlights current strategies involved in management of MS and NAFLD.

Keywords: Activity, behavior, cardiovascular disease, cardiovascular risk, global health, hepatology, intervention, lifestyle, liver disease, metabolic syndrome, obesity, overweight, south Asians, type 2 diabetes, wellness.

INTRODUCTION

Metabolic abnormalities, which include glucose intolerance, hypertension, central obesity and dyslipidemia, are often referred to as "Metabolic Syndrome (MS)". Health risks associated with MS include diabetes and cardiovascular disease (CVD). Non-alcoholic fatty liver disease (NAFLD) is an associated metabolic abnormality that may play a role in the pathogenesis of diabetes and cardiovascular disease, but little is known about the relationship. South Asian countries and particularly India have very high prevalence rates of MS and

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NAFLD. This chapter reviews how MS is related to obesity and the risk for CVD and NAFLD. It also discusses the controversies surrounding MS and highlights current strategies involved in management of MS and NAFLD.

HISTORY OF METABOLIC SYNDROME (MS)

The concept of MS, or insulin resistance syndrome, or 'Syndrome X' as it was once called, was introduced in 1988 by Gerald Reaven in his Banting lecture titled "The role of insulin resistance in human disease". The underlying pathophysiology of metabolic syndrome was elegantly described by Reaven in terms of a string of metabolic abnormalities including hyperinsulinaemia, hypertension, hyperglycemia and dyslipidaemia with the suggestion that insulin resistance was the core defect [1]. It took several years for Reaven to bring in the theme of central adiposity as a critical factor underlying the pathology of the syndrome which was one of the highlights of his Claude Bernard Lecture several years later. Yet, the 'Syndrome X' described by Reaven was imprecise and had several shortcomings when it came to identifying individuals with the syndrome in terms of the number, combination and cut points of the abnormalities constituting the syndrome [2]. Earlier, Kylin [3] and Jean Vague [4] proposed the association between diabetes, atherosclerosis, central adiposity and gout during the 1920s and 1940s respectively. In 1985, Michaela Modan [5] proposed hyperinsulinemia as the major connecting link between glucose intolerance, obesity and hypertension. 'Syndrome X' has now come to be referred to as the Metabolic syndrome (MS). The original definition of MS included hyperinsulinemia, impaired glucose tolerance, hypertriglyceridemia, reduced HDL cholesterol and hypertension. More expanded definitions have been proposed over the past two decades with the inclusion of alternative traits like prothrombotic state, microalbuminuria and central obesity as components of metabolic syndrome. The existence of various definitions has led to considerable ambiguity and the question of whether MS should be considered as a specific entity at all has arisen. Yet, in its defense, MS has, over time, made physicians and patients aware of the interactions between the individual components of the syndrome and the benefits of lifestyle modifications in its management.

DEFINITIONS OF MS

Current Criteria for MS

Several definitions of MS have been put forth by different organizations like the World Health Organization (WHO) (1999) [6], International Diabetes Federation

(IDF) (2005) [7], the U.S. National Cholesterol Education Program and the Adult Treatment Panel III (NCEP- ATP III) (2001) [8], and the European Group for the Study of Insulin Resistance (EGIR) (1999) [9]. The definitions are summarized in Table **1**.

Table 1. Different criteria for metabolic syndrome.

Components of MS	IDF Consensus (2005)	NCEP ATP III Criteria (2001)	WHO Criteria (1999)	EGIR (1999)
Obesity/Abdominal obesity	Waist circumference ≥ 90 cm (M), ≥ 80 cm (F)-South Asians	Waist circumference ≥ 102 cm (M), ≥ 88 cm (F)	Body mass index (BMI) ≥ 30 kg/m^2 and/or waist-to-hip ratio > 0.90 (M), > 0.85 (F)	Waist circumference ≥ 94 cm (M)), ≥ 80 cm (F)
Blood pressure	> 130 / >85 mm Hg or on medication	> 130 / >85 mm Hg or on medication	≥ 140 / ≥ 90 mm Hg or on medication	≥140/90 mm Hg or on medication
Fasting glucose	≥ 100 mg/dl or pre-existing DM	≥ 110 mg/dl or on medication	Diabetes, impaired glucose tolerance (IGT) or insulin resistance	IGT or Impaired Fasting Glucose (IFG) but not diabetes
Triglycerides	≥ 150 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl	TG ≥ 177 mg/dl and/or HDL-C
HDL Cholesterol	< 40 mg/dl (M), < 50 mg/dl (f)	< 40 mg/dl (M), < 50 mg/dl (F)	Not in criteria	< 39 mg/dl or treated for dyslipidemia
Insulin-resistance	Not in criteria	Not in criteria	glucose uptake below the lowest quartile under hyperinsulinemic, euglycemic conditions	Plasma insulin > 75th percentile
Microalbuminuria	Not in criteria	Not in criteria	Urinary albumin excretion rate ≥20 µg/min or albumin:creatinine ratio ≥30 mg/g	Not in criteria
Metabolic syndrome-definition	Obesity plus two of the other criteria	At least three risk factors	Diabetes, impaired glucose tolerance or insulin resistance plus any two or more risk factors	Insulin resistance plus any two of the other risk factors

Apart from the above major definitions there also exist other definitions with minor variations. For instance, in 2004, the NCEP definition was revised as rNCEP definition by lowering the threshold for fasting glucose to ≥ 100 mg/dl according to the American Diabetes Association (ADA) criteria for impaired

fasting glucose (IFG) [9]. Also the South Asian modified (SAM)-NCEP definition has been introduced for the South Asian ethnic group [10].

MS - GLOBAL OVERVIEW

It is difficult to compare the published data on the prevalence of MS in different populations because they differ widely in terms of sample selection, study design, the definition of MS used as well as the age and gender structure of the population. The prevalence of MS in a Chinese population was reported to be 33.7% [11]. Using different definitions, Pakistan showed prevalence ranging from 18-46% comparable to other south Asian nations [12]. Azizi *et al*. based a study in Iran using ATP III definitions and found MS to be prevalent in 30.1% of the population [13]. A study carried out in several geographical regions of Turkey, showed that 27% of males and 38.6% of females had metabolic syndrome by the ATP III criteria [14].

Ireland reported a prevalence of 25% by WHO criteria and 20.7% by ATP III criteria in a survey population recruited from a primary care setting [15]. In the United States, native Americans in the age group of 45-49 showed a prevalence of 50.1% whereas Mexican Americans showed a prevalence of 29% in men and 32.8% in women and among non-Hispanic whites, 23% had MS [16, 17]. The estimated prevalence of MS in a Canadian population was 19.1% [18].

MS in Asian Indians

The prevalence of MS in the south Asian population is high. With the development of MS in the south Asian population, there are many potential risk factors including decreased physical activity, urbanization, high carbohydrate intake, lower intake of w-3 PUFAs, high fat intake and increased life expectancy [19].

Using the ATP III definition (modified for waist circumference as appropriate for Indians), the prevalence of MS has been found to be 41.1% [20]. In another study which used the EGIR definition, the prevalence was reported to be 11.2% in the same population [21]. A study from south India has estimated the prevalence of MS to be 25.8% by the IDF criteria, 23.2% by the WHO criteria and 18.3% by the NCEP ATP III criteria [22]. Moreover the conventional risk factors comprising the metabolic syndrome are highly prevalent in Asian Indians. It has been shown that the prevalence of abdominal obesity is 31.4%; hypertension 55.4%; low HDL 65.5% and raised fasting glucose 26.7% [23-25]. However, the prevalence of MS

in a rural area population was found to be as low as 5% in central India [26] compared to an urban area population, where about one third of individuals have MS [23]. The high prevalence of MS in Asian Indians could be attributed to the higher prevalence of insulin resistance [27]. Even in younger populations the prevalence of insulin resistance has been shown to be fourfold higher than that of other ethnic groups [28]. Moreover, Asian Indians show very low levels of HDL compared to other populations which could increase their risk of MS [29]. The levels of LDL and atherogenic small dense LDL have also been reported to be higher among the south Asians [30].

The overall prevalence of MS among the expatriate south Asian population was shown to vary between 21% to 46%. Tan *et al.* [31] have shown that the prevalence of MS in Asian Indians according to NCEP-ATP III criteria was 13.1% in males and 11% in females whereas the modified NCEP-ATP criteria was estimated the prevalence to be 20.9% in males and 15.5% females living in Singapore. In another study done by Tillin *et al.* [32] using WHO criteria, the prevalence of MS in South Asians was determined to be 46% in males and 31% in females. By NCEP-ATP III criteria the prevalence was 29% in males and 32% in females living in London [32]. Hence there is a wide variation in the prevalence of MS in expatriate south Asians according to the degree of urbanization, socio-economic factors and patterns of life style.

MANAGEMENT OF THE RISK FACTORS

Abdominal Obesity

In individuals with MS and abdominal obesity, the first priority is to reduce body weight by means of increasing their physical activity and decreasing their caloric intake [33]. See Fig. (**1**) for the components and causes of metabolic syndrome. The Chennai Urban Population Study (CUPS), an epidemiological study conducted on a south Indian population has shown that the prevalence of MS increased with decrease in physical activity [34]. Radhika *et al.* in a population of urban Asian Indians have shown that the consumption of refined grains was associated with insulin resistance and metabolic syndrome [35]. The initial target of weight reduction could be set to bring about a reduction of about 8- 10% from the original weight in a time span of one year which translates to bringing about a decrease of about 500 calories per day [33]. Attainment of the required amount of weight loss would greatly reduce the severity of most of the metabolic parameters. Obesity could also be managed by means of drugs, but the currently available

options are not desirable [36]. In selective cases, bariatric surgery may offer a treatment option [37].

Elevated Blood Pressure

The specific treatment goal for elevated blood pressure in subjects with MS should stress on lifestyle changes. Mild elevations in blood pressure could be adequately managed by control of body weight *via* increased physical activity and by the consumption of a diet rich in fresh fruits and vegetables, and low in salt and fatty foods [38]. Apart from diet and physical activity, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers are currently preferred.

Elevated Fasting Glucose

Ford *et al.* (2008) had compared the association between MS and the incidence of diabetes after a follow up period of 6 years using various criteria used for MS [39]. It was found that the hazard ratio by the NCEP definition was 4.6 while that of the IDF definition was 4.5. Among the various components of MS, abdominal obesity and hyperglycemia were most strongly associated with incidence of diabetes [39]. In a population of Pima Indians, hyperinsulinemia, body size, blood pressure, and lipid metabolism had been shown to be more closely related to the incidence of diabetes. Hence, in patients with MS, implementing effective weight reduction or increased physical activity would delay the onset of frank diabetes. Oral hypoglycemic agents like metformin, acarbose or glitazones are conventionally recommended by physicians for the treatment of type 2 diabetes.

Atherogenic Dyslipidemia

Dyslipidemia in south Asians characterized by high circulating levels of apolipoprotein B, lipoprotein a and lower levels of Apo A1 and HDL cholesterol predisposes this population to higher risk of diabetes, metabolic syndrome and coronary heart disease [40]. Controlling LDL-C is the major target of lipid lowering therapy and the next target is the elevated triglyceride levels. Apart from these major targets, an elevated level of apolipoprotein B is also important in lipid lowering therapy [41].

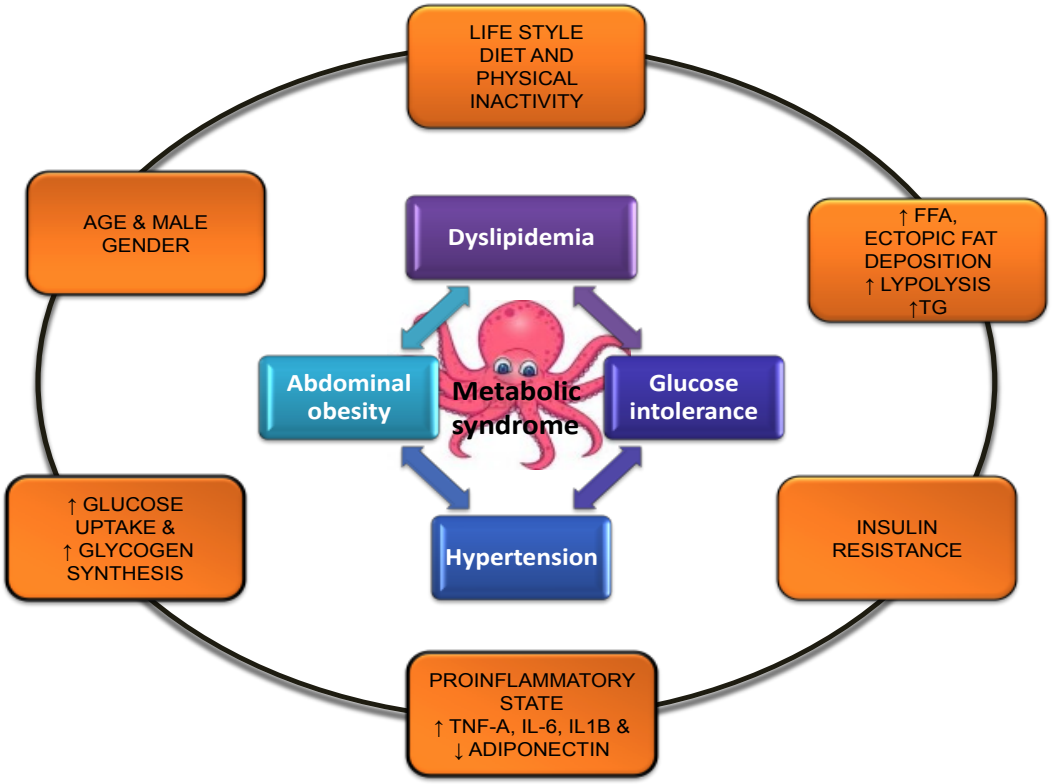

Fig. (1). Components and causes of metabolic syndrome.

Inflammation is a biological response elicited by the tissues to pathogens or cellular stress like high blood glucose/lipids or damaged cells [42]. Persistent inflammation also called chronic inflammation features the migration of macrophages to the site of injury and obesity, an integral component of MS has been shown to be associated with chronic low grade inflammation [43]. We have shown that MS is characterized by the reduced levels of the adiponectin, an anti-inflammatory and anti-atherogenic adipocytokine secreted by the adipose tissue [44]. Moreover MS also shows increased levels of inflammatory markers like high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-a) [45] and atherogenic markers like vascular cell adhesion protein 1 (VCAM), soluble P-selectin and CD40 ligand (CD40L) [46] and Angiopoitein-2 [47]. Also, inflammatory mediators secreted by immune cells such as cytokines Th-1 and Th-2 were also increased in subjects with MS [48]. Intimal media thickness (a surrogate marker for sub-clinical atherosclerosis) has also been found to be

associated with metabolic syndrome and glucose intolerance in Asian Indians [49].

MS AND DIABETES

MS and Cardiovascular Vascular Disease (CVD)

A number of longitudinal studies have ascribed the cardiovascular risk associated with MS [50-54]. Meta analysis studies have shown that metabolic syndrome is associated with a higher cardiovascular risk in women when compared to men. After an 8 year follow up, it was shown that the MS group had a 17.9% incidence as against 4.9% in the non-MS group [55]. In subjects without Type 2 DM, it was shown that in MS group, the incidence of CVD was 10.2% and the non-MS group showed an incidence of 4.9% [56]. Among Japanese men, the CVD prevalence was 12.3% in the MS group compared to 6.5% in the non-MS group [57]. In patients without diabetes, the incidence of myocardial infarction after a follow up of 10 years was found to be 5.8% in the MS group and 2.9% in the non-MS group [58]. In a general population, the incidence of MI was found to be 9.1% in the MS group compared to 5.7% in the non- MS group after a follow up of 6 years [59].

Irrespective of the definition used, MS was noted to be associated with an increased risk of CVD mortality. In non-obese men, the CVD mortality in the MS group after a follow up of 10 years was found to be 1.99% compared to 0.53% in the non-MS group [60]. Also, in the general population, the MS group showed a higher CVD mortality of 7.3% compared to 2.4% in the non-MS group [61]. According to the revised NCEP definition for MS, the CVD mortality in the MS group was found to be 7.5% *vs* 3.9% in the non-MS group [62].

CONTROVERSIES AND UTILITY OF MS

Controversies Regarding the Metabolic Syndrome

Due to the existence of various criteria for metabolic syndrome, there are concerns over the etiology of the syndrome itself. Every combination of the proposed risk factors could impart a different degree of risk for the occurrence of CVD [63]. Also the risk for the occurrence of CVD due to MS appears to be equal to that of the sum of its components. Further, other CVD risk factors, such as inflammatory markers, are not included as components of MS [45]. Hence MS would not account for the actual underlying CVD risk that an individual is subjected to. Though insulin resistance has been widely accepted as a causative factor in the pathogenesis of MS, it is likely that insulin resistance could be just

another demonstration of an underlying causative factor. Even if MS is identified, the patient is treated only for its individual components. There is no unifying treatment strategy for MS as a whole and this might raise questions about the utility of diagnosing MS [64]. Further, it communicates to the patients that they have a disease even if they do not have one and hence detracts from the need to prioritize treatment based on benefits, risks and cost.

Utility of the Diagnosis Of Metabolic Syndrome

Irrespective of the question of a common etiology underlying the components of MS, identification of MS clearly recognizes individuals at heightened risk for diabetes and cardiovascular diseases [58, 59, 65]. The recommendations proposed by NCEP-ATPIII clearly state that there is a dire need for emphasizing life style interventions to combat the CVD risk factors [66]. Hence diagnosis of MS leads to enhanced treatment strategies. Also conducting research on MS could throw light on the pathophysiological mechanisms that link insulin resistance and CVD risk factors (Fig. **2**). Apart from predicting CVD risk in patients with diabetes, individuals who do not have diabetes can also be assessed for their CVD risk. MS as a risk factor for NAFLD, steatohepatitis, cirrhosis, and as an independent risk factor for CVD warrants a discussion of the topic below.

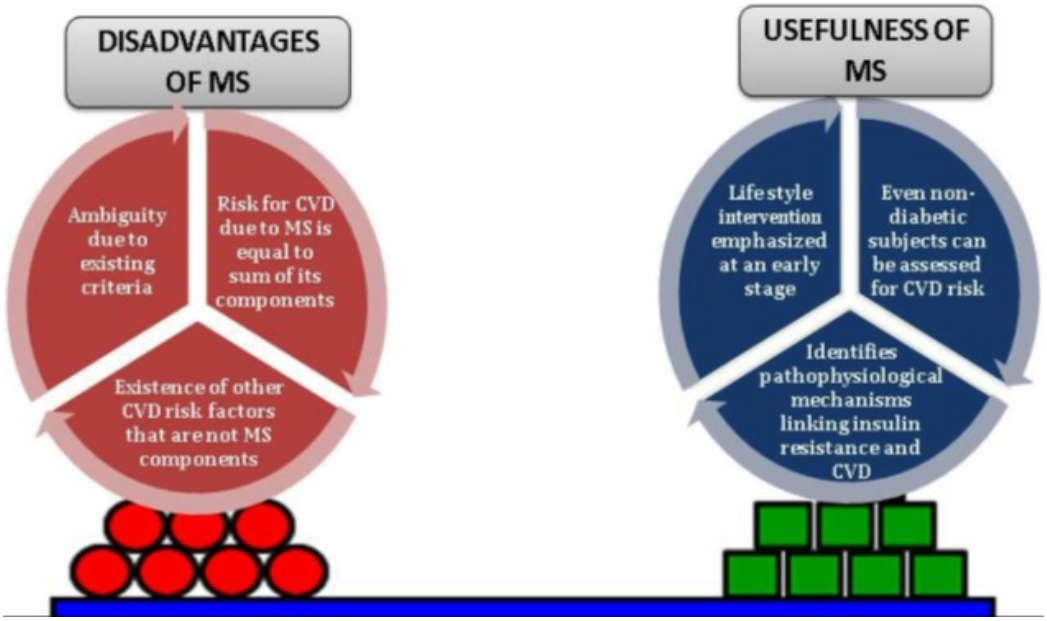

Fig. (2). Disadvantages and usefulness of metabolic syndrome.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

It is a spectrum of liver pathology seen in persons without significant alcohol consumption that includes four stages i) simple steatosis or non alcoholic fatty liver (NAFLD), ii) steatosis with inflammatory cells (Non alcoholic steatohepatitis or NASH) and iii) fibrosis with cirrhosis also referred as cryptogenic cirrhosis which may be rarely complicated by iv) hepatoma (see also CHAPTER 7, From Fatty Liver to Cirrhosis: The Toll Rises!). The diagnosis and management of NAFLD is well reviewed recently by three leading professional societies of Gastroenterology in the US, the American Association of Liver Diseases (AASLD), the American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA) [67]. NAFLD mostly occurs in association with other features of MS although it may be seen in non-diabetics or prediabetics as well.

DIAGNOSIS OF NAFLD AND NASH

NAFLD is often a diagnosis of exclusion on the basis of the following:

- There is evidence of steatosis in the liver noted in histology or in an imaging study

- There is no other cause for steatosis (hepatitis C, B, medications, autoimmune hepatitis, hemochromatosis and malnutrition) and there is no significant alcohol consumption. Although the definition of non-alcoholism or "significant alcohol consumption" is debatable, the threshold has been set as 20g/day for men and 10g/day for women recently [68].

Further in a large, well-characterized population with biopsy-proven NAFLD, modest alcohol consumption was associated with lesser degree of severity as determined by lower odds of the key features that comprise a diagnosis of steatohepatitis, as well as fibrosis. NAFLD is most often clinically silent and hence the prevalence markedly underestimated. The diagnosis is often incidental. A routine liver chemistry or an imaging study such as abdominal ultrasound may pick up the hepatic abnormality. Patients are often noted to have a greater increase in serum levels of alanine amino transferase (ALT) than aspartate amino transferase (AST). The levels are typically elevated less than five times the upper limit of normal, with AST /ALT ratio being less than one except when the disease has progressed to cirrhosis. An initial abdominal ultrasound or CT scan of abdomen will reveal increased echogenicity. Other non-invasive tests such as

fibroscan would help in the assessment of liver stiffness. Liver biopsy is expensive, not practical in most patients and is associated with some degree of risk and should be considered only in selected few patients who have competing etiological factors for fatty liver and or in those at risk for advanced fibrosis [67].

The following histologic diagnostic criteria based on the US Pathology Committee system's recommendation suggests semi quantitative estimation of four features a) steatosis, b) lobular inflammation c) hepatocyte ballooning and d) fibrosis [69]. Significant steatosis is defined as fat accumulation in more than 5% of hepatocytes. NASH is diagnosed histologically when there is associated necroinflammation, hepatocyte ballooning and inflammatory infiltrates with or without fibrosis. NAFLD activity score is a term (NAS) that denotes an unweighted composite of steatosis, inflammation and ballooning. NAS is a useful tool to assess the progress in liver histology in clinical trials. A new marker is a serum fragmented Cytokeratin 18 level that reflects the histologic activity score of NASH [70].

PATHOGENESIS OF NAFLD

NAFLD is closely associated with MS and in particular with insulin resistance (IR). IR increases hepatic free fatty acid flux by inhibiting lipolysis and increasing *de novo* lipogenesis. Apoptosis and oxidative stress contribute to disease progression. A two hit or multiple hit hypothesis suggests initial accumulation of fat in the liver that leads to a second hit in some by free fatty acids, cytokines and oxidative stress. An imbalance between pro inflammatory TNF-alpha and adiponectin is a major pathogenetic factor. TNF-alpha is pro-apoptotic and recruits inflammatory cells and promotes insulin resistance. Adiponectin stimulates oxidation, inhibits fatty acid uptake, and decreases insulin resistance [66].

DIABETES AND NAFLD

The prevalence of NAFLD was found to increase in parallel with the severity of glucose intolerance. Kim *et al.* reported an independent association between moderate/ severe NAFLD and incident diabetes compared to patients with mild NAFLD [71]. Elevation in the levels of aminotransferases in the plasma has been shown to increase the risk of type 2 diabetes [72]. Diabetic patients were also found to have almost an 80% increase in intrahepatic fat content than their non-diabetic counterparts [73]. Reports also show that diabetes and insulin resistance

are significantly associated with ectopic fat deposition in the liver and hepatic steatosis and hepatic insulin resistance often occur in conjunction. In animal models, it has been shown that insulin resistance is the major pathogenic factor in the initiation and progression of steatohepatitis *via* increases in lipogenic, inflammatory and fibrogenic genes [74]. However, whether hepatic triglyceride accumulation causes insulin resistance or vice versa and the mechanistic pathways involved are not yet clear [75].

CORONARY ARTERY DISEASE AND NAFLD

The overall health risks of patients with NASH are not confined to the liver. There is growing evidence that NAFLD increases the risk for coronary artery disease (CAD) [76-78]. NAFLD may be a mediator of CAD and not just a marker. The 10-year risk of all-cause mortality, fatal and non-fatal CVD and CAD events in relation to elevated ALT was assessed in 1439 subjects participating in the Hoorn Study, using Cox survival analysis. The predictive value of ALT for coronary events, seemed independent of traditional risk factors [77]. The severity of histological abnormality in the liver was noted to be closely associated with markers of early atherosclerosis such as greater carotid artery wall thickness and lower endothelial flow mediated vasodilatation.

As a component of MS, NAFLD is logically expected to be associated with CVD, but NAFLD as a predictor of CVD is rather surprising [79]. Earlier cross sectional studies have demonstrated associations between NAFLD and intima-media thickness and/or plaques of carotid artery as measures of early atherosclerosis [70]. However, whether the observation is an epiphenomenon is to be studied further [68]. In a recent study Targher *et al.* found that CVD is the leading cause of death in patients with advanced NAFLD [80].

TREATMENT OF NAFLD

Treatment options are available only for the manifestations of the components of MS as the syndrome does not have a known single cause. Modification of life style such as bringing about weight loss *via* administration of a healthy diet and increasing physical activity is the first treatment option. When more than one abnormality is present, a more aggressive approach may be considered. The strongly established association between NAFLD and MS does indeed suggest NAFLD is the hepatic manifestation of MS. Also, more mechanistic insights into how lipid overload in MS leads to fibrogenesis and extracellular matrix deposition

in the pathogenesis and progression of NAFLD should be ascertained by future studies so that more aggressive treatment strategies could be formulated to combat MS and NAFLD. NAFLD also impacts vascular physiology leading to increased risk of cardiovascular diseases. Irrespective of the definitions used to define MS, obesity and insulin resistance are the major features that play an important role in the pathogenesis of MS, CVD and NAFLD. Hence, in a population like Asian Indians, which is at high risk for insulin resistance and higher body fat percentage, health care workers could use MS and NAFLD to identify patients who are at high risk for diabetes and cardiovascular disease and thus help to decrease morbidity and mortality due to these conditions.

CONCLUSION

Treatment options address the components of MS rather that the syndrome per se. Because the pathogenesis is poorly understood, the treatment focuses on weight management. Modification of life style to achieve weight loss that focuses on a healthy diet and on increasing physical activity is the foundation of treatment. When multiple abnormalities are present, a more aggressive approach may be needed to treat each risk factor separately.

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CONFLICT OF INTEREST

The authors confirm that this chapter contents have no conflict of interest.

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