Metabolic syndrome in adults: relation with diet and other lifestyle factors

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Abstract

Metabolic syndrome is a constellation of risk factors that has the potential of developing into cardiovascular disease or increase the susceptibility to it. It is present worldwide with now even developing countries getting overwhelmed by its burden. With a shift towards unhealthy diet coupled with sedentary lifestyle, development of metabolic syndrome is on the rise even among young adults. One of the main causes of this problem is faulty diet, so any means to reduce the incidence of the syndrome involves the modification of the existing diets rich in saturated fat, sodium and cholesterol. This review focusses on efficacy of different dietary patterns for combating the syndrome along with other lifestyle risk factors. It also highlights newer advancements in the field of Metabolic Syndrome, which can serve as potential strategies to combat it. Public health interventions targeting adults, therefore, should center on prevention through education, modification of diet and lifestyle, and focusing on environment, so that these changes are acceptable and sustainable.

Keywords

Metabolic Syndrome; Diet; Lifestyle

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Introduction

Metabolic syndrome (MetS) is a complicated disorder that increases a person's risk to cardiovascular diseases (CVD) and diabetes (DM). It is a cluster of interrelated factors characterized by high fasting blood glucose, increased level of triglycerides, low levels of high density cholesterol (HDL), elevated blood pressure and abdominal obesity [1]. However, defining MetS is a complicated task as there is no one universal definition. With its increasing prevalence in childhood and adulthood, it poses immense future implications on the global burden of disease relating to obesity and sedentary lifestyle. MetS thus can be viewed from both a public health as well as a clinical perspective. While in the public health arena it focuses on modification of lifestyle, at clinical level, it confluences on diagnosis of risk factors related to MetS including lifestyle related factors. Despite there being a disagreement on the consensus of one universal definition, there appears to be an agreement that MetS poses risk for developing CVD and DM [2,3]. Though MetS is not an absolute risk factor, it presents a impressive risk of developing CVD in future [4,5]. The concept of 'Syndrome X' which was renamed as MetS later, was pioneered by Reaven [6], estimating it as an importante factor in the development of CVD and DM. He identified insulin resistance and subsequent hyperinsulinemia as the indispensable underlying risk factors for hypertension, hyperlipidemia, diabetes and eventually CVD. Although, he did not acknowledge obesity as caused by insulin resistance, he did acknowledge its correlation with Syndrome X or MetS. It was inferred then that weight maintenance and physical activity were the pivotal elements for the treatment [7]. The beginning of defining MetS began in 1998, by a consultation group on the definition of diabetes for the World Health Organization (WHO) [8]. This was followed by the European Group for the study of Insulin Resistance (EGIR) [9] in 1999, the National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII) [10] in 2001, the American Association of Clinical Endocrinology (AACE) [11] in 2003, the International Diabetes Federation (IDF) [12], and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) [13] in 2005. The criteria for defining MetS vary among all these definitions (Table I).

Another pertinent aspect relating to the MetS is the applicability of the above defined criteria in relation to various ethnic groups. Ethnicity poses an important question for diagnosis of MetS. Due to mixed ethnicity in the world, it is important to be pragmatic with this aspect. A primary perspective lies in the fact that a common definition to diagnose MetS must be used worldwide, keeping into consideration the difference between sexes and ethnic groups. The different proposed definitions of MetS have varied applicability across various ethnicities. The dilemma arises in the case of defining obesity cut offs as type 2 DM is at lower levels of obesity in Asians in contrast to Europeans. Solution to this dilemma has been recognized by IDF that has supported new ethnic cutoffs to diagnose MetS. However, it is imperative to possess one definition that is applicable worldwide, keeping in view the amplifying epidemic of CVD and type 2 DM [4]. Regardless of the varying criteria proposed by different definitions, the prevalence of MetS is on the rise in both western and Asian countries [14-16]. Increment in the proportion of diagnosed individuals can be related to increase in age and BMI [17]. Not only the western societies, but also the developing countries are now getting overwhelmed in the burden of this problem. This rise can be attributed to the transition in the lifestyle from a traditional to a western one. The genesis of MetS and obesity in developing countries relates to demographic transition (shift to low fertility, low mortality, and higher life expectancy), and epidemiological transition (from widely prevalent infectious diseases to a pattern of a high prevalence of lifestyle related diseases) congregating genetics and environment [5,18-20].

The double burden of under and over nutrition in the developing countries is leading to the increased risk for CVD and sequential morbidity and mortality. Health interventions focusing on favorable dietary and lifestyle practices are the need of the hour in developing countries simultaneous with the adequate support of government and legislative bodies. Therefore, this review was undertaken to assess the current dietary patterns and newer advancements effective in combating MetS.

Expert group/ organization	Diagnostic criteria				
	Glycemia	Obesity	Dyslipidemia	BP	Any other
World Health Organization (WHO), 1998	>100 mg/dl	WHR: men>0.9, women>0.85; BMI>30 kg/m²	TG:150 mg/dl or greater and/or HDL-C: men<40 mg/dl, women<50 mg/dl	140/90 mmHg or greater	Microalbuminuria 20 µg/min or greater 30 mg/g or greater
	Insulin resistance plus two of the above				
European Group for the Study of Insulin Resistance (EGIR), 1999	110 mg/dl or greater	WC: men 94 cm or greater, women 80 cm or greater	TG: 150 mg/dl or greater and/or HDL-C: <39 mg/dl in men or women	140/90 mmHg or greater	
	Insulin resistance plus two of the above				
National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII) 2001	110 mg/dl or greater	WC: men>102 cm, women>88 cm	TG: 150 mg/dl or greater, HDL-C: men<40 mg/dl, women<50 mg/dl	130/85 mmHg or greater	
	Any three or more of the above				
American Association of Clinical Endocrinology (AACE), 2003	Impaired Glucose Tolerance	BMI: 25 kg/m² or greater	TG: 150 mg/dl or greater and/or HDL-C: men<40 mg/dl, women<50 mg/dl	130/85 mmHg or greater	
	IGT plus two or more of the above				
American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), 2005	100 mg/dl or greater	WC: men 102 cm or greater, women 88 cm or greater	TG: 150 mg/dl or greater; HDL-C: men< 0 mg/dl, women<50 mg/dl	130/85 mmHg or greater	
	Any three of the above				
International Diabetes Federation (IDF), 2005	100 mg/dl or greater	BMI>30 kg/m²	TG: 150 mg/dl or greater; HDL-C: men<40 mg/dl, women<50 mg/ dl	130/85 mmHg or greater	
	Central obesity plus two of the above				
Consensus definition (incorporating IDF and AHA/NHLBI definitions), 2005	100 mg/dl or greater	Elevated WC (according to population and country-specific definitions)*	TG: 150 mg/dl or greater; HDL-C: men<40 mg/dl, women<50 mg/dl	130/85 mmHg or greater	
	Any three of the above				

Table I. Differential criteria proposed by various expert groups to define Metabolic Syndrome

* Waist circumference: for Europeans, > 94 cm in men and > 80 cm in women; and for South Asians, Chinese, and Japanese, > 90 cm in men and > 80 cm in women. For ethnic South and Central Americans, South Asian data are used, and for sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations, European data are used.
BMI = Body Mass Index; BP = Blood Pressure; IFG = Impaired fasting glucose; HDL- C = High Density Lipoprotein-Cholesterol; TG = Triglycerides; WC = Waist circumference ; WHR = Waist Hip ratio

This current review focusses on efficacy of various existing dietary patterns for combating the syndrome along with other lifestyle risk factors. It also highlights newer advancements in the field of Metabolic Syndrome, which can serve as potential strategies to combat it.

Methodology

In this article, we have reviewed existing literature regarding the current prevalence of MetS with focus on its relationship with diet as the most important modifiable factor. Besides this, relationship with other lifestyle factors and newer advancements to combat MetS has also been looked upon. Literature search was carried out using PubMed (National Library of Medicine, Bethesda, MD, USA), Medline, Cochrane Library, Science Direct, and Google Scholar databases. The keywords used were Metabolic Syndrome, diet, lifestyle, oxidative stress, gut microbiota, non-communicable diseases, prevalence, adults, inflammation and genetics. Published studies which have been listed in the above mentioned databases have been included in this review.

Prevalence patterns of MetS in the developing world

The prevalence of MetS is on the rise across the world. Twenty five percent of new cases of CVD are accounted by MetS. However according to the Framingham study in absence of DM, the risk of CVD is not increased by more than 20% (less than 10% for females, and between 10-20% for males) [21]. Variation in prevalence occurs with respect to sex, age and ethnicity [22,23]. MetS is even affecting the developing countries such as India and China. In India, urban Indians are most susceptible to its development owing to affluence of middle class, urbanization, mechanization, marked changes in diet (increased consumption of "calorie-dense foods") and sedentary habits [24], without overlooking the facet of rural Indian populations who are being affected by it as well [25-27]. This is an important matter, as without effective intervention strategies, it can lead to T2DM and CVD in future. Moreover, in comparison with Whites, South Asians exhibit CVD onset and diagnosis at a younger age [28]. The term "South Asian" refers to the "1.5 billion people belonging to the southern region of the Asian continent comprising the sub-Himalayan countries". These countries include India, Pakistan, Nepal, Sri Lanka, Bangladesh, Bhutan, Maldives, and the British Indian Ocean Territory [29].

In case of South Asians, MetS affects the migrants where its prevalence is around 20-25% [30,31]. Specifically, in urban India, the prevalence of MetS was estimated by ICMR task force during 1992-94 in a collaborative study, according to which it was 30% in urban areas of Delhi and 11% in rural Haryana using the ATPIII criteria. Prevalence of 30% in urban slum population of Delhi [5] and 41% in urban area of Chennai was reported among adults using modified ATPIII criteria [32]. The difference, though not completely, is characterized by usage of various definitions of MetS used and implies that prevalence across studies cannot be compared. These high prevalence rates in India especially among the urban population are of immediate concern, with cardiovascular prevention as its focal point.

A cross-sectional study of adults above the age of 18 years, conducted in the rural district of Wardha, Central India, delineated that MetS was significantly higher among females (7.6%) in comparison to males (2.9%) using the ATPIII guidelines for diagnosis. However, the prevalence notched up to 10.7% and 8.2% among males and females respectively when Asia Pacific guidelines modified for waist circumference were used [25]. MetS is also marked by gender differences owing to different cutoffs set for waist circumference and HDL values, hence, potentially significant for diagnosis and prevention [33,34]. Socio economic status has been shown to have association with the prevalence of MetS [35-37]. Inverse relationship appears between MetS and socio economic status, more strongly for women in comparison to men in developed countries [36-40]. On the contrary, no association was seen with the overall prevalence of the metabolic syndrome and socio economic status in a subset of the participants (n=839) from the 1986 Jamaica Birth Cohort who were evaluated at ages 18-20 years. This absence of association was attributed to lack of statistical power [41]. However, in the developing countries, prevalence is marked by affluence. This difference across the countries is attributed to the available

income for expenditure. In the developed countries, inverse association is accredited to the availability of low-cost energy dense foods that lead to insulin resistance to those with limited income. Moreover in women, low household income results in likely unemployment, reduced physical activity and stress, thus, leading to the syndrome [36]. In contrast, among developing countries, rise in income is associated with increase in consumption of foods high in energy and fat, animal foods and processed foods [42]. This leads to a great potential of poor health and subsequent development of MetS.

Considering age as an important determinant of MetS, a study to assess the prevalence of MetS in Iran was conducted with randomly selected adults >20 years selected using stratified sampling [43]. The prevalence was 23.7%, being same in men and women. Significant age related increase was observed in both sexes ranging from 7.5% (20-29 year age group) to 44.7% (> 60 years of age). Other studies have also reported an increase in prevalence of the syndrome with age (Table II). Studies conducted in India using variable criteria to determine the MetS prevalence showed that in South Indian population, it was 25.8% using IDF as compared to 18.3% by ATPIII, in individuals > 20 years of age [44]. Dissimilar trends were observed in Bangalore, where it was higher using the ATPIII criteria (40.3%) as compared to IDF criteria (34.9%) [18]. Prevalence studies in the rest of the world using different criteria have also demonstrated varying results (Table II). Engaging in different types of jobs is another important factor that has an implication in the development of MetS. Studies providing evidence for MetS have determined prevalence rates among laborers (11.8%), office employees (9.3%), and managers (7.7%) [45].

Design	Country	Sample	Salient Finding(s)	Reference
Cross-sectional	Korea	N=21,796 (aged 30 years and above)	High prevalence was observed in housewives in women (men 41.3%, women 33.7%) and office workers in men (men 30%, women 9.8%) who were the reference group to other occupations.	[46]
Cross-sectional	Korea	N=3,288 (aged 19 years and above)	Prevalence of the syndrome among young female workers (<50 years) was high (OR=1.95) compared to non-manual workers.	[47]
Cross-sectional	Korea	N=9,726	Association between occupation and MetS was observed in men but not in women. Risk of the syndrome was high in white collar workers compared to blue collar workers (OR=1.4).	[48]
Cross-sectional	Iran	N=429 male bus and truck drivers	Prevalence – ATPIII criteria: 35.9%. Positive correlation between BMI, DM, HT and MetS (p<0.001). No positive correlation between smoking and MetS (p<0.06).	[49]
Cross-sectional	China	N=3,953 adults aged 20-88 years (2,429 females, 1,524 males).	Prevalence – ATPIII criteria: men 13.0%, women 15.3%, who were alcohol drinkers.	[50]
Cross-sectional	China	N=2,334 adults aged 60 to 95 years (943 men, 1,391 women)	Prevalence – ATPIII criteria: 30.5% (17.6% in men, 39.2% in women), IDF criteria: 46.3% (34.8% in men, 54.1% in women). Odds ratio for CVD, stroke and PAD are higher among those with MetS (irrespective of criterion).	[51]
Cross-sectional	China	N=16,342 subjects aged 20-90 years (8,801 males, 7,541 females)	Age-standardized prevalence of MetS was 13.2%. Prevalence was more in males (15.7%) compared to females (10.2%).	[52]
Cross-sectional	Korea, Japan	N=6,824 (aged 20-79 years)	Prevalence – IDF criteria: men 13.5%, women 15%.	[53]

Design	Country	Sample	Salient Finding(s)	Reference
Cross-sectional	India	N=19,973 for Questionnaire survey; 10,442 biochemical testing (Industrial population, aged 20-69 years)	Prevalence – ATPIII criteria: 26.6% (men 20.9%, women 36.3%); IDF criteria: 35.4% (men 29.4%, women 46.1%).	[54]
Cross-sectional	Turkey	N=15,468 adults	Prevalence of MetS was 17.91%, being more in females than males. Prevalence of the syndrome and related disorders are significantly different according to the geographical region.	[55]
Cross-sectional	Korea, Japan	N= ,824 (aged 20-79 years)	Prevalence – ATPIII criteria: men 14.2%,women 17.7%. Moderate exercise (2-3 sessions/week) and light alcohol drinking (<15 g/d) had inverse association with MetS.	[56]
Cross-sectional	Oman	N=1,419 adults (≥20 years)	Age adjusted prevalence – ATPIII criteria: 21.0% (men 19.5%, women 23.0%; p=0.236).	[57]
Cross-sectional	Australia	N=5,850 of which 4,060 had biochemical examination	Prevalence – IDF criteria: 22.8 (men 26.4%, women 15.7%); ATPIII criteria: 15.0% (men 19.4%, women 14.4%).	[58]
Cross-sectional	Greece	N=9,699 adults	Age adjusted prevalence – IDF criteria: 43.4%; ATPIII criteria: 24.5%. Lower vascular risk in those with IDF defined MetS than with ATPIII defined (p<0.0001).	[59]
Cross-sectional	Spain	N=1,030 adults	Age adjusted prevalence – WHO criteria: 28.0%; EGIR criteria: 15.9%; NCEP criteria: 23.0%; Revised NCEP criteria: 28.2%. High prevalence of the syndrome irrespective of the criteria used.	[60]
Cross-sectional	Venezuela	N=3,108 men and women (≥20 years)	Prevalence – ATPIII criteria: men 31.2%, women 24.1%. Family history of diabetes, obesity, HT and sedentary lifestyle were positively associated with the MetS.	[61]
Cross-sectional	U.S.A	N=3,601 adults (>20 years)	Prevalence – ATPIII criteria: 34.5% (men 33.7%, women 35.4%); IDF criteria: 39.0% (men 39.9%, women 38.1%).	[62]
Cross-sectional	Japan	N=8,144 individuals (19-88 years)	Prevalence – ATPIII criteria: 19% men, 7% women. Significantly more in men than women (OR=3.08). HT was the most common component in all the individuals diagnosed with the syndrome.	[63]
Prospective	Mexico	N=2,282 (1990-1992), N=1,764 (1993-1995), N=1,754 (1997-1999)	Prevalence – ATPIII criteria: 38.9% (men 1990-1992), 43.4% (men 1993-1995), 39.9% (men 1997-1999); 65.4% (women 1990-1992), 65.7% (women 1993-1995), 59.9% (women 1997-1999). No change in syndrome's prevalence was observed in men (p=0.349) between 1990-1992 and 1997-1999, but it decreased in women (p<0.001).	[64]
Cross-sectional	China	N=2,893	Prevalence – ATPIII criteria: 16.7%. Age related increase in the prevalence from 3.1% (25-29 years) to 41.0% (>70 years).	[65]

Design	Country	Sample	Salient Finding(s)	Reference
Prospective	U.S.A	N=6,436 men and women (≥20 years) from NHANES III (1988-1994) and 1,677 participants from NHANES 1999-2000	Age adjusted prevalence – ATPIII criteria: 24.1% (NHANESIII), 27.0% (NHANES 1999-2000); p=0.088. Increase in prevalence was more among women (p=0.021) than men (p=0.831).	[66]
Prospective, Case-Control	U.S.A	N=32,826 women (cases) and N=785 (controls)	Baseline levels of TNF, IL, and CRP were significantly higher in cases than controls (p≤0.001). Significant association of CRP with risk of DM (OR:3.99, p<0.001).	[67]
Cross-sectional	Finland	N=2,049 adults (FINRISK study) aged 45-64 years; N=522 adults of the Finnish Diabetes Prevention Study (DPS) with IGT	Prevalence modified WHO criteria FINRISK cohort: 38.8% men, 22,2% women; DPS Cohort: 78,4% men, 72,2% women.	[68]
Cross-sectional	Greenland	N=917 adults	Prevalence – WHO criteria: 20.7%; ATPIII criteria: 17.9%. Moderate agreement between 2 definitions (κ=0.56).	[69]
Cross-sectional	Tehran	N=103,68 adults (4,397 men and 5,971 women) aged 20 years and over	Prevalence: 33.7%, increased with age in both sexes. MetS and its abnormalities were more common in women in comparison to men (p<0.001).	[70]
Cross-sectional	U.S.A	N=8,814 men and women (aged 20 years or older)	Prevalence – ATPIII criteria: 23.7%. Age related increase in prevalence was seen from 20 to 29 years and 60 to 69 years.	[23]
Cross-sectional	Korea	N=3,305 black, 3,477 Mexican American, and 5,581 white men and non-pregnant or lactating women (aged 20 years and older)	Prevalence – ATPIII criteria: 22.8% men, 22,6% women. Mexican American ethnicity was more prone to develop MetS.	[71]
Cross-sectional	Irish	N=890 (aged 50-60 years)	Combined prevalence according to WHO and ATPIII criteria: 13.1%. Age related increase in prevalence was seen. Moderate correlation between both criteria (κ=0.53, 0.46-0.60).	[72]

Table II. Prevalence of MetS according to Age, diagnostic criteria and Occupation

ATPIII = Adult Treatment Panel III; BMI = Body Mass Index; CRP = C Reactive protein; CVD = Cardiovascular Disease; DM = Diabetes Mellitus; EGIR = European Group for the study of Insulin Resistance; HT =Hypertension; IDF =International Diabetes Federation; IL = Interleukin; NCEP = National Cholesterol Education Program; NHANES = National Health and Nutrition Education Survey; TNF = Tumor Necrosis Factor; WHO = World Health Organization

Limitation nevertheless exists in the data published on the prevalence of MetS among adolescents and young adults. Estimates vary from 1% among adolescents in Japan (mean age-15 years), 6.4% in United States (12-19 years), 6.5% in Mexico (10-18 years) to10% in Iran (10-19 years) [10,45]. Young adulthood is marked by transition from the carefree adolescent phase to a more responsible phase

that brings along the pressure of finding new jobs and adjusting into them, coupled with changes in diet and lifestyle [73]. Though MetS portrays low prevalence among youth, clustering of risk factors can result in the progression towards the syndrome in adulthood, thus, advocating early identification for alleviation of the problems related to the syndrome is essential [74,75]. This holds true especially, in the Indian context, as the prevalence of all the individual components of the syndrome is on the rise.

Causes and risk factors

MetS is a challenging condition due to its varying definitions, cut-offs, and limited data for certain populations especially the young adults and elderly. It is not a discrete entity but consists of multitude of risk factors. The risk varies in an individual depending on the aggregation of metabolic and non-metabolic risk factors [13]. According to the AHA statement [13], atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose are the most familiar risk factors. Abdominal obesity [71,76,77], insulin resistance [6,78], along with physical inactivity [71,79], aging [23], hormonal imbalance [80], and atherogenic diet (a diet rich in saturated fat and cholesterol) can exacerbate the risk for developing MetS, and consequently CVD [1]. Relationship of MetS with sex, age, degree of obesity and socio-economic status has also been confirmed [81,82]. A solitary factor cannot purport to development of the syndrome; therefore, interaction amongst various domains relating to it, holds colossal worth that needs to be evaluated with the help of longitudinal studies [24].

Diet and metabolic syndrome: a complex relationship

Chronic diseases develop through a continuum from birth to adulthood with the interplay of genetics and environment. It has been gathered through the recent data that fetal/metabolic programming in utero due to poor maternal diet results in MetS, which is eventually responsible for all chronic diseases in future. Insulin resistance owing to thrifty genotype is the basic etiological factor leading to MetS. Though, the "Stone Age/Cave Man" diet of our hunter gatherer ancestors was far healthier from what we eat today; experience of alternate periods of abundance and scarcity during that time, led to an adaptive trait to survive the situation resulting in quick insulin release and lipid synthesis during starvation, to provide energy. However, with the advent of agriculture and urbanization, current diets have changed extremely from being healthy to those that are rich in saturated fat and cholesterol, which coupled with sedentary lifestyle leads to rapid glucose release and eventually positive energy balance. Whereas on one hand, thrifty genotype lead to increased survival chances with meager food supply, in times of abundant food availability it has led to development of chronic diseases and sedentary lifestyle [83]. Therefore, it emerges that faulty diet is a major root-cause of the problem and is the preventive measure that needs to be taken to ameliorate MetS or at least reduce its prevalence.

Effective dietary patterns

Mediterranean diet

A dietary pattern consisting of fruits, vegetables, whole grains, legumes, and fish, dairy products, wine and nuts in moderation is categorized as the Mediterranean Dietary pattern. When taken appropriately and adhered to properly, it results in improvement of health and quality of life [84]. The efficacy of Mediterranean diet on MetS has been observed through many studies [85-89]. However, when the Mediterranean dietary pattern is not strongly adhered, there are no changes in the metabolic risk factors. Fruit, vegetables, cereals, whole fat dairy products, MUFA and moderate alcohol intake in the form of

red wine had a protective effect, while intake of red meat resulted in increased risk [90]. Similar results with respect to red meat were indicated in the Oxford EPIC cohort [91] with more than 11000 subjects aged 20-79 years, wherein, no consumption of meat, fish, eggs or dairy products resulted in decrement in the blood pressure levels by 2-4 mmHg compared to regular meat consumers.

Incidence in the reduction of MetS can be brought about with proper diet strategies incorporating the components of Mediterranean diet [92] such as adequate consumption of omega-3 fatty acids, reduction of saturated and trans fats, and high intake of fruits, vegetables, whole grains, and nuts (Table III). In a randomized control trial, the experimental group following a prudent dietary pattern over a period of 2 years in Naples (n=180) (Italy), resulted in reduction of 55.6% in prevalence of MetS compared to 13.3% reduction in the control group. A meta-analysis of 12 studies with more than 1.5 million individuals tracked for 3-18 years for their health and health habits [93] demonstrated the effectiveness of Mediterranean diet in age related morbidity conditions especially MetS, CVD (pooled relative risk 0.91) and overall mortality (pooled relative risk 0.91), as has been proven over time94. Rumawas et al. [87] examined prospectively association between the Mediterranean-style dietary pattern and metabolic syndrome in the Framingham Heart Study Offspring Cohort for 2730 participants, out of which 378 diabetic patients and 318 patients reporting missing information were excluded, being followed up for 7 years. Prudent dietary pattern – rich in whole grains, fruit, vegetables, nuts, and omega-3 fatty acids and low in refined grains and saturated and trans fats, has revealed to propose a substantial protection against heart disease.

Design	Country	Sample	Salient Finding(s)	Reference
RCT	U.S.A	Control: N=44 women (Mediterranean-style low-glycemic-load diet). Intervention: N=45 women (diet + medical food containing phytosterols, soy proteins)	Decreases in fat and sugar intake (p<0.001), and increase in DHA and EPA (p<0.001) were observed in both groups. Significant reduction in all components of MetS (p<0.05) and plasma homocysteine levels was seen in the diet + medical food group (p<0.01) as compared to diet only group.	[86]
Prospective	U.S.A	N=2,730 adults	Significantly lower incidence of MetS was seen among those following a Mediterranean style dietary pattern (p=0.01). Mediterranean diet also led to significant lowering of waist circumference (p<0.001), fasting plasma glucose (p=0.03), and triglycerides (p<0.001) and higher HDL cholesterol (p=0.02).	[87]
RCT	Iran	N=100 obese adolescents (aged 12-18 years)	Significant decrease in weight after 3 months of intervention (p<0.05) in the intervention group. Significant decrease in BMI and increase in fruit and vegetable consumption was seen in the intervention group.	[88]
RCT	Germany	N=101 adults (N=48 med diet group+100 hrs of education vs N=53 written advice only group)	Increase in the consumption of fish, fruits/vegetables and moderately of canola/olive oil and increased plasma concentrations of long-chain n-3 polyunsaturated fatty acids. No change in the markers of inflammation like hs-CRP, fibrinogen, fasting insulin, homocysteine, serum lipids and plasma fatty acids	[89]

Design	Country	Sample	Salient Finding(s)	Reference
RCT	Italy	N=180 adults (99 men and 81 women) with MetS (ATPIII criteria)	Post 2 years significant increase in fruit, vegetables, whole grains, olive oil and nuts consumption (p<0.001), and decrease in mean body weight was observed in the intervention group (p<0.001). Significant improvement in the endothelial function score (p<0.001) and reduction in the Hs-CRP values (p=0.01) and insulin resistance (p<0.001) was also observed in the intervention group	[90]
RCT	Spain	N=45 sedentary adults (50-66 years)	Significant weight loss and improvement in MetS components was achieved with hypocaloric, normoproteic Mediterranean diet (p < 0.05). More significant weight loss was chieved with the combination of MeD and moderate intensity physical activity post 12 weeks compared to MeD alone (p<0.05)	[95]
Cross-sectional	Spain	N=578 adults (>18 years)	Prevalence – ATPIII criteria: 24.4%. Red meat and vegetable intake were positively associated with syndrome. Fruit intake, dairy products, moderate alcohol (red wine), cereals, and high MUFA: saturated fat demonstrated a protective effect.	[96]

Table III. Role of Mediterranean diet in the improvement of MetS

BMI = Body Mass Index; CRP = C Reactive Protein; DHA = Docosa Hexanoic Acid; EPA = Eicosa Pentanoic Acid; MeD = Mediterranean Diet; MUFA = Mono Unsaturated Fatty Acid

Specifically, each component of Mediterranean dietary pattern has its own significance that holds a key in obviating MetS. In the Bogalusa heart study, 1420 subjects aged 19-38 years were followed to make comparisons in the dietary intake of those who suffered from the syndrome with those who didn't [97]. MetS was evident in 12% of the young population (NCEP ATPIII criteria). Dietary patterns revealed consumption of fruits, fruit juices, vegetables, low-fat dairy products, diet beverages, less sweetened beverages and alcohol among those with no risk factors. No relation was found for red meats or processed meats. Thus, poor fruit and vegetable consumption and high consumption of sweetened beverages can serve as independent risk factors for MetS.

The Mediterranean diet can be considered a function of the prudent dietary pattern; however, its relation with insulin resistance and metabolic risk factors for CVD in non-Mediterranean populations is largely unexplored. Another meta-analysis of 50 studies and 534,906 individuals to ascertain the effect of Mediterranean diet on MetS and its components has come up with findings from prospective studies, clinical trials as well as epidemiological trials, that it is beneficial in the reduction of the syndrome [98]. Therefore, Mediterranean diet as a function of the prudent dietary pattern has shown its beneficial effects in the improvement of MetS substantially as projected by the evidence gathered through the years. Certain studies have demonstrated that high intake of saturated fatty acids [99-101] and low intake of n3 fatty acids [102] are responsible for MetS. Dairy products being a rich source of calcium have also shown to be beneficial in reducing the risk of blood pressure [103,104] MetS (Table IV), coronary heart disease [105], and inversely related to BMI. In a prospective study by Azadbakht et al. [106], it was seen that high intake of dairy was associated inversely with MetS, enlarged waist circumference and hypertension. The beneficial effect of the dairy products has been attributed by the presence of calcium in them that mediates the process of reducing the incidence of adiposity, hypertension and CVD, as

reported by various researchers [107-110]. Similar results with dairy calcium have been shown by Lin et al. [111]. They proposed that weight loss was more with dairy rich diets than calcium rich diets alone, which can also be due to the anti-obesity effect of protein in it [112]. A cross sectional study showed the same effect with calcium, however, some confounding factors such as physical activity, intake of fruits and vegetables were not taken into account [113]. In a 10 year long prospective study comparisons were made with respect to the amount of dairy intake and its ability to reduce the incidence of MetS [114]. However, similar causal reduction in the MetS incidence was not noticed in this study.

Year	Design	Sample	Finding	Reference
2009	Intervention	N=153 obese adults with MetS randomised to intervention or control for 16 weeks	Significant improvement observed in body composition (p<0.01), physical and cardio-metabolic fitness (p<0.01) with minimally prescriptive lifestyle intervention program.	[115]
2005	Cross-sectional	N=827 subjects (357 men, 470 women); 18-74 years	Inverse association of diary consumption with MetS (p<0.02), WC (p<0.001) and HT(p<0.02).	[106]
2005	Cross-sectional	N=34 hyperlipidemic men and women	Reduction in CRP was observed with cholesterol lowering diet (p=0.001) and statins (p=0.013).	[116]
2005	Cross-sectional	N=11,686 women; ≥45 years	Mg intake was inversely associated with CRP (p<0.0001) and MetS (p=0.0008).	[117]
2003	NHANES survey (prospective)	N=17,030, 20 years or older both men and women	Higher Ca intake led to lower age-related increase in blood pressure (p<0.001).	[103]
2002	Cross-sectional	N=192 individuals with MetS and 384 disorder-free control subjects, matched by age and gender	Inverse association between serum Mg levels and MetS (OR=6.8), dyslipidemia (OR=2.8) and high blood pressure (OR=1.9).	[118]
2002	Prospective	N=3,157 black and white adults (18-30 years)	Inverse association of dairy products consumption with MetS in overweight adults (OR=0.79).	[114]
2003	Cross-sectional	N=27,862 apparently healthy men and women (25-82 years)	Positive association of protein intake with BMI and weight gain/obesity.	[112]
2001	Prospective	N=5,765 men (35-64 years)	No association between milk consumption and CVD mortality.	[105]
2000	Cross-sectional	N=7,543 men and 8,053 women (25-69 years)	Negative association between Ca intake and blood pressure in both sexes (p<0.05).	[104]
2000	Prospective (RCT)	N=54 normal weight young women (18-31 years)	High Ca intake led to lower weight gain and body fat after 2 years of intervention.	[111]
2000	Cross-sectional	N=2,537 women and 2,439 men	Inverse association between dairy products and bread consumption and MetS in men.	[113]
1998	Cross-sectional	N=180 postmenopausal women (45-64 years), and 197 men (30-64 years)	Both diet and exercise together led to decrease in the LDL levels after 1 year among women (p<0.05) and men (p<0.01).	[119]

Table IV. Relationship between dairy products and MetS

BMI = Body Mass Index; Ca = Calcium; CRP = C Reactive Protein; CVD = Cardiovascular Disease; HT = Hypertension; LDL = Low Density Lipoprotein; Mg = Magnesium; WC = Waist Circumference; MetS = Metabolic Syndrome

Various epidemiological studies have suggested that magnesium can be an independent risk factor for the development of DMT2 [120-122], being a co-factor in number of enzymatic reactions that regulate glucose metabolism and insulin homeostasis [123,124]. In a cross-sectional study, an inverse association was reported between serum magnesium levels and MetS [118]; similar relationship was also seen with dietary magnesium intake [117]. In the CARDIA study, a total of 608 cases with MetS were identified in young adults (18-30 years; n=4637), wherein, magnesium intake was found to be inversely associated with it. Of particular significance, were the inverse associations of magnesium with blood pressure and triglycerides which were subsequently attenuated with lifestyle and dietary factors adjustment [51]. But the important question which arises is that, will a higher intake of magnesium prevent MetS? A question which can only be answered with more data from randomized control trials.

Vegetarian dietary pattern

The type of diet consumed also has various implications on MetS. A vegetarian diet consists of mostly food items that are from plants and plant products and does not have items resulting from death of animals. However, they may consume dairy products, milk and eggs [125]. The vegetarian dietary pattern can further be subdivided into lacto-ovo vegetarian (consuming milk, dairy products and eggs), lacto vegetarian (consuming milk and dairy products) and vegans (consuming no animal product). This vegetarian dietary pattern has shown to lower the risk of MetS. Rizzo et al. [126] studied various dietary patterns and looked at their association with MetS and its risk. Among subjects (n=773) of 30-94 years of age, dietary intake was assessed using a quantitative self-administered food frequency questionnaire and classified them into three categories – as vegetarian (consuming meat, poultry or fish <1 time in a month), semi-vegetarian (consuming fish at any frequency but other meats <1 time in a month), and non-vegetarians (consuming red meat or poultry ≥1 time/month). BMI was lowest in vegetarians and highest in non-vegetarians. MetS was classified according to the ATPIII criteria, with maximum number of components (i.e.5) for non-vegetarians. TG, FBG, BP, WC and BMI was significantly lower in vegetarians as compared to non-vegetarians (p<0.05). MetS was highest in non-vegetarians (39.7%), followed by semi-vegetarians (37.6%) and vegetarians (25.2%); with vegetarians having a lower odds for developing the syndrome (OR-0.44; p<0.001). Similar findings [127] were observed in case of male and female vegans and lacto-ovo vegetarians; with significantly lower BMI, TG level, TC/HDL ratio among vegans as compared to lacto-ovo vegetarians (p<0.05). Vegans also demonstrated more favorable serum lipid profile as compared to lacto-ovo vegetarians.

De Baise et al. [128] tried to compare levels of TG, LDL-cholesterol and HDL-cholesterol between vegetarians (lacto-ovo vegetarians [n=19], lacto vegetarians [n=17] and vegans [n=18]) and omnivores (n=22). For the same, blood samples were drawn from 76 adults and it was observed that there was a significant difference for these biochemical parameter values among all groups except for HDL-cholesterol. HDL/TC ratio was significantly higher in vegans (p<0.01), while TC and LDL-cholesterol values were highest for omnivores as compared to vegans (p<0.001). Cardiovascular risk [125] was also ascertained in a cohort of 201 individuals (35-64 years) in Brazil after classifying them as vegetarians (n=67) and omnivores (n=134). Levels of BP, FBG, TG, TC and LDL-cholesterol were significantly lower among vegetarians (p<0.001) except for HDL-cholesterol which showed no difference. Overall, vegetarians had a significantly lower cardiovascular risk (p<0.001) compared to omnivores whose diet consisted of animal protein and more fat.

Various studies related specifically to the Indian dietary pattern have shown risk for MetS and eventually CVD [129]. Whereas consumption of dairy foods, fried snacks and sweets consumption was associated positively with abdominal obesity; inverse relationship was observed with vegetables and pulses consumption for DM and hypertension. Vegetable and mustard oil consumption has also been proven beneficial [130]. The risk factors were more prevalent among the South Indians than North Indians [131].

Other lifestyle risk factors

Alcohol

Moderate alcohol consumption exerts a protective effect on MetS. Specifically, red wine consumption (0.1-19.9 g/day) resulted in a two-fold decrease in the prevalence of high blood pressure among women compared to non-consumers [132]; and has also been shown to improve the CVD risk profile in a Spanish population based study [133]. In the National heart study and DESIR French study, higher HDL values were observed in alcohol consumers. The underlying mechanism of this protective effect is the direct effect that alcohol has on HDL cholesterol synthesis, by modifying the activity of lipoprotein lipase, hepatic lipase, and cholesterol-esterase [134].

Inverse association of HDL cholesterol, triglycerides and blood pressure with alcohol consumption has an impact on the MetS [134,135]. Alcohol consumption of less than 40 g/day for men and less than 20 g/day for women suggested lower prevalence of MetS in comparison to non-alcoholics, as demonstrated by a meta-analysis of seven observational studies136. Protective effect in wine drinking women (n=4232) with lower odds ratio of syndrome development (OR=0.60, p<0.05) has been seen compared to men in Sweden [137]. Opposing to this, are detrimental effects in case of heavy alcohol consumption such as increase in waist circumference, triacylglycerols, blood pressure, and glucose, thus, augmenting the risk of metabolic syndrome [135,138-140].

Smoking

Studies have indicated that smokers have a higher risk of becoming insulin resistant, hence, smoking can be considered as a modifiable risk factor for MetS [141,142]. In a cross-sectional study of 3452 men, ≥20 years of age from a nationally representative sample of Koreans, a positive association between smoking and MetS was found [143]. Statistically significant association of current smoking amounts (p=0.023), total packs of cigarettes smoked during lifetime (p=0.040), with MetS, indicated smoking as an independent factor for the syndrome [144]. Evidence generated from different population groups has also supported the relation of smoking with hypertension [145,146] and type 2 diabetes [147,148].

With limited data on early identification of indicators of MetS before the development of the syndrome, a pilot study by Corwin et al. [149] estimated the risk scores in 41 subjects aged 18 to 39 years with 20 smokers and 21 non-smokers for three indicators: cardiovascular, metabolic, and immune related. Total risk scores were significantly greater in men (p=0.02) compared to women with only mixed effects of cigarette smoking. Similar effects of smoking on MetS have also been demonstrated by earlier studies [141,142,144]. Therefore, interventions focusing on modifiable risk factors should be undertaken.

Newer advancements

Oxidative stress

With still so many defining criteria for diagnosis of MetS, and an unclear picture on its pathophysiology, there is still uncertainty about the concept of syndrome as a whole. It is characterized by altered antioxidant status and sub-clinical inflammation, and has shown association with oxidative stress [150]. Therefore, a combined condition of hyperglycemia and inflammation (both characteristics of MetS), leads to increased production of reactive oxygen species and eventually increased oxidative stress. The main reactive oxygen species generated is super oxide anion which is produced by NADPH oxidase [151]. Oxidative damage occurs as a result of enzymatic and non-enzymatic components (vitamins E and C), and in case of physiological conditions, cells exhibit anti-oxidative mechanism to counteract the damage. However, when there is increased production of reactive oxygen species, balance between

enzymatic and non-enzymatic components is disturbed leading to a pro-oxidative condition [150]. Specifically, in MetS, there is decrease in both enzymatic components as well as in the levels of vitamin C and E due to decreased total antioxidant status [151,152], which eventually leads to increased oxidative stress proportionally [153]. Thus, has emerged the role of measurement of plasma oxidative stress which can identify MetS patients who are at an increased risk and those who may require intensive treatment.

Gut microbiota

Environment and epigenetics are two important factors that need to be considered in the origin of metabolic diseases as can be seen with gradual transition in eating habits, and increased consumption of fatty diets. However, it is still an unexplained concept as to why some people are sensitive and other resistant to metabolic disorders such as obesity and diabetes; therefore, individuality is an important concept that needs to be provided attention to. Therefore, four main factors emerge that are often overlooked in development of metabolic diseases-genetics, environment, individuality and rapid development of metabolic diseases. In this regard, role of intestinal and tissue microbiota is emerging that is linked to the development of metabolic diseases such as obesity and diabetes. The molecular mechanism underlying hyperglycemia and increased body weight have been related to inappropriate energy expenditure. In case of T2DM, there is increased hepatic glucose production and decreased insulin action and secretion; whereas in case of obesity, there is actually decreased requirement of food intake and energy expenditure, so when that does not occur, molecular factors lead to adipose tissue development and body weight gain [154]. A newer concept explaining it describes that having a fatty meal triggers bacterial factors that cause modification in intestinal microbiota and enter the host through innate immune system, triggering inflammation [155]. These bacteria then go to metabolic tissues such as adipose tissue and liver. Inflammatory mediators impair insulin secretion and lead to more adipose tissue development. Therefore, treatment targeting at the right bacterial translocation for therapies or prevention of metabolic diseases is important. Various trials on mice have demonstrated the use of probiotics such as *bifidobacterium lactis B420* in preventing insulin resistance [156].

Immune system and its changes lead to rapid increase in metabolic disorders; hence, it becomes all the more important to understand interaction between immune system and microbiota in order to know the underlying process in the development of metabolic diseases.

Early roots of Metabolic Syndrome: critical window of intervention

MetS has its roots early in life starting from the mother's womb itself. Intrauterine growth has positive relationship with the syndrome's occurrence. In the Atherosclerosis Risk in Young Adults (ARYA)-study, 744 young adults aged 26-31 years, were tracked on their birth weight [157]. Findings of the study revealed that those who were in the lower tertile of birth weight (1,250-3,209 and 3,210-3,649 g) had 1.8 times greater risk of developing MetS compared to those in the highest tertile (3,650-5,500 g). The syndrome is on the rise among young adults [158,159], with its roots embedded early in life [160-164]. A cohort of healthy young individuals in Amsterdam was followed for 24 years from the age of 13 years to 36 years to ascertain the prevalence of MetS (NCEP-ATPIII criteria) in relation to fatness, fitness and lifestyle. The prevalence was estimated as 10.4% (18.3% in men and 3.2% in women) at 36 years of age. Significant increases in the BMI and skinfold(s) ratio, compared to a significant decrease in the cardiopulmonary fitness was observed from adolescence to adulthood in adults with MetS, particularly at the ages of 21, 27, 32, and 36 years. Similar likelihood towards higher energy intake was observed throughout the years [165].

Prevalence of the MetS is widespread in Asia, with India contributing 30% of it [30]. However, according to the theory of developmental origin of health and disease, thrifty gene hypothesis is substantiated to be the underlying factor for the syndrome [166]. The triad of low birth weight and stunting due to malnutrition in early life availability of energy-dense foods at a later age in life, and sedentary habits, eventually leading to obesity with alteration in the body composition in terms of fat deposition, insulin resistance, and diet related chronic diseases [83]. MetS continues to evolve over a period of lifetime as evident in case of Delhi birth cohort which indicated prevalence of CVD risk factors highest among the ages of 29-36 years [167]. Young adulthood is a critical period to target intervention strategies that prevent excess weight gain and central fat deposition. Public health interventions targeting young people by focusing on the modifiable risk factors for the syndrome like weight control and regular physical activity can go a long way in restraining the development of DMT2 and CVD in future [165].

Conclusion

The problem of MetS is inevitable especially in a country like India, being a major public health challenge [83]. Given the magnitude of the problem, the public health responses should be strong, committed and focused both on primary and secondary prevention. Since, it is an emerging problem, the most important way of combating it, is to reduce its incidence by preventing its complications from developing. Prevention, by means of education – of both health professionals and public regarding healthy diet and lifestyle is required [168,169]. This will ensure minimization of health services cost to achieve maximum benefit to tackle this problem with available resources on a long term basis. Moreover, the rationale behind the therapeutic strategy for treatment of MetS highlights the fact that it is essential to correct insulin resistance, hyperinsulinimea and other metabolic abnormalities [170]. Therefore, the emphasis needs to be laid on comprehensive lifestyle change including both diet and physical activity; wherein, diet quality holds prime importance. Measurement of plasma oxidative stress and therapies targeting gut microbiota are current advancements in the field of MetS that are needed to be incorporated as strategies for early prevention of the syndrome. With long term management and regular follow up, the lifetime risk of MetS can be substantially reduced [13]. The need of the hour is to create awareness among treating physicians as well as the people regarding early diagnosis and comprehensive treatment as well as prevention of all components of MetS in an "available, accessible and affordable" manner. Therefore, adoption of healthy diets such as the Mediterranean and vegetarian diet along with changes in lifestyle including regular physical activity and foregoing smoking and alcohol can be of utmost public health importance, as these changes are not only cost-effective for primary and secondary prevention of MetS, but feasible to implement by all population groups and various cultures.

Questions for further research

MetS is a complicated disorder that is increasing at an alarming rate. Prevention is the best way to reduce the incidence of the syndrome. Though studies have focused on modifying various risk factors such as diet, alcohol, smoking and physical activity; diet overweighs all the other factors in terms of its magnitude as well as its relationship with the syndrome. Future research needs to be carried out to identify newer dietary patterns or dietary modifications which have a potential to combat the syndrome. Newer techniques for identifying at-risk patients should also be developed which can go a long way in reducing the burden of disease as well as the increased healthcare costs that it imposes on the nations.

The review in brief	
Clinical question	Faulty diet is one of the major root causes of Metabolic Syndrome and needs maximum attention, as it can reduce the incidence of the syndrome. The present review assesses the efficacy of various existing dietary patterns for combating the syndrome.
Type of review	Narrative
Search of the literature	PubMed (National Library of Medicine, Bethesda, MD, USA), Medline, Cochrane Library, Science Direct and Google Scholar databases. The keywords used were Metabolic Syndrome, diet, lifestyle, oxidative stress, gut microbiota, non-communicable diseases, prevalence, adults, inflammation and genetics.
Conclusions	The present review concludes that: • MetS is a major public health challenge. • The best way to combat it is to prevent it. • Poor diet is a significant contributor to the syndrome and needs more focus. • Prudent dietary patterns such as the Mediterranean diet and the vegetarian diet are protective in nature and have shown their efficacy to reduce the syndrome. • Oxidative stress measurement is an emerging technique to identify MetS patients at increased risk. • Role of gut microbiota is also important in identifying the syndrome; however, it is still a newer concept. • Early intervention is the need of the hour. • Preventive strategies for MetS should be acceptable, affordable, feasible and most importantly sustainable.
Limitations	Studies have shown that dietary modification can go a long way in preventing the syndrome. However, only a few dietary patterns have been identified in this regard. More research needs to be carried out to explore and identify newer dietary modifications that can reduce the syndrome or prevent it. Public health programs should focus on prevention through education but emphasis needs to be laid on developing programs that ensure sustainability.

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